The anticancer mechanism of action of selected polyphenols in triple-negative breast cancer (TNBC)

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Abstract

Breast cancer is a leading cause of cancer-related deaths in women globally, with triple-negative breast cancer (TNBC) being an aggressive subtype that lacks targeted therapies and is associated with a poor prognosis. Polyphenols, naturally occurring compounds in plants, have been investigated as a potential therapeutic strategy for TNBC. This review provides an overview of the anticancer effects of polyphenols in TNBC and their mechanisms of action. Several polyphenols, including resveratrol, quercetin, kaempferol, genistein, epigallocatechin-3-gallate, apigenin, fisetin, hesperetin and luteolin, have been shown to inhibit TNBC cell proliferation, induce cell cycle arrest, promote apoptosis, and suppress migration/invasion in preclinical models. The molecular mechanisms underlying their anticancer effects involve the modulation of several signalling pathways, such as PI3K/Akt, MAPK, STATT, and NF-κB pathways. Polyphenols also exhibit synergistic effects with chemotherapy drugs, making them promising candidates for combination therapy. The review also highlights clinical trials investigating the potential use of polyphenols, individually or in combination therapy, against breast cancer. This review deepens the understanding of the mechanism of action of respective polyphenols and provides valuable insights into the potential use of polyphenols as a therapeutic strategy for TNBC, and lays the groundwork for future research in this area.

1. Introduction

According to the world health organization, non-communicable diseases are responsible for 41 million death yearly, equal to 74% of all deaths worldwide. After cardiovascular disease accounting for 17.9 million death, cancer with 9.3 million death stands as the second leading cause of death globally and around 70% of cancer death occurs in low- and middle-income (LMICs) (World Bank’s classification based on each country’s economic status) countries [1]. In LMICs, there is often a lack of established cancer registries, as well as limited resources such as healthcare infrastructure, access to advanced medical treatments, and comprehensive cancer care services. As a result, people in these countries face challenges in accessing early detection programs, adequate screening services, timely diagnosis, and appropriate treatment options. These limitations contribute to higher rates of cancer-related deaths, including breast cancer [2,3]. With the diagnosis of 2.3 million women in 2020, breast cancer (BC) has been recognized as the most commonly diagnosed cancer worldwide. Of note, BC still stands first in terms of mortality, with 685,000 deaths in 2020, among women globally [4,5].

BC treatment generally consists of local therapy including surgery and radiation therapy and/or systemic therapy to treat and/or reduce the risk of recurrence or cancer metastasis [6]. However, despite all advances in breast cancer therapy, the triple-negative breast cancer (TNBC) subtype still remains a major challenge to manage and treat due to its particular characteristics. TNBC accounts for approximately 15% of all BCs and is the most invasive and metastatic subtype with higher susceptibility to early relapse and poor prognosis contributing to a shorter survival rate and mortality rate of 40% within the first 5 years after diagnosis in TNBC patients compared to other BC subtypes. It is characterized by the lack of expression of estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER-2) which makes it unresponsive to hormonal or HER2 targeted therapy. Currently, combination regimens of various chemotherapy drugs, including anthracycline, cyclophosphamide, taxane, fluorouracil, and cisplatin, are the main systemic treatment option available for TNBC patients but the development of chemoresistance and the emergence of severe side effects, relapse, and poor prognosis have limited its successful effectiveness. In addition, due to the high heterogeneity of this

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Considering the emerging significant role of polyphenols in TNBC therapy, this study aims to discuss the anticancer efficacy of the most widely studied polyphenols including resveratrol, quercetin, kaempferol, genistein and EGCG as well as their chemosensitivity role against TNBC, and highlight their promising multitarget action. The study also highlighted the clinical trials investigating the potential use of polyphenols, individually or in combination therapy, against breast cancer. Therefore, gathered information will provide an in-depth understanding of the molecular mechanism underlying their anticancer activity, as shown in Fig. 1, which can be beneficial in designing future studies and clinical trials for TNBC management and treatment.

2. Anticancer effect of selected polyphenols against TNBC: molecular mechanism

Various polyphenols are well known to have anticancer properties against TNBC in which numerous molecules and signaling pathways may serve as potential targets. TNBC is a multistage process where a large body of evidence has demonstrated the promising role of selected polyphenols, resveratrol, quercetin, kaempferol, genistein, and epigallocatechin gallate, as the potent anticancer agent which may
interfere with initiation, promotion, and progression both in vitro and in vivo TNBC models.

2.1. Resveratrol (RSV)

Resveratrol, RSV, 3,5,4'-trihydroxy-trans-stilbene, consists of two phenol rings that are attached to each other via an ethylene bridge and belongs to the stilbenes category of polyphenol compounds (Fig. 2). RSV is a phytoalexin produced by plants in response to pathogen attacks, such as bacteria and fungi, and mechanical injury. It has been found in abundance, particularly in grapes, red wine, berries, peanuts, cocoa, and dark chocolate. RSV has demonstrated a broad spectrum of beneficial health effects including, anti-inflammatory, estrogenic/antiestrogenic activity, neuroprotective, cardioprotective, antioxidant, antimicrobial, blood-sugar-lowering properties, antiaging, and anticancer activities [15,16]. In addition, its anticancer activity has been well documented in TNBC preclinical models which will be focused in the following section.

2.1.1. Cell cycle and apoptosis regulation by RSV

RSV induced p53-dependent apoptosis in MDA-MB-231 cells. It enters its effect through binding to integrin αvβ3 receptor, ERK1/2 activation, nuclear COX-2 accumulation, and p53 phosphorylation which further triggered the expression of pro-apoptotic genes [17,18]. In addition, DNA polymerase delta-1 (POLD1) gene encodes the catalytic and proofreading subunit of DNA polymerase-delta, a protein complex involved in DNA replication and DNA repair. POLD1 is generally highly expressed in BC tissues and correlated with an increased risk of BC and poor prognosis [19]. A recent study has demonstrated that RSV inhibited POLD1 expression which resulted in apoptosis induction in MDA-MB-231 invitro and invivo models. This was supported by observed downregulation of PCNA and Bcl-2 expression along with upregulation of cleaved-PARP1 and -caspase3 in treated TNBC models [20]. However, the antiproliferative activity of resveratrol in MDA-MB-231 cells was correlated with the inhibition of ribonucleotide reductase, which mediates the synthesis of the DNA precursors, and the occurrence of non-apoptotic cell death in treated cells [21,22]. Moreover, RSV may inhibit cancer progression through microRNA-mediated Bcl-2 regulation. The study found that RSV modulated miRNAs, including miR-122–5p, miR-542–3p, and miR-200c-3p in MDA-MB-231 cells. This resulted in the downregulation of anti-apoptotic proteins (XIAP and Bcl-2), increased caspase-8 and –9 activities, and downregulation of cell cycle proteins (CDK2, CDK4, and CDK6). Consequently, it led to G1 cell cycle arrest and cell death in treated cells [23].

Moreover, the regulation of key signaling pathways has been attributed to RSV anticancer activity. It was found that RSV-induced apoptosis in MDA-MB-231 cells and xenografts models was associated with the modulation of MAPK signaling and the inhibition of proteins involved in protein translation [24]. Similarly, in a recent study, researchers cultured MDA-MB-231 cells under hypoxic conditions (1% O2) to mimic the central microenvironments of solid tumor. The study found that a high concentration of RSV inhibited cell growth, induced autophagy and apoptosis via activation of MAPK signalling in TNBC cells [25]. This effect was attributed to the antioxidant activity of RSV, demonstrated by the upregulation of SOD3 and FAM213B, increased catalase activity, and elevated NAD(P)H levels [25]. Furthermore, in both MDA-MB-231 and MDA-MB-468 cells, harboring constitutively active STAT3, the inhibitory effect of RSV on Src tyrosine kinase activity led to the suppression of the STAT3 signaling pathway. This, in turn, resulted in apoptosis induction and cell cycle arrest in G1 and S phases in those cell lines, respectively [26].

2.1.2. Inhibition of cell migration and metastasis by RSV

The anti-metastatic effect of RSV in TNBC preclinical models has also been reported. RSV downregulated VEGF, and EGFR expression and inhibited EGFR/Pi3k/AKT signaling in MDA-MB-231 cells. As a result, downstream targets such as MED2B, MMP-9 expression, and NF-κB DNA-binding activity were also inhibited. Ultimately, this led to the suppression of cellular migration and angiogenesis in xenografts models [21,27]. Furthermore, RSV reversed TGF-β1-induced epithelial-mesenchymal transition (EMT) in MDA-MB-231 cells. It upregulated E-cadherin expression and downregulated MMP-2, MMP-9, fibronectin, SMA, vimentin, Snail1, and Slug levels in the treated cells. Besides, RSV-suppressed Pi3K/AKT and Smad signaling led to the inhibition of lung metastasis in a xenograft-bearing mouse model [28]. Additionally, inhibition of sodium-dependent inorganic phosphate transporter has been reported to be likely another mechanism underlying RSV-induced anti-migratory effect in MDA-MB-231 cells [29]. In another experiment with MDA-MB-231 cells exposed to cancer-associated fibroblast-conditioned media (CAF-CM), the anti-proliferative and anti-invasive effects of RSV were observed. These effects were linked to the suppression of cyclin D1, c-Myc, MMP-2, and MMP-9 expression. [30].

2.1.3. Epigenetic regulation by RSV

RSV is also considered a dietary epidrug in which alteration of the methylation status of cancer-related genes is another mechanism underlying its anticancer action. A genome-wide analysis of DNA methylation, based on promoter DNA microarrays, has shown that RSV reverses DNA methylation changes of specific genes and pathways in MDA-MB-231 cells. It also restores the hypermethylated and hypomethylated status of crucial tumor oncopgenes and suppressor genes, respectively, which are correlated with cellular pathways commonly dysregulated in breast cancer. Further transcriptome profile analysis also revealed that these methylation modifications were concordant with alterations in mRNA expression [31]. It was found that RSV-induced up-regulation of ATF2A3 was linked to the suppression of HDAC activity and inhibition of nuclear HDAC2 expression. As a result, apoptosis was induced in MDA-MB-231 cells [32]. In another study, RSV acted as an acetylation inhibitor, resulting in a decrease in acetylated STAT3 levels in MDA-MB-231 and MDA-MB-468 cells. This led to demethylation and activation of the estrogen receptor-α gene. As a result, the tumor cells became more sensitive to anti-estrogens. [33].

Overall, RSV exerts its anticancer effects through modulation of various signaling pathways (MAPK, STAT, EGFR/Pi3k/AKT, and NF-KB) as well as multiple mechanisms including inhibition of cell proliferation, induction of apoptosis and autophagy, cell cycle arrest, antioxidant activity, reversal of EMT, suppression of migration and angiogenesis, as well as regulation of gene methylation and acetylation of cancer-related genes in TNBC models.

2.2. Quercetin (QUE)

Quercetin, QUE, 3,3′,4′,5,7-pentahydroxyavone, is nature’s most common flavonoid belonging to the flavonoids group which is found in many fruits and vegetables (e.g. citrus fruits, apples, onions, kale), seeds, olive oil, nuts, coffee, red wine, and tea. Therefore, it is one of the most prominent dietary antioxidants in the diet showing broad spectrum
biological activities on human health including antiviral, anti-fungal, anti-diabetic, anti-allergic, and anti-inflammatory. It is also non-toxic and possesses hepatoprotective and cardioprotective activities [34,35]. The anticancer effect of QUE against TNBC has also been extensively studied in many in vitro and in vivo studies attributed to various mechanisms.

2.2.1. Cell cycle and apoptosis regulation by QUE
QUE reduced cell viability and induced apoptosis via both intrinsic and extrinsic caspase-dependent pathways in MDA-MB-231 cells. This was accompanied by increased cytosolic Ca$^{2+}$ levels, reduced mitochondrial membrane potential, activation of caspase-3, -8, and -9, upregulation of FAS, Bax, and downregulation of Bcl-2 and XIAP. In addition, cell cycle arrest was induced through the down-regulation of cyclin A and B and up-regulation of p57 [35]. QUE also upregulated JNK activation and its downstream target FoxO3a, leading to increased Fasl expression in MDA-MB-231 cells [36,37]. QUE inhibited the expression of FASN and β-catenin in MDA-MB-231 and MDA-MB-157 cells. This inhibition resulted in the induction of caspase 3-dependent apoptosis and tumor growth inhibition in a TNBC model. MDA-MB-231 cells were more sensitive to QUE than MDA-MB-157 cells [38]. In addition, QUE inhibited the expression of Hsp27, Hsp70, and Hsp90, involved in cell survival, in MDA-MB-231 cells. This inhibition led to apoptosis, characterized by increased caspase activity and PARP cleavage [39]. Furthermore, Iron homeostasis is essential for cell survival, and cancer cells are more iron-dependent and sensitive to ferroptosis, a type of programmed cell death, than normal cells. It was found that QUE was able to induce ferroptosis in MDA-MB-231 cells [38,39].

2.2.2. Inhibition of cell migration and metastasis by QUE
The anti-migratory and -invasive potential of QUE has been well documented. QUE inhibited proliferation, suppressed colony formation, invasion and migration cells via inhibition of MMP-3 enzyme activity in MDA-MB-231 [40,41]. In addition, QUE inhibited the AKT and β-catenin signaling pathway by suppressing AKT phosphorylation and reducing the nuclear localization of β-catenin. As a result, downstream targets such as E-cadherin and vimentin (EMT markers), cyclin D1, and c-myc were modulated in MDA-MB-231 and MDA-MB-468 cells [42]. Furthermore, QUE treatment induces a transition from a spindle to a cuboidal shape, representing a shift from mesenchymal to epithelial phenotype in TNBC cells. This is accompanied by a reduction in migration due to the targeting of PI3K/AKT, STAT, and MAPK pathways. This effect is more notable in mesenchymal-like subtypes compared to basal-like subtypes. [43]. Besides, Hu-antigen R (HuR) is a RNA binding protein involved in posttranscriptional gene regulation. Overexpression of HuR has been correlated with breast cancer progression, aggressiveness, drug resistance and is associated with poor prognosis in TNBC [44]. A recent study has shown that QUE-mediated inhibition of adhesion and migration of TNBC cells was through the suppression of HuR-β-catenin axis and CD44, independently, in MDA-MB-231 and MDA-MB-468 cells [44]. QUE also exhibited growth and invasion inhibitory effects on MDA-MB-231 cells and an animal model. These effects were mediated by the upregulation of miR-146a and suppression of VEGF. Ultimately, this resulted in the induction of mitochondrial-mediated apoptosis in the treated cells [45].

IGF1R protein is highly expressed in approximately 22–46% of patients with TNBC stimulating cell proliferation and promoting cell survival in TNBC cells. In a recent study, QUE inhibited the metastatic and aggressive phenotype of TNBC in cell-based and xenograft animal models via suppression of IGF1/IGF1R-mediated EMT. QUE downregulated the expression and phosphorylation of IGF1R and its downstream kinase targets, Akt and Erk1/2, as well as reducing IGF1 secretion. These inhibitions led to the downregulation of mesenchymal (Snail, Slug, fibronectin, and vimentin), and upregulation of epithelial markers (keratins 18 and 19). Stemness-related markers (Sox2, Oct4, and Nanog) were also downregulated and eventually invasion and metastasis were inhibited in TNBC models [46,47]. Moreover, the change in glucose metabolism is one of the most significant factors involved in metastasis. QUE was found to suppress TNBC cell mobility by blocking cell glycosylation, which serves as the primary energy source for tumor cell migration. This inhibition occurs through the inactivation of the Akt-mTOR signaling pathway, leading to the induction of autophagy in MDA-MB-231 cells and in vivo model. The findings revealed the downregulation of cell migration markers (MMP-2, MMP-9, VEGF) and glycosylation-related proteins (PKM2, GLUT1, LDHA) [48]. QUE-mediated inhibition of COX-2 expression and COX-2-mediated angiogenesis was also correlated with the inactivation p300 signaling pathway in MDA-MB-231 [49]. QUE has shown the ability to target and suppress breast cancer stem cells (CSCs). This effect was attributed to its downregulatory impact on ALDH1A1, CXCR4, MUC1, and EpCAM. These molecules are associated with the MDA-MB-231/CD44 + /CD24-phenotype, which is linked to tumorigenesis and the progression of CSC-mediated metastasis [50].

2.3. kaempferol (KAE)
Kaempferol, KAE, (3,5,7-trihydroxy-2-(4-hydroxyphenyl)- 4-H-benzopyran-4-one), belongs to the flavonoid family that shows structural similarity with the hormone estrogen. It is a secondary metabolite that is richly found in many vegetables, fruits and plant-derived foods such as grapes, tomato, tea, broccoli, strawberries cabbage, beans, etc. exhibiting many pharmacological activities including cardiovascular, neuroprotective, antioxidant, anti-bacterial, anti-oxidative, anti-inflammatory, and anti-tumor properties [51,52]. Multiple studies have shown the impact of kaempferol on various molecules and pathways associated with cancer in TNBC.

2.3.1. Cell cycle and apoptosis regulation by KAE
KAE treatment suppressed proliferation, and induced cell cycle arrest at G2/M phase in MDA-MB-231 cells. It also resulted in DNA damage correlated with NF-κB inhibition and mitochondrial-mediated apoptosis. These effects were accompanied by activating caspases and increased expression of H2AX, and p-ATM, which are involved in the DNA damage response in MDA-MB-231 cells [53,54]. Likewise, KAE demonstrated its anti-proliferative effects on MDA-MB-453 cells by downregulating CDK1, cyclin A, and cyclin B, resulting in cell cycle arrest at the G2/M phase. Additionally, KAE induced apoptosis through the phosphorylation and activation of p53 in respective cells [55]. Another study has reported the potential of KAE to inhibit cellular proliferation, induce DNA damage, and eventually S-phase cell cycle arrest in MDA-MB-468 [56]. Besides, P-21 activating kinase-4 (PAK4) has the crucial role in breast tumorigenesis. PAK4 plays a significant role in cell proliferation, migration, and invasion by activating the PI3K pathway in MDA-MB-231 TNBC model [57,58]. Additionally, there is a correlation between PAK4 overexpression and clinicopathological characteristics such as lymph node metastasis, larger tumor size, and advanced stage cancer in breast cancer patients. Therefore, high levels of PAK4 expression have been specifically associated with poor disease-free or overall survival in these patients [57,59]. A recent silico-based study has suggested KAE as the potential PAK4 inhibitor in TNBC [60].

2.3.2. Inhibition of cell migration and metastasis by KAE
The efficacy of KAE in reducing epithelial to mesenchymal transition (EMT) and its anti-metastatic effects has been established in TNBC models. KAE demonstrated inhibition of migration and invasion of MDA-MB-231 and MDA-MB-453 cells. This effect was achieved by blocking RhoA and Rac1 activities and downregulation Rho signalling which plays an important role in microfilament rearrangement and migration of cancer cells. Additionally, KAE affected the expression of EMT markers (E-cadherin, Vimentin, Snail and Slug) and MMPs (MMP2, MMP-3 and MMP9) in treated TNBC cells [40,61]. It was also reported that KAE inhibits invasion by blocking PKCδ/MAPK/AP-1 cascade. This
cascade, in turn, regulates the expression and activity of MMP-9 in MDA-MB-231 cells. The inhibitory effect of KAE on lung metastasis was further confirmed in an animal model [62].

Furthermore, the upregulation of stemness markers induced by chemotherapy contributes to chemoresistance, invasiveness, and metastatic properties of the existing tumor. In a recent study, the efficacy of KAE was evaluated on tumor explants from TNBC patients who received neoadjuvant chemotherapy. The study demonstrated that KAE reduced the expression of stem cell and EMT markers including ALDH1, NANOG, CD44, and MDR1, induce G2/M cell cycle arrest, and upregulate H2AX in ex-vivo primary BCSC and MDA-MB-231 cells. These effects contribute to regulating chemoresistance and maintenance of stemness in TNBC models [64]. Additionally, KAE has been found to act as a sirtuin modulator, specifically targeting SIRT3 and SIRT6 protein expression. These proteins play a role in stemness properties in TNBC cells. This effect has been demonstrated through in silico and in vitro experiments conducted on MDA-MB-468 cells, highlighting KAE’s potential in exerting an anti-metastatic effect [56].

2.4. Genistein (GEN)

Genistein, GEN, 4,5,7-trihydroxyisoflavone is the most predominant polyphenolic isoflavone, that belongs to flavonoid family and is highly abundant in soybean products and other food sources for instance legumes, fava beans, kudzu, lupin. It is showing both agonistic and antagonistic effects on ERs and has various biological functions [65,66] as well as substantial potential for inhibition of TNBC development and progression as discussed below.

2.4.1. Cell cycle and apoptosis regulation by GEN

GEN induced cell cycle arrest, inhibited proliferation of MDA-MB-231 and MDA-MB-231/ERβ1 sub-line cells and suppressed tumor growth in TNBC models. These effects were mediated via a down-regulation of cyclin D1 and upregulation of p21 expression [67]. In addition, GEN treatment led to the inhibition of Notch-1 pathway in MDA-MB-231 cells. As a consequence, NF-κB activation was also suppressed, along with its downstream targets, cyclin B1, Bcl-2 and Bcl-xL. This collective effect resulted in G2/M cell cycle arrest and subsequent TNBC cell death [68]. The absence of functional BRCA1 results in the activation of GPR30 signalling, leading to increased cell proliferation through Akt phosphorylation. In BRCA1 impaired breast cancer cells, MDA-MB-231 and HCC1937, GEN induces G2/M arrest by suppressing GPR30-Akt signalling [69]. Additionally, GEN induces Nrf2 activation, resulting in the suppression of ROS production and regulation of antioxidants gene expression in HCC1937 cells [69].

Fatty acids (FAs) are essential for energy production, cell membrane structure, and regulation of signaling pathways. Fatty acid oxidation (FAO) plays a crucial role in the metabolic reprogramming of TNBC cells and fueling their growth. In addition, TNBC tumor cells strongly depend on FAO to support proliferation, invasion, and metastasis. CD36, high-affinity fatty acid (FA) receptor, is involved in FA uptake by cancer cells and plays a significant role in FAO. Its expression is closely linked to the availability of FAs and the metabolic demands of cancer cells [70,71]. GEN treatment suppressed CD36 expression and activated phospho-p38 MAPK. Consequently, modulation of the CD36/phospho-p38 MAPK axis promoted apoptosis and inhibited TNBC cell growth [72]. A former study also reported the suppression of the MEK5/ERK5/NF-κB pathway resulted in Bcl-2 downregulation and induction of caspase-3-dependent apoptosis pathway in MDA-MB-231 cells [73]. However, high concentration of GEN induced phosphorylation of ERK1/2 while suppressing Akt phosphorylation in MDA-MB-231 cells. This treatment also elevated Bax/Bcl-2 ratio resulting in apoptosis occurrence [74]. Furthermore, miR-155 play a crucial role in the regulation of more than 100 cancer-related pathway and cell cycle regulatory molecules and has been correlated with TNBC [75,76]. GEN treatment has demonstrated a decrease in miR-155 expression in MDA-MB-435 and Hs578T cells. This reduction led to the upregulation of miR-155 targets such as FOXO3, PTEN, casin kinase, and p27, resulting in an anti-proliferative and proapoptotic effect in respective cells [77]. Besides, GEN inhibited the proliferation of CD44+/CD24 cancer stem cells (CSCs) derived from MDA-MB-231 and suppressed their invasion ability [78].

In addition, omics approaches have provided a comprehensive assessment of alterations induced by GEN treatment in TNBC models. The phosphoproteomics analysis has shown that GEN treatment in MDA-MB-231 cells modulated phosphorylation sites on various proteins involved in cell cycle pathway and DNA damage response. This was achieved via the activation of ATR and BRCA1 complex in MDA-MB-231 cells [79]. Moreover, protein profiling of MDA-MB-231 cells exposed to GEN has revealed significant changes in the abundance of proteins involved in lipid catabolism, extracellular matrix degradation, and RNA splicing. These changes ultimately hinder the growth and invasion of TNBC cells [80]. Additionally, a metabolomic analysis demonstrated that GEN modulates metabolism by inhibiting glutamine uptake in MDA-MB-231 cells, which rely on glutamine as a key nutrient. This inhibition is linked to defective glucose import and ultimately affects protein biosynthesis [81].

2.4.2. Epigenetic regulation by GEN

Epigenetic regulation also links GEN to its anticancer effect against TNBC. Transcriptomics analyses in TNBC tumors isolated from preclinical patient-derived xenograft (PDX) orthotopic mouse models has shown the ability of GEN to modify the expression and activity of epigenetic modulators, Dnmt3b, Tet3 and Hdac2. DNA methyltransferases (DNMT3b) is an enzyme that adds methyl groups to DNA, ten-eleven translocation (Tets) methylcytosine dioxygenase is involved in DNA demethylation, and histone deacetyltransferase (Hdac2) removes acetyl groups from histone proteins. Therefore, GEN influenced DNA methylation and histone deacetylation process which contributed to its inhibitory effects on PDX tumor growth [82]. The findings also revealed that GEN induced alterations in the expression of multiple genes associated with tumor formation, progression, and metastasis. Out of the 20 significantly differentially expressed genes, 9 genes showed upregulation, while 11 genes exhibited downregulation which has been discussed in details in [82]. These alterations may have the impact on various important biological processes, cellular components, and metabolic pathways. Notably, GEN treatment led to the downregulation of Cd74, which subsequently suppressed the NF-kB/Bcl-xl/TAp63 signaling pathway in the TNBC model [82]. In addition, overexpression of aryl hydrocarbon receptor (AHR) is correlated with epigenetic silencing of BRCA1 in TNBC [83]. It was found that GEN acted as the antagonism toward AHR and inhibited its binding/activity at the BRCA1 promoter in HCC38 invito and invivo models. This effect led to lower GpG methylation, rescued BRCA1 expression and eventually may contribute to restoring the sensitivity of TNBC to antiestrogen therapy [84].

2.5. Epigallocatechin gallate (EGCG)

Epigallocatechin gallate (EGCG), also known as epigallocatechin-9-gallate, is the main active catechin in green tea which belongs to the subgroup of flavanols of the flavonoids family. EGCG is linked to the majority of health benefits in various diseases such as obesity, diabetes, stroke, Parkinson and cancer [85,86]. It has been also documented to be effective as a potential treatment against TNBC through its regulatory
role on numerous molecules.

2.5.1. Cell cycle and apoptosis regulation by EGCG
EGCG was able to inhibit the proliferation, induce G1 cell cycle arrest via downregulation of cell cycle proteins (CDK 1, CDK 4, Cyclin E, Cyclin D, and PCNA) and activate apoptotic cell death in MDA-MB-231 both in vitro and in vivo [87,88]. It also reduced the cell viability of metastatic BT-20, and MDA-MB-436, BT-549 cells [89]. The previous study also showed the EGCG-induced apoptosis was mediated via increased expression of p53 expression and its phosphorylation, Bax/Bcl2 ratio, induction of cytochrome c release, Apaf-1, caspase-3 activation, and PARP cleavage in MDA-MB-468 cells [90]. Additionally, the anticancer effect of EGCG was correlated with apoptosis induction and ROS modulation in Hs578T cells. It exhibited a dual function in TNBC cells, acting as both a pro-oxidant and an antioxidant which depended on the concentration and exposure time [91].

2.5.2. Inhibition of cell migration and metastasis by EGCG
There is the association of overexpression of β-catenin with clinicopathological characteristics (high TNM stage, lymph node metastasis, and ER-negative status) and poor prognosis in TNBC patients [92]. EGCG suppressed β-catenin, p-Akt and cyclin D1 expression via inhibition of PI3k in MDA-MB-231 cells [92]. In addition, EGCG binds directly to the EGFR extracellular domain, suppressing AREG binding and reducing phosphorylation levels of EGFR, AREG, and downstream target ERK. This contributes to its anti-proliferative and anti-migratory effects in MDA-MB-231 cells [93]. Furthermore, cellular communication network factor 5 (CCN5) is a gatekeeper gene belonging to the CCN family of growth factors that has a regulatory role in TNBC viability, ER-α, and stemness features [94,95]. EGCG also reduced cell viability in TNBC cells (MDA-MB-231, HCC70) by activating CCN5. EGCG upregulated CCN5 expression leading to growth suppression, apoptosis, MET, and reversal of stemness in vitro and in vivo [96]. In addition, the previous study also revealed that EGCG-activated FOXO3a resulted in ER-α expression which reversed the invasive phenotype of TNBC cells [97]. Besides, EGCG has been found to inhibit the activation of HIF-1α and NF-κB, resulting in the suppression of VEGF expression. This, in turn, leads to anti-migratory and anti-angiogenic effects in TNBC cells. [88,98].

2.5.3. Metabolism regulation by EGCG
The anti-TNBC effect of EGCG has also been linked to its regulatory role on metabolism observed in preclinical studies. Overexpression of proline dehydrogenase (PRODH) involved in proline catabolism may depend on the metabolism observed in preclinical studies. Overexpression of PRODH and its target proteins, as well as modulated the concentration and exposure time [91].

2.5.4. Epigenetic regulation by EGCG
The anticancer activity of EGCG on TNBC has also been attributed, in part, to epigenetic regulation. It was found that EGCG modulated the DNA methylation and histone acetylation status of the ERα promoter. This led to the remodeling of chromatin structure and reactivation of ERα in MDA-MB-231 cells. This effect was also accompanied by the reduced binding of the transcription repressor complex, Rh/p130-ERF4/5-HDAC1-SUV39H1-DNMT1, in the regulatory part of the ERα promoter upon RGGC treatment [102]. In addition, the reduced in cell viability observed in MDA-MB-231, MDA-MB-157, and HCC1806 cells following EGCG treatment was attributed to the differential restoration of key protein expression. EGCG treatment effectively restored the expression levels of DNMT, P27, PTEN, and ERα proteins, as well as modulated the expression of EMT markers in a cell-line-specific manner [103].

3. Chemosensitizing effect of selected polyphenols in TNBC preclinical studies
There are multiple reports showing the ability of the above-mentioned polyphenols to act as a chemosensitizer in TNBC studies. It was found that RSV was able to enhance the inhibitory impact of cisplatin on cell migration, invasion, and tumor growth in MDA-MB-231 in vitro and in vivo models which were mediated via regulation of EMT markers and PI3K/AKT, JNK, ERK, and NF-kB signalling pathways [105]. GEN also exhibits a synergistic effect with Dox on 4T1 breast cancer cells and enhances its cytotoxicity through induction of cell cycle arrest and ROS generation in TNBC model [106]. Additionally, epigenetically restore ERα expression following GEN treatment may also contribute to enhancing tamoxifen-induced anti-cancer efficacy in vitro and invivo models [107]. The radiosensitizing effect of GEN was also reported to be correlated with inhibition of DNA repair, induction of G2/M cell cycle arrest by the activation of the ATM/Chk2/Cdc25C/Cdc2 checkpoint pathway, and increased mitochondrial apoptosis pathway via p73 mediated manner in MDA-MB-231 cells [108]. Besides, the chemosensitizing role of EGCG has also been reported in MDA-MB-231 invitro and invivo models. EG was able to improve the effectiveness of cisplatin in combinational therapy and enhance apoptosis rates. This chemosensitization is related to its antioxidant role possibly through activating Nrf2-ARE signaling in TNBC models [109]. Moreover, kaempferol in combination with doxorubicin or cisplatin synergistically inhibited the growth of MDA-MB-231 cells [110].

QUE also synergistically potentiates the anti-migratory effect of 5-fluorouracil on the MDA-MB-231 via inhibition of MMP-2 and MMP-9 expression in these cells [111]. Another report also showed that QUE decreased the motility induced by doxorubicin in TNBC cells via inhibition of the TGF-β1 signaling in MDA-MB-231 cells [42]. In addition, QUE was found to enhance the effectiveness of the doxorubicin-cyclophosphamide treatment for TNBC, while also reducing its cardiotoxicity in both in vitro and in vivo models. The study showed that QUE’s potent anti-oxidant properties led to a decrease in ROS levels, which activated the ERK1/2 pathway in cardiomyocytes. On the other hand, QUE inhibited the activation of ERK1/2 and downstream targets such as c-myc and MMP-9 in treated MDA-MB-231 cells [112]. Another study showing the capability of QUE to improve the therapeutic index of Dox in TNBC invitro and invivo models. It was observed that QUE interfered with cell metabolism, GST activity, cytoskeleton, and invasive properties of MDA-MB-231 cells [113,114]. QUE was also able to enhance chemosensitivity to DOX by inhibition of the P-glycoprotein ATPase subunit which resulted in increased intracellular concentration of doxorubicin in MDA-MB-231 [115,116]. Moreover, the
synergistic action of QUE-docetaxel combination was mediated via regulation of PI3K/AKT, MAPK/ERK, and JAK/STAT3 signaling pathways and apoptosis induction in MDA-MB-231 cells [117]. In addition, the letrozole and QUE combination inhibited MDA-MB-231 cell growth via induction of mitochondrial apoptosis [118].

4. Anticancer effect of other polyphenols in TNBC

4.1. Apigenin (API)

The anti-proliferative and apoptosis induction action of apigenin (API) was correlated with DNA damage, G2/M phase cell cycle arrest, ROS generation, PARP cleavage and inhibition of AKT phosphorylation in MDA-MB-231 and MDA-MB-468 [119–121]. In addition, API was able to inhibit telomerase activity by downregulating the enzyme’s catalytic subunit in HCC1806 and MDA-MB-231 cells [122]. A recent study has also shown that aglycone API, free of sugars, triggers apoptosis more effectively than API-glycoside in TNBC spheroid model, due to higher cellular uptake. It also reduces the viability of TNBC human patient-derived organoids. The findings also revealed the significant role of hnRNA2A2, an RNA-binding protein involved in mRNA and co-transcriptional regulation, in API chemosensitizing activity of TNBC spheroids via upregulation of the expression of ABCC4 and ABCG2 efflux transporters and intrinsic apoptosis induction [123].

The Hippo pathway is a crucial signaling pathway that regulates cell growth, proliferation, and differentiation. YAP (Yes-associated protein) and TAZ (Transcriptional co-activator with PDZ-binding motif) are two downstream effectors of the Hippo pathway that their overexpression or aberrantly activation are correlated with various TNBC-related properties such as cancer stem cell (CSC) activity, high histological grade, resistance to chemotherapy, and metastasis [124–126]. Apigenin can act as a potential YAP/TAZ inhibitor which resulted in suppression of MDA-MB-231 and MDA-MB-436 cellular proliferation, migration as well as stemness characteristics of TNBC cells in vitro and in vivo model [127]. Another study has reported the tumor growth inhibitory and anti-invasive effect of apigenin in the MDA-MB-231-derived xenograft model which is mediated via the suppression of IL-6 expression and inhibition of its downstream targets including N-cadherin, STAT3, ERK, Akt [128]. Another study conducted on 3D spheroids derived from MDA-MB-231 cells showed that API inhibited factors that could promote TNBC invasiveness, such as MMP1 expression and CYP1A1 activity [129]. Besides, API was capable of indirectly reducing the aggressive phenotype of MDA-MB-231 cells stimulated by the senescence-associated secretory phenotype (SASP) [130].

Constitutive expression of programmed death-ligand 1 (PD-L1) is correlated with immune evasion of BC cells and associated with poor prognosis. It was found that the immune-modulating effect of apigenin was associated with the inhibition of interferon (IFN-β) and IFN-β-induced PD-L1 upregulation in MDA-MB-468, but not MDA-MB-231, and was correlated with reduced of STAT1 phosphorylation and increased T cell proliferation [131]. Moreover, other studies using whole transcriptomic analysis have reported the modulatory effect of API on the pro-inflammatory activating action of TNFs in MDA-MB-231 and MDA-MB-468 cells [132–134].

4.2. Fisetin (FIS)

Fisetin (FIS) inhibited the proliferation of MDA-MB-231 and MDA-MB-468 cells via induction of cell cycle arrest and intrinsic and extrinsic-mediated apoptosis in TNBC cells [135]. It was also able to induce DNA double-strand break (DSB) in TNBC cells and was involved in impairing the repair of radiation-induced damage which was partially dependent on its inhibitory effect on V-box binding protein-1 (YB-1). However, these effects were cell-line dependent [136]. Further study also revealed that FIS physically entered the nucleus of the TNBC cells and suppressed RNA polymerase I activity and rRNA biogenesis in SUM159, MDA-MB-468, and 4T1 cells which were correlated with its negative impact on MAPK/ERK pathway in treated cells [137]. Moreover, FIS was also able to effectively inhibit migration, invasion and metastasis in MDA-MB-231 and BT549 cells. This was achieved by reversing of EMT by inhibition of PTEN-Akt-GSK-3β signaling pathway. Similarly, it inhibited the growth and metastasis of TNBC in vivo [138]. Likewise, another study reported the migration-inhibitory role of FIS in a panel of nice TNBC cell lines which was correlated with targeting kinase signalling including PI3K/AKT, MAPK and STAT pathways [43]. Further studies on TNBC 4T1 and MDA-MB-453 has also demonstrated the regulation of the PI3K/Akt/mTOR pathway as the underlying mechanism of FIS antiproliferative and metastatic effects [139,140].

4.3. Hesperetin (HES)

Cancer cells are highly dependent on glucose as the source of energy to support their rapid growth and proliferation. It was found that hesperetin (HES) was able to impair glucose uptake in MDA-MB-231 cells caused by downregulation of glucose transporter 1 (GLUT1) and 4 (GLUT4), suppression of phosphorylation of the insulin receptor-beta subunit (IR-beta) and Akt which eventually led to inhibition of TNBC proliferation [141]. HES also induced mitochondrial-mediated apoptosis in similar cells as evidenced by the activation of caspase-9, caspase 3/7, and an increase in Bax/Bcl2 ratio in treated cells [142,143].

Besides, a recent study has revealed that the inhibitory effect of HSP on TGF-β1-induced migration and invasion is correlated with the suppression of the Fyn/paxillin/RhoA signalling pathway in MDA-MB-231 cells [144]. Suppression of ICAM-1 was found to be another mechanism underlying the growth inhibitory and anti-metastatic effect of HES via miR-486-5p/H19/ICAM-1 axis in TNBC cells. HES upregulated miR-486-5p and downregulated oncogenic lncRNA H19, acting as upstream regulators for ICAM-1, ultimately leading to the suppression of ICAM-1 in TNBC cells [145,146].

4.4. Luteolin (LUT)

Luteolin (LUT) induced G2/M and S cell cycle arrest and apoptotic cell death by downregulating the expression of PLK1, cyclin B1, cyclin A, CDC2, CDK2, and Bcl-xl, while upregulating p21 and Bax expression in MDA-MB-231. Additionally, LUT inhibited tumor growth in animal models [147]. This anticancer activity was mediated via its inhibitory actions on EGFR pathway and suppression of phosphorylation of ERK, p38 and AKT in treated cells [147]. Furthermore, the whole genome microarray analysis has shown the significant downregulation of AP2B1, APP, GPNMB, and DLST in LUT treated MDA-MB-231 cells where these genes are involved in cell proliferation and apoptosis, HDAC inhibition and drug resistance [148]. LUT was also able to inhibit NF-κB/c-Myc activation which resulted in the inhibition of human telomerase reverse transcriptase (hTERT) expression and eventually reduction of telomerase activity in MDA-MB-231 cells. This effect was accompanied by the downregulation of cyclin D1, survivin and Bcl-2 and the upregulation of p21, Bax and caspase-3 in treated cells [149].

It was found that LUT inhibited the invasion and migration of MDA-MB-231 and BT5–49 cells and suppressed lung metastases of breast cancer in xenograft model through reversing EMT, which was mediated by B-catenin downregulation [150]. Similarly, in a recent study LUT treatment has resulted in suppression of proliferation, metastasis and EMT reversal in BT-20 cells, androgen receptor-positive TNBC, which was attributed to the inactivation of AKT/mTOR signaling pathway and eventually epigenetic-mediated downregulation of MMP-9 in treated cells [151]. Another study on MDA-MB-231 and MDA-MB-435 cells as well as their derived mouse models has linked the anti-metastatic effect of LUT to the inhibition of VEGF production and VEGF receptor-2-mediated activity [152]. LUT also was able to induce proteasome-dependent degradation of YAP/TAZ and therefore downregulate YAP/TAZ expression at the post-translational level which
resulted in inhibition of tumor growth, migration, and EMT transition in MDA-MB-231, 4T1 calls and animal models [153]. It was also found that LUT decreased cancer cell viability, induced apoptosis and hindered TGFβ1-induced EMT in MDA-MB-453 as evidenced by an increase in Bax/Bcl2 ratio, caspase-3 cleavage, downregulation of vimentin, Zeb1 and N-cadherin, as well as upregulation of E-cadherin in treated cells. This anticancer effect was correlated with LUT-induced miR-203 expression and suppression of Ras/Raf/MEK/ERK signalling in TNBC cells [154]. Moreover, LUT suppressed TNBC stemness properties via inhibition of CSCs-related markers including the ATP-binding cassette transporter G2 (ABCG2), CD44, aldehyde dehydrogenase 1 activity as well as suppressed the sphere formation properties of breast CSCs. This inhibitory effect was attributed to the downregulation of antioxidant proteins Nr2f2, heme oxygenase 1 (HO-1), and Cripto-1 in MDA-MB-231 cells [155].

5. Synergistic anticancer effects of polyphenol combinations

While the anticancer mechanisms of action of individual polyphenols have been extensively investigated, research on polyphenol combinations specifically in the context of TNBC remains quite limited. This section aims to explore the current knowledge surrounding the effects of polyphenol combinations in TNBC.

In a study using a three-dimensional model of MDA-MB231 breast cancer spheroids combined with immobilized lymph endothelial cell monolayers, simultaneous treatment with 20 mM luteolin and 20 mM apigenin synergistically suppressed the invasation of cancer cells more effectively than using 20 or 40 mM of either compound alone. The observed synergism between apigenin and luteolin might be correlated with suppression of pro-invasion trigger factors including MMP1 expression and CYP1A1 activity as well as inhibition of Ca2+ signaling in the TNBC model [129]. Additional research has shown that luteolin (0.5 μM) in combination with quercetin (0.5 μM) has a synergistic effect in suppressing the growth and preventing the formation of colonies in nicotine-treated MDA-MB-231 Cells. These effects are associated with the inhibition of the PI3K/AKT signaling pathway, leading to a decrease in the expression of nicotinic acetylcholine receptors in these cells [129].

In addition, it was found that kaempferol and fisetin co-treatment has a greater impact on reducing cell proliferation compared to using each flavonol individually. This synergistic impact was attributed to the inhibition of the PI3K/Akt pathway, which occurs due to ROS-mediated DNA damage and the activation of the mitochondria-mediated apoptosis in MDA-MB-231 cells [156]. Moreover, individual treatment (0.5 μM) of quercetin, resveratrol, and catechin, did not affect TNBC cell growth or cell cycle progression. However, their combination treatment, at 0.5, 5, or 20 μM each, exerts a synergistic inhibitory effect, cell cycle arrest in MDA-MB-231, and reduced the growth of primary tumours in the animal models [157]. Similarly, it was found that a combination of quercetin, resveratrol, and catechin is more efficient than individual compounds at inhibition of cell proliferation, cell cycle progression, cell migration, as well as apoptosis induction in metastatic MDA-MB-435. Additionally, combined polyphenols suppressed both primary tumor growth and metastatic cancer progression via inhibition of NF-kB signalling pathway [158]. The combined treatment of quercetin and curcumin has also a synergistic effect in inhibiting the survival and migration of MDA-MB-231 and MDA-MB-468 breast cancer cells. This synergistic action is attributed to increased histone acetylation in the BRCA1 promoter region, leading to enhanced expression levels of BRCA1 [159].

6. Clinical trials

Polyphenols have been extensively studied for their potential anticancer effects. In particular, the use of polyphenols as a complementary or alternative therapy for TNBC has gained considerable attention in recent years. Numerous preclinical studies have shown that polyphenols possess various anticancer properties, such as antioxidant, anti-inflammatory, anti-proliferative, and anti-metastatic properties through several mechanisms which may inhibit tumor growth and progression. To translate these findings into clinical applications, several clinical trials have been conducted to evaluate the safety and efficacy of polyphenols in breast cancer. In this section, we provide an overview of the clinical trials investigating the use of selected polyphenols (Table 1), which have been discussed before, in breast cancer.

A phase II single group assignment trial conducted on 19 metastatic breast cancer patients, has assessed the effectiveness of administering gemicitabine hydrochloride and genistein, having a different mechanism of action, to stop the growth of tumor cells as a combined treatment for women diagnosed with stage IV breast cancer. In this trial, patients received oral dietary supplement genistein once daily on days –7–1. Patients also received gemicitabine hydrochloride IV on days 1 and 8 and oral genistein once daily on days 1–21. This treatment was repeated every 21 days unless the disease gets worse or the side effects are too severe [160]. In this trial no mortality has been reported, however, several side effects have been observed in ≤ 5 of patients [160]. In addition, a randomized phase II trial engaging 126 participants has investigated the preventive effect of genistein in women at high risk for breast cancer. In this study, patients were given orally genistein (ARM I) or placebo (ARM II) once daily for up to 6 months and further followed at 30–37 days. However, this study showed that a 6-month intervention did not reduce breast epithelial proliferation in healthy, high-risk adult Western women, suggesting a lack of efficacy for breast cancer prevention and a possible adverse effect in premenopausal women [161].

Another phase I double blinded trial has investigated the preventive role of genistein against breast cancer in 30 healthy, post-menopausal women. In this study, participants in Arm I and Arm II received a high oral dose of genistein and placebo, respectively, twice daily on days 1–84 and participants were followed at different time intervals. As a part of the study, DNA damage, apoptosis, and changes indicative of estrogenic stimulation were investigated [162]. There were no clinically significant changes in estrogenic/antiestrogenic laboratory measurements between the groups. In addition, no evidence for genotoxicity was reported suggesting that short-term supplementation with high doses of soy isoflavones appears to be safe and well tolerated in healthy post-menopausal women at doses of 900 mg per day [162].

Furthermore, a double-blind, placebo-controlled, phase 2 randomized clinical trial has investigated the efficacy of EGCG in reducing radiation-induced dermatitis (RID) in breast cancer patients undergoing postoperative radiotherapy. In this study, 180 patients received either an EGCG solution or placebo sprayed to the whole radiation field from day 1 of the radiation until 2 weeks after radiation completion. The findings revealed that the EGCG solution significantly reduced the incidence and severity of RID in patients receiving adjuvant radiotherapy for breast cancer, suggesting the EGCG as the potential candidate of skin care for patients receiving radiotherapy [163]. Moreover, in phase II, randomized, double-blind, placebo-controlled trial has conducted to investigate the efficacy of green tea extract on biomarkers of breast cancer risk. In this trial, 1075 healthy postmenopausal women with a high risk of breast cancer, due to high breast density, were enrolled and received two green tea extract capsules (containing 800 mg EGCG per day) or two placebo capsules twice daily after breakfast and dinner for one year. This study aims to elucidate the mechanisms by which green tea may reduce breast cancer risk, however, the researchers have not released the results of the trial [164].

A randomized phase I dose-escalation trial of oral green tea extract (Poly E) has been conducted in women with a history of stage I–III hormone receptor-negative breast cancer. In this study, 40 women were randomized into 10 to placebo, 30 to Poly E (16 at 400 mg, 11 at 600 mg, 3 at 800 mg). This trial has reported 600 mg bid as the maximum tolerated dose for Poly E and highlighted the significance of toxicity assessment for any chemopreventive agents being developed [165]. Another non-randomized interventional study has investigated the effect of green
Including the combination of quercetin, zinc, metformin, and EGCG will may cause inflammation and damages nearby healthy cells. However, be investigated as adjuvant therapy for early, metastatic breast cancer clinical trials in 200 participants the effect of quadruple therapy and their effect on DNA damage will be investigated in HBOC female consisting of dietary components, selenium, magnesium, carotenoids, ovarian cancer syndrome (HBOC) decreases after the nutritional inter-

...leukin 6, cathepsin L, and also epigenetic DNA methylation. In this...reduce their therapeutic efficacy [169]. Despite the promising role of polyphenols, which are abundant in dietary sources, in TNBC prevention and treatment, there are several limitations associated with short-term EGCG treatment have been investigated [166].

Chemotherapy may induce the formation of senescent cells which may cause inflammation and damages nearby healthy cells. However, FIS is able to eliminate senescent cells. A phase II randomized double-blind placebo-controlled trial is recruiting 88 breast cancer survivors to investigate the effectiveness of the FIS on improving physical function in postmenopausal women who have received chemotherapy for stage I-III breast cancer treatment [168]. Furthermore, there is a clinical trial to evaluate if the DNA damage in patients with hereditary breast and triple-negative breast cancer. This treatment targets numerous mechanisms at tumorigenesis, metastasis, autophagy, apoptosis, interleukin 6, cathepsin L, and also epigenetic DNA methylation. In this study, 100 women having different types of breast cancer will be taken orally once a day of 500 mg quercetin, 50 mg zinc sulfate, 300 mg EGCG and 850 mg metformin during chemotherapy courses and until last stage of treatment [168].

7. Challenges and limitations of polyphenols as anticancer agents in TNBC therapy

Despite the promising role of polyphenols, which are abundant in dietary sources, in TNBC prevention and treatment, there are several limitations associated with their therapeutic applications. These compounds are sensitive to environmental conditions such as light, pH, and heat, which makes them chemically unstable and therefore can be easily degraded. Besides they have poor water solubility and are rapidly metabolized in the body which resulted in low bioavailability and reduce their therapeutic efficacy [169–172].

Nano-carriers offer a potential solution to address these challenges by improving the stability of bioactive compounds in various environmental and gastrointestinal conditions, as well as enhancing their water
solubility. Additionally, the utilization of nano-carriers allows for a decreased dosage requirement to achieve biological activity, thereby mitigating the risk of potential side effects [173,174]. A wide range of nanoformulations, comprising polymeric, lipid-based, metallic, magnetic and inorganic nanoparticles, have been successfully developed to encapsulate and deliver various polyphenols such as resveratrol [175–178], quercetin [179–181], EGCG [182,183], fisetin [184,185], apigenin [186]. Polyphenols formulated at the nanoscale as targeted drug delivery systems exhibit superior efficiency and stability. They demonstrated improved drug loading capabilities and sustained release profiles specifically within the tumor. Therefore, nanoformulation techniques have shown potential to improve the pharmacokinetics and pharmacodynamics of polyphenols in TNBC treatment as cited above [187,188]. However, the safety of these compounds in their nano-formulated state is an important consideration that must be thoroughly addressed during both preclinical and clinical stages.

8. Conclusion

The development of effective therapeutic strategies for TNBC is urgently needed due to its high aggressiveness, poor prognosis, and lack of targeted therapies. Polyphenols, having the advantage of being safe, cost-effective, and widely available represent a promising class of compounds for the prevention and treatment of TNBC. This review paper has shown that various polyphenols, including resveratrol, quercetin, kaempferol, genistein, epigallocatechin-3-gallate, apigenin, fisetin, hesperetin and luteolin can exert a potent anticancer effect in TNBC which is attributed to the multiple mechanisms of action, including inhibition of proliferation, induction of apoptosis, autophagy, cell cycle arrest, inhibition of migration, invasion and angiogenesis as well as epigenetic and metabolic modulation as shown in Fig. 1. They exerted their anti-TNBC effects through their regulatory role on multiple molecules involved in key signaling pathways such as PI3K/Akt, MAPK, STAT, and NF-κB and their downstream targets which eventually inhibited cancer growth and effectively suppress the metastatic and aggressive phenotype of TNBC in vitro and in vivo models. In addition, some polyphenols have been shown to sensitize TNBC cells to chemotherapy and radiotherapy, indicating that they may have a synergistic effect when combined with conventional treatments. Therefore, polyphenols have the potential to improve the efficacy of current therapies and reduce the risk of recurrence in TNBC patients. However, despite the encouraging results from preclinical studies, the translation of polyphenols to clinical trials for breast cancer therapy especially TNBC is still limited. Besides, the existing results have been mixed, with some studies suggesting a potential benefit while others finding no significant effect or even adverse effects. Therefore, while the findings presented in this review paper are promising, there are still several challenges that need to be addressed before polyphenols can be used in clinical practice. These include issues related to bioavailability, dosage, and toxicity, as well as the need for further preclinical and clinical studies to determine the safety and efficacy of polyphenols in TNBC patients.

Declaration of Competing Interest

None.

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