Review Article
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Insight into the Role of Phytochemicals in the Treatment of Triple-Negative Breast Cancer

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Abstract

Triple-negative breast cancer (TNBC) is the most aggressive subtype of breast cancer which is characterized by the absence of progesterone receptor, estrogen receptor, and human epidermal growth factor receptor 2, thus, TNBC patient tumour does not respond to the endocrine therapy. TNBC is highly invasive, highly metastatic, and shows poor prognosis, recurrence, and short survival rate. Surgery, chemotherapy, and radiotherapy are now used as treatments. Despite the wide range of treatment choices, the main drawbacks of current therapies include drug resistance, decreased effectiveness, recurrence within 5 years, and a variety of side-effects. A unique targeted approach is therefore desperately required for the treatment of TNBC. Researchers now have fresh perspectives on the tailored strategy for treating TNBC thanks to phytochemicals. Phytochemicals have shown antiproliferative properties in TNBC and also overcome the drawbacks like recurrence, toxicity, adverse effect, and quality of life. This review highlights different phytochemicals and their potential to target signalling pathways and gene expression to induce apoptosis, cell cycle arrest, inhibition of metastasis, and angiogenesis.

Keywords: Triple-negative breast neoplasms, Genetics, Phytochemicals, Chemotherapy, Signalling

Introduction

Every year 2.09 million people are diagnosed with breast cancer worldwide.[1] Breast cancers are the principal cause of mortality in women. Triple-negative breast cancer (TNBC) is a subtype of breast cancer which comprises approximately 10%-15% of breast cancers.[2,3] TNBC is distinguished from other breast cancer types by the absence of progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2).[4] Among the other types of breast cancers, TNBCs are highly metastatic, more aggressive, and show poor prognosis.[5] The mortality rate of TNBC is higher than any other subtype of breast cancer.[6] According to studies, the average TNBC patient survives for 5 years following

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diagnosis.[7] TNBC is further split into six molecular subtypes, including luminal androgen receptor (LAR), immunomodulatory (IM), mesenchymal (M), basal-like (BL1 and BL2), mesenchymal stem-like, and another unidentified group (UNS).[8] TNBC is a more heterogeneous kind of cancer due to its variety in markers. African-American women are more likely than those of European and Asian heritage to develop the TNBC tumor subtype.[9] Hormonal therapy, sedimentary life-style, obesity, exposure to carcinogens and germline mutation in the BRCA1 gene are the cause of TNBC.[10,11,12]

Over the past few years, advancement in the research and technologies of breast cancers has given better treatment options which improved survival rates of TNBC patients, but some adverse effects affect the overall quality of life.[13] TNBC is diagnosed using imaging methods and a sample, which is then subjected to morphological analysis, biomarker analysis, and immunohistochemical characterisation of the tumor.[14,15] Certain endocrine treatments may slow tumor development in certain forms of normal breast cancer, but standard hormonal targeted therapies are ineffective because they lack drug target receptors.[16] Current treatments include surgery, radiation therapy, and chemotherapy.[17] Combined chemotherapy treatment with anthracyclines or taxanes exhibits good tumour regression rates but also carried out recurrence during the first 5 years after therapy.[18] Radiation therapy is a preferred option depending on certain characteristics of the tumour.[19] Radiation therapy is given post-surgery to prevent recurrence or along with chemotherapy. These conventional treatments are somewhat effective, but they still have several downsides, including medication toxicity, drug resistance, tumor recurrence, and a variety of adverse effects.[20] Because there is no one conventional therapy for treating all diseases due to their variability, combination therapies are often advised.[21,22]

Understanding the limitations of available treatment options in TNBC, the need for new targeted treatment options which are less toxic and cause minimum side-effects are critically needed. Plant-based secondary metabolites (phytochemicals) have drawn the attention of researchers as a natural candidate for the TNBC treatment which may overcome the issue of recurrence, drug resistance, metastasis inhibition and major adverse effects in the patient.[23,24]

Genetics of TNBC

Human normal cells have controls on their growth rate, frequency of division, and lifespan. Cells need proteins involved in cell cycle control to operate correctly in order for them to carry out these tasks. Any mutation in DNA repair, tumor suppressor, or oncogene genes results in aberrant proteins, which ultimately cause unchecked cell division.[25,26] Germline mutations in these genes lead to inheritable cancer[27] which were enlisted in table 1. Among those, important genes regarding their role in TNBC cancer are discussed below and their distribution among TNBC patients was shown in figure 1.

BRCA1 and BRCA2

BRCA1 and BRCA2 are autosomal dominant genes, commonly associated with inheritable TNBC.[29] BRCA1 and BRCA2 are located on chromosome number 17 and 13, respectively.[30] BRCA1 and BRCA2 are involved in double-stranded DNA break repair mechanism, transcription, cell cycle regulation, and DNA damage response to repair mechanism.[31] Therefore, there is a relationship between increased TNBC risk and BRCA1 and BRCA2 gene mutation. According to studies, triple-negative disease affects around 71% of people with BRCA1 gene mutations, compared with just 25 percent of patients with BRCA2 mutations.[32] In general, TNBC is nearly three times more likely associated with inherited BRCA1 gene compared to the BRCA2 gene. Both genes suppress tumour growth, thus called tumour suppressor genes or anti-oncogenes.[33] BRCA1 mutations associated with the patients include a younger age woman population with a median age of 39 years that shows higher grade tumour and higher stage tumour.[34,35]

Checkpoint kinase 2 (CHEK2)

CHEK2 gene encodes an enzyme serine-

threonine kinase, that acts as a cell cycle checkpoint regulator and tumour suppressor gene by DNA repair activity.[36] Mutations in CHEK2 will affect the DNA repair mechanism negatively which may induce tumour formation. Germline CHEK2 mutation leads to hereditary breast cancer.[37] CHEK2 mutation is vulnerable to chemotherapy drugs because it induces resistance to drugs.[38]

Ataxia telangiectasia mutated (ATM)

An enzyme called phosphatidylinositol (3,4,5)-trisphosphate (PIP3)-kinase, which is encoded by the ataxia telangiectasia mutation, activates downstream proteins involved in DNA repair and cell cycle control.[39] A mutation in ATM changes how the cell cycle and DNA repair mechanisms are regulated. ATM is recruited when a double-stranded break in DNA is sensed. In one study, it is found that one woman out of 158 with TNBC harboured a mutation in ATM.[40]

PALB2

A protein known as a partner and colocalize with BRCA2 and promotes recombination repair and checkpoint functions by stabilization and localization within nuclear matrix and chromatin.[41] PALB2 mutation accounts small percentage of TNBC. PALB2 mutation carrying tumours presented TNBC phenotype more often than other familial or sporadic breast cancer patients and are a more aggressive type of tumour.[42]

RAD51

RAD51 has a compensatory function for BRCA1.[43] RAD51 gene encodes proteins involved in homologous recombination (HR) in TNBC.[44] Mutation in RAD51 is associated with TNBC by altered homologous recombination. According to one research, polymorphisms in the RAD51 gene may be used to predict the development of TNBC since they statistically significantly enhance the risk of TNBC in a group that has the C allele for the variation 135C allele of the gene.[45]

Other genes

The mutation of many other genes like tumour protein 53 (TP53), phosphatase and tensin homolog (PTEN), STK11, B cell lymphoma 2 (BCL2), MSH2, PIK3CA, BARD1, epidermal growth factor receptor (EGFR), fibroblast growth factor (FGFR) and vascular endothelial growth factor receptor (VEGFR) are involved in TNBC by inhibiting apoptosis, inhibiting tumour suppressor genes, absence of DNA damage repair mechanism and inducing oncogenes.

Signalling pathways in TNBC

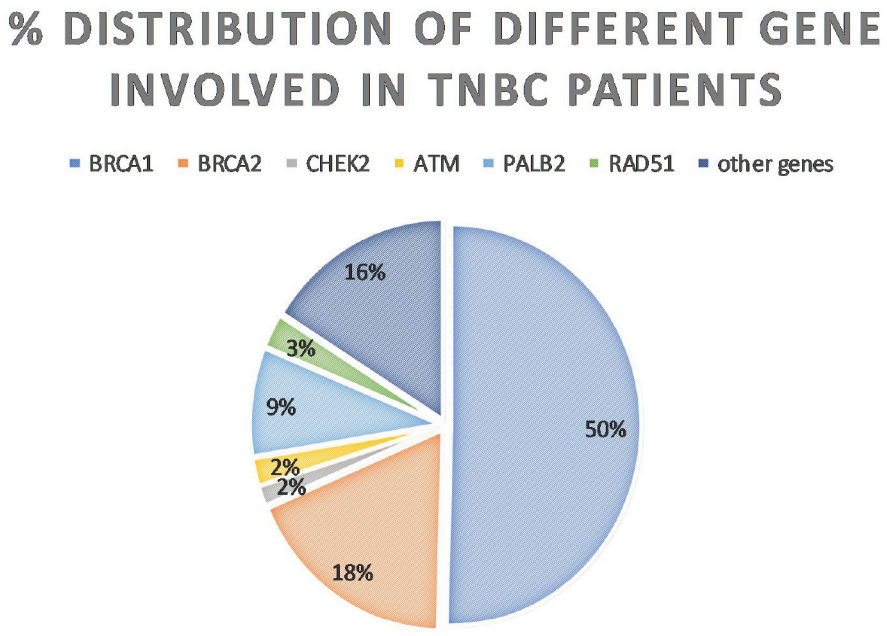

Figure 1. This figure shows the distribution of germline mutation in various genes among the women (n=692) with TNBC.[28]
TNBC: Triple-negative breast cancer

Unregulated cell proliferation or the inhibition of apoptotic pathways may be caused by uncontrolled and incorrect signal transduction, ineffective signal response, or both. These conditions may lead to the development of tumors. The following discussion covers many signalling pathways connected to the development of TNBC.

Wingless-related integration site (Wnt)/β-catenin signalling

The role of Wnt/β-catenin signalling pathway was first identified in mouse mammary tumour virus-mediated oncogenic transformation in human cells.[63] Wnt ligands binding to a Frizzled receptor (FZD) as well as the co-receptor low-density lipoproteins 5/6 (LRP5/6) initiates Wnt/β-catenin signalling.[64] It leads to activation of FZD, which allows binding of Dishevelled (Dvl) protein, and phosphorylation of cytoplasmic motifs of LRP5/6 receptor.[64] Phosphorylation in a single motif is adequate to activate Wnt signalling.[65] LRP5/6 that has been phosphorylated may interact with Axin, the motif of β-catenin destruction complex. Thus, β-catenin stays intact and accumulates in the cytoplasm before entering the nucleus, where it binds to transcription factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors and displaces transcriptional repressor Groucho, resulting in transcription of Wnt target genes.[66]

When the Wnt signal is absent, β-catenin

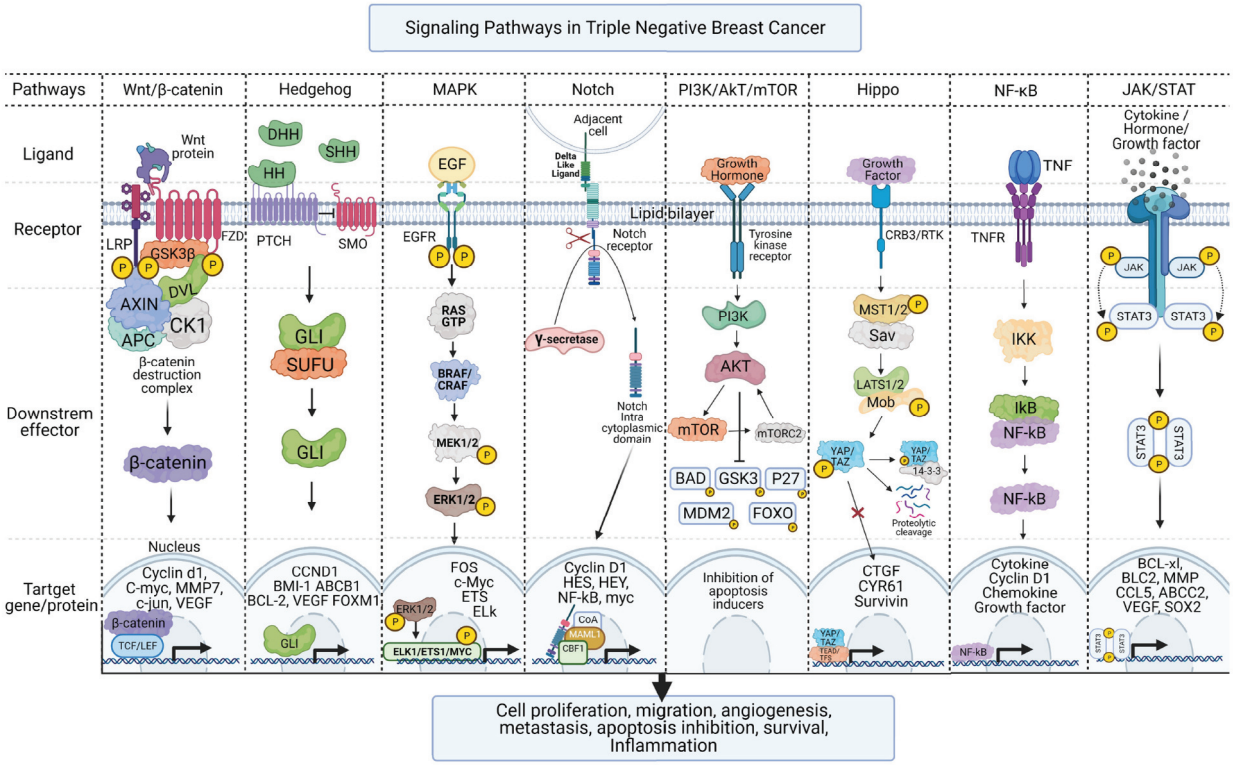

Figure 2. Different signalling pathways are involved in TNBC. Any aberration in signalling pathways leads to the transformation of cell. On binding of ligand to receptor cause a confirmational change in receptor and recruits downstream effector protein that inhibits or permits the function of transcription factors and regulatory proteins by multiple events of a signalling cascade to promote cell proliferation, metastas's, angiogenesis, apoptosis, survival and, inflammation.

ABCB1: ATP-binding cassette sub-family B member 1; ABCC2: ATP-binding cassette subfamily C member 2; APC: Adenomatous polyposis coli; BAD: BCL2 associated agonist of cell death; BMI1: B lymphoma Mo-MLV insertion region 1; CBF1: Centromere binding protein 1; CCND1: Cyclin D1; CK1: Casein kinase 1; CTGF: Connective tissue growth factor; CYR61: Cysteine rich angiogenic inducer 61; DHH: Desert hedgehog; DVL: Dishevelled; EGF: Epidermal growth factor; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal regulated kinase; ETS: E26 transformation specific; FOXM1: Forkhead box protein M1; FZD: Frizzled; GLI: Glioma associated oncogene homolog; GSK-3β: Glycogen synthase kinase 3 beta; Hes: Hairy/enhancer of split; Hey: Hairy/Enhancer of split related with YRPW motif; HH: Hedgehog; IKB: Inhibitor of nuclear factor kappa B; IKK: Inhibitor of nuclear factor kappa B kinase; JAK: Janus kinase; LATS1/2: Large tumour suppressor kinase 1/2; LEF: Lymphoid enhancer factor; LRP: Lipoprotein receptor related Protein; MAML1: Mastermind like transcriptional coactivator 1; MEK: Mitogen-activated protein kinase; Mob: Mps1 binder related; MST1/2: Mammalian sterile 20-like protein 1/2; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa B; PI3K: Phosphatidylinositol-3-kinase; PTCH: Patched; RAF: Rapidly accelerated fibrosarcoma; RTK: Receptor tyrosine kinase; SAV: Scaffold protein salvador; SHH: Sonic hedgehog; Smo: Smoothened; SOX2: SRY-box transcription factor 2; STAT: Signal transducer and activator of transcription; SUFU: Suppressor of fused homolog; TCF: T-cell factor; TEAD: TEA domain family member; TNF: Tumour necrosis factor; TNFR: Tumour necrosis factor receptor; Wnt: Wingless related integration site.

Table 1. Mechanism and mutation of gene in TNBC

Gene	Location	Function	Type of mutation	Reference
BRCA1	17q21	DNA damage response and repair, Tumour suppression	Inactivation	31,46
BRCA2	13q12	Tumour suppression, Homologous recombination	Inactivation	31,47
CHEK2	22q12.1	cell cycle checkpoint regulation, DNA repair	Inactivation	36
ATM	11q22.3	cell cycle regulation, DNA repair mechanism	Inactivation	39
PALB2	16p12.2	DNA recombination repair and checkpoint functions by stabilization and localization within nuclear matrix and chromatin	Inactivation	41
RAD51	15q15.1	Homologous recombination	Inactivation	44
TP53	17p13.1	Apoptosis and DNA repair	Inactivation	48,49,50,51
PTEN	10q23.31	Tumour suppression, Cell cycle regulation	Deletion, Inactivation	52,53
PIK3CA	3q26.32	Proliferation, Differentiation	Activation	54,55
BCL2	18q21.33	Anti-apoptosis	Overexpression	56,57
EGFR	7p11.2	Cell proliferation, Metastasis	Overexpression	58,59
VEGFR2	6p21.1	Angiogenesis, Invasion	Overexpression	60
FGFR1	8p11.23	Cell proliferation, survival	Overexpression	61,62

ATM: Ataxia telangiectasia mutated; Bcl2: B cell lymphoma 2; BRCA: Breast cancer gene; CHEK2: Checkpoint kinase 2; EGFR: Epidermal growth factor receptor; FGFR: Fibroblast growth factor; PALB2: Partner and localizer of BRCA2; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN: Phosphatase and tensin homolog; TNBC: Triple-negative breast cancer; TP53: Tumour protein 53; VEGFR: Vascular endothelial growth factor receptor

continuously undergoes the cycle of synthesis and degradation by the polyubiquitin mediated proteasomal degradation recruited by the β-catenin destruction complex. Wnt target genes translate proteins involved in cell proliferation and differentiation.[67] Upregulation of Wnt/β-catenin signalling leads to the tumour development, thus, this pathway is highly active in cancer cells.[68] Inhibiting or downregulating the Wnt/β-catenin pathway may give new hope in TNBC tumour suppression.

Notch signalling

Notch signalling is a type of juxtacrine signalling in which transmembrane receptors of one cell interact with neighbouring cell ligands.[69] Notch signalling is involved in multiple spheres of tumour progression, including regulation of cell proliferation, apoptosis, stem cells, angiogenesis and transition from epithelial-to-mesenchymal cell type.[70] When a ligand binds to the Notch receptor, γ-secretase is recruited and cleaves the Notch intracytoplasmic domain (NICD). Multiple enzymes further modify NICD. NICD penetrates the nucleus and encourages transcription of genes that encourage cell growth.[71] For patients with TNBC, inhibiting γ-secretase activity and controlling aberrant Notch signalling are potential treatments.[72]

Hedgehog (Hh) signalling

Hh signalling induces tumour growth, metastasis, and chemotherapeutic drug resistance.[73] In absence of Hh signal smoothened protein is inactive, thus, downstream effector GLI1 is inactivated in the cytoplasm by suppressor of fused protein (SUFU) protein by phosphorylation followed by degradation. Degradation products of GLI1 protein, GLI2 and GLI3 act as repressors after modification processing.[74] When the Hh signal binds to the patched receptor, smoothened protein becomes active and stops the degradation of the GLI1 protein.[74] GLI1 separates from SUFU and functions as a transcription factor for genes involved in cell motility, invasion, proliferation, and angiogenesis.[75,76] It is investigated in a preclinical study that unregulated Hh signalling leads to a more aggressive and highly metastatic tumour phenotype in the TNBC subtype.[77] Higher level of signal Sonic hedgehog (SHH) is correlated with overall poor survival of patients compared with patients whose tumour expressed a lower SHH level.[78] Downregulating the Hh pathway and prolonging suppression of GLI protein may control the proliferation of tumours (Figure 2).

Phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR)

PI3K/AKT/mTOR signalling pathway is involved in the regulation of cell proliferation, angiogenesis and apoptosis.[79] PI3K, AKT kinase and mTOR pathways are inhibitors of apoptosis.[80]

Table 2. Role of various phytochemicals in TNBC

Sr. No	Phytochemical	Role	Mode of action	Reference
1.	Gossypol	Antimetastatic, Antiproliferative, Apoptosis,	The upregulation of proapoptotic genes TNFRSF9, BNIP3, and GADD45A genes. downregulation of Bcl2.	94,110
2.	Lycopene	Apoptosis, cell cycle arrest	Inhibits phosphorylation of Akt kinase and mTOR, Upregulation of pro-apoptotic Bax protein	98
3.	Curcumin	Apoptosis, Antiangiogenic, Immunomodulatory	Downregulate EGFR expression, Inhibition of Hedgehog, Notch signalling and Wnt/B-catenin signalling	100,101, 103,104
4.	Genistein	Antiproliferative, Apoptosis, cell cycle arrest	Inhibits protein tyrosine kinases, Upregulation of BRCA-1 expression,	108,109
5.	Quercetin	Apoptosis, Antimetastatic	The upregulation of caspase-3 protein activity and downregulation of Bcl-2 protein and β-catenin.	111,112
6.	Luteolin	Apoptosis, Antimetastsic	The upregulation of Bax protein and downregulation of Bcl-2 protein alters the β-catenin pathway	113,114
7.	Fisetin	Cell cycle arrest, apoptosis	Suppress phosphoinositol 3-kinase (PI3K)-Akt-GSK-3 β signalling pathway,Reverses epithelial to mesenchymal transition, Decrease histone H3 phosphorylation	115,116
8.	Resveratrol	Apoptosis, Antiangiogenetic, Antimetastsic	Fas/Fas ligand-mediated apoptosis Inhibits the matrix metalloproteinases enzymes	117,118
9.	Capsaicin	Apoptosis, cell cycle arrest	Increases in cytochrome C release, caspase 3/7 activity. Down-regulation of cyclin D1	119
10.	Indole 3 carbinol	Induction of autophagy	p21/CDKN1A and GADD45A overexpression	120
11.	Rutin	Antitumour activity	The modulation of diverse macromolecular targets	121
12.	Rosmarinic acid	Cell cycle arrest and apoptosis	The upregulation of GADD45A BNIP3 upregulation	122
13.	Apigenin	Inhibit Proliferation and migration of tumour	The downregulation of CXCL10, IL22RA2, ROS1, SLITRK6 and MMP13. Decrease YAP/TAZ activity and expression of CTGF and CYR61	123,124
14.	Chalcones	Apoptosis, antimetastatic, regulates proliferation	The upregulation of PARP, caspase 3, caspase 8. Inhibits the activity of MMP-9. Potent inhibitors of HDACs.	125,126
15.	Piperine	Apoptosis, Antimetastatic	The inhibition of Akt activation, Inhibit expression of metalloproteinase-2 and 9	127,128
16.	Deguelin	Antiproliferative, Apoptosis, Antimetastatic	Decrease PCNA level Downregulation of EGFR, p-AKT, p-ERK, c-met, NF-κB	129
17.	Maximiscin	DNA damage response, Cell cycle arrest	Phosphorylation of p53, Chk1, and Chk2	130
18.	Cyclopamine	Antiproliferative	Inhibit Hedgehog pathway	131

Bax: BCL2 Associated X; BCL-2: B-cell lymphoma 2; BRCA: Breast cancer gene; CDKN1A: Cyclin-dependent kinase inhibitor 1A; CHK: Checkpoint kinases; CTGF: Connective tissue growth factor; CXCL10: C-X-C motif chemokine ligand 10; CYR61: Cysteine-rich angiogenic inducer 61; EGFR: Epidermal growth factor receptor; ERK: Extracellular Signal-Regulated Kinase; Fas: Fatty acid synthase; GADD45A: Growth arrest and DNA damage-inducible alpha; GSK: Glycogen synthase kinase; HDACs: Histone deacetylase; IL22RA2: Interleukin 22 receptor subunit alpha 2; MMP: Matrix metalloproteinase; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor-kappa B; PARP: Poly (ADP-ribose) polymerase; PCNA: Proliferating cell nuclear antigen; SLITRK6: SLIT and NTRK like family member 6; TAZ: Transcriptional coactivator with PDZ-binding motif; TNFRSF9: TNF receptor superfamily member 9; YAP: Yes-associated protein;

Protein kinase B, commonly known as AKT kinase, is a serine/threonine kinase that serves as the major mediator of PI3K-initiated signalling.[80] PIP3 kinase phosphorylates AKT kinase. AKT kinase inhibits apoptosis by inhibiting apoptosis-inducing proteins like BCL2 associated agonists of cell death (BAD), Bim, P53 and Mcl1.[81] Thus, apoptosis can be induced by inhibition of the PI3K/AKT/mTOR pathway and promote cell cycle arrest.[82] Inhibition of PI3K/AKT/mTOR pathway can be a promising approach in the treatment of TNBC.

Mitogen-activated protein kinases (MAPK)

MAPK pathways play an important role in proliferation, development, differentiation, apoptosis, and transformation.[83] MAPK signalling

has a very important role in the development of TNBC.[84] Within protein kinase cascades, three conserved active enzymes are present in series: MAPK kinase (MAPKKK), a MAPK kinase (MAPKK), and a MAP kinase (MAPK).[85] Stimulation of receptor Ras, rapidly accelerated fibrosarcoma (RAF), MEK, and extracellular signal-regulated kinase (Erk) is phosphorylated in a cascade manner.[86] RAF-MEK-ERK cascade is responsible for the control of the G1/S progression in the cell cycle, since Cyclin D transcription is a result of signal transduction.[83] Unrestrained MAPK may result in the perpetuation of TNBC cell proliferation.[87] TNBC patients with overexpression of the MAPK pathway exhibit anthracycline resistance and a higher risk of disease recurrence.[88] TNBC patients with higher levels of ERK protein expression had a worse survival rate.[89]

The interplay between Wnt/β-catenin signalling pathway, Notch pathway, Hh pathway, and other oncogenic signalling pathways like PI3K, Akt, mTOR, transforming growth factor-beta (TGF-β) signalling pathway, Ras androgen receptor (AR), EGFR, were thought to play important role in tumour development.

Phytochemicals in TNBC

Phytochemicals are chemical compounds produced by the plant from the primary or secondary metabolic pathway. Phytochemicals are known for their antioxidant, anti-inflammatory and anticancer and antiviral properties.[90] Mostly being secondary metabolites, they are produced in a very low amount from a plant.

Based on their chemical makeup and features, several well-known phytochemicals have been grouped into six broad groups. Alkaloids, phenolics, terpenoids, lipids, carbohydrates, and other nitrogen-containing molecules are some of these categories. Phytochemicals have been studied for the treatment of breast cancer during the last 20 years, with promising results as a natural contender for TNBC treatment.

Gossypol

Gossypol (GOSS) is a polyphenol compound, present in Gossypium hirsutum L (cotton) seeds in minor concentrations.[91] In China, Gossypol is traditionally used to cure viral infections. Gossypol is suggested to be an effective anticancer agent against TNBC.[92] In many studies, gossypol exhibited antimetastatic and antiproliferative effects in many human cancer types.[93] The antiproliferative property of gossypol is achieved by inducing apoptosis in TNBC cells.[92]

Messeha et al. examined the antitumour effects of gossypol in both MM-468 and MM-231 cell lines in-vitro. Real-time quantitative reverse transcription PCR (qRT-PCR) test of gossypol treated cell lines was performed to study the genes associated with gossypol induced apoptosis.[94] The expression of apoptosis-related genes was significantly upregulated by the compound. In both cell lines gossypol remarkably increases the expression of proapoptotic genes TNFRSF9, BNIP3, and growth arrest and DNA damage-inducible alpha (GADD45A) genes. More than 90% inhibition in BIRC5 (inhibitor of apoptosis) was noticed in MM-468 as well as an MM-231 cell line.[94] In another study, it was found that (-) enantiomer of gossypol exhibit more therapeutic effect in TNBC compared with the racemic mixture of gossypol.[95]

Lycopene

In tomatoes and many other red and pink foods, lycopeneóa significant carotenoidóis naturally present in higher amounts. It has antioxidant properties and prevents reactive oxygen species from damaging DNA in cells.[96] Lycopene's primary function in cancer cells is to stop the cell cycle and start apoptosis.[97] AKT kinase inhibits the production of proteins that cause apoptosis when it is phosphorylated.[81] Lycopene prevents Akt kinase and the downstream protein mTOR from being phosphorylated.[98] It results in the upregulation of proapoptotic Bax protein to induce apoptosis in TNBC cells. Mikako Takeshima et al. investigated in a study that treating MDA-MB-468 cell line with lycopene for 168 h shows lower half-maximal inhibitory concentration (IC50) value of 10.3 μM.[99] while shortening exposure time to 72 hours, IC50 values increased. Thus, a longer duration (>72 hours) of lycopene exposure is required to exhibit its true antiproliferative activity in the MDA-MB-468 cell line.[99] FACS

analysis of 50 µM lycopene treated MDA-MB-468 cells shows the declined growth mediated by cell cycle arrest in the G0/G1 phase as well as induction of apoptosis.[99]

Curcumin

Curcumin is a yellowish polyphenol compound present in turmeric extracted from the plant roots of Curcuma longa. Curcumin is a traditional Indian Ayurvedic medicine used in inflammation for centuries. Being pleiotropic in nature, curcumin acts as an antioxidant, proapoptotic, antiangiogenic, and immunomodulatory by acting on multiple signalling pathways.[100] The therapeutic effects of curcumin on the MDA-MB-231 TNBC cell line were studied by Xiao-Dong Sun.[101] The growth inhibition rate in a cell line treated with curcumin at various doses was substantially different from untreated cell groups in a cell line treated with 30 mol/ml of curcumin. Curcumin-treated cells had a considerably greater rate of apoptosis (26.34%) than cells from the control group (2.76%).[101] It was found in the MTT assay that curcumin concentration of 30 µmol/ml increases inhibition of MDA-MB-231 cell proliferation.[101] Flow cytometry result shows that apoptosis rates of 30 µmol/ml curcumin-treated MDA-MB-231 cells were 26.34%, while control shows only 2.76%. EGFR is predominantly involved in cell proliferation in TNBC.[102] Curcumin suppressed the activation of the EGFR signalling cascade by reducing the amount of pEGFR expression in an MDA-MB-231 cell line after a 48-hour curcumin treatment.[101] Curcumin blocks Hh, Notch, and Wnt/β-catenin signaling, according to a second research.[103,104] Numerous research on curcumin and its promising outcomes provide fresh perspectives on the management of TNBC.

Genistein

Genistein is a natural polyphenol compound which belongs to a class of isoflavones that is extracted from the Genista tinctoria flowering plant and Soybean.[105] For its anticancer effectiveness in TNBC, its potential for antimetastatic, apoptosis induction, cell cycle arrest, and antiangiogenetic capabilities have caught the interest of researchers.[106] According to several research, eating soy products, which are high in genistein, prevents breast cancer from spreading.[107] Hong Pan et al. studied the anticancer effect of Genistein on the MDA-MB-231 cell line.[108] It was explored that 20 µM genistein shows 60.64% apoptosis and arrest cell cycle of 30.95% cells in the G2/M phase. Genistein repressed NF-κB activation via inactivation of Notch signalling. In another study, genistein promotes BRCA1 activation by an epigenetic factor that promotes inhibition of TNBC cell proliferation (Table 2).[109]

Quercetin

It is a plant metabolite that belongs to the flavonoid class mostly found in apples, tea, onion and broccoli.[132] Quercetin promotes apoptosis in many cancer cell lines including lung, breast, stomach and colon.[133] Ahmed S Sultan studied the effect of Quercetin in MDA-MB157 and MDA-MB-231 cell lines.[111] In both cell lines, a 48-hour quercetin administration results in a 50% viability suppression. By upregulating the activity of the caspase-3 protein and downregulating the expression of the BCL-2 protein and β-catenin, quercetin promotes apoptosis. According to a different research, quercetin controls the -catenin pathway to stop TNBC migration.[112]

Luteolin

It is a bioflavonoid that may be found in fruits and medicinal plants. It has long been used to treat cancer and inflammation.[134] The primary apoptosis induction, antiangiogenesis, and antiproliferative properties of luteolin are responsible for its anticancer effects.[135] Luteolin inhibits the cell cycle, survival, angiogenesis, and metastasis of TNBC cells.[113] Dan Lin looked at whether TNBC cells treated with luteolin prevented cell invasion and migration. It alters the β-catenin pathway by repressing the mRNA of β-catenin.[113] Liming Huang studied that 30 µM of luteolin treatment for 48 h triggers apoptosis in MDA-MB-231 increasing the expression of Bax protein while a decrease in the expression of BCl-2 protein.[114]

Conclusion

We tried to summarize the phytochemicals as

possible future anticancer agents in targeted TNBC therapy. Being heterogeneous in nature, conventional chemotherapy has produced insignificant results in TNBC. Phytochemicals have proven effective at targeting numerous signalling pathways and gene expression in TNBC. The molecular-level understanding of TNBC has given researchers new insights into the targeted approach to treat TNBC. In addition to having antiproliferative effects on TNBC, phytochemicals have also been able to overcome problems with recurrence, toxicity, side-effects, and quality of life. Apoptosis, cell cycle arrest, metastasis inhibition, and angiogenesis are just a few of the impressive anticancer properties of phytochemicals. Combination treatment is suggested by the variety of indicators. In combination with traditional chemotherapy agents, phytochemicals show synergic effects by overcoming the limitation of another agent. Thus, further investigation should focus on in vivo testing and clinical trials of phytochemicals in TNBC. Additional studies are required to examine the safety, efficacy, bioavailability, tolerance, and drug delivery options of phytochemicals in the treatment of TNBC.

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Conflict of Interest

None declared.

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