PHARMACIA

Pharmacia 72: 1–11
DOI 10.3897/pharmacia.72.e143465

Review Article

Natural products as part of triple negative breast cancer

Yozlem Kobakova[1,2], Maria Moneva-Sakelarieva[1,2], Spiro Konstantinov[1], Georgi Momekov[1], Stefka Achkova Ivanova[3], Ventseslava Atanasova[4], Maria Chaneva[2], Radoslav Tododrov[2], Nikolay Bashev[2], Petar Atanasov[2]

1 *Faculty of Pharmacy, Medical University – Sofia, Sofia, Bulgaria*
2 *Clinic of Internal Diseases UMHATEM "N. I. Pirogov", Sofia, Bulgaria*
3 *Bulgarian Pharmaceutical Science Society, Sofia, Bulgaria*
4 *Bulgarian Pharmaceutical Union, Sofia, Bulgaria*

Corresponding author: Stefka Achkova Ivanova (ivanovastefka_pharm@yahoo.com)

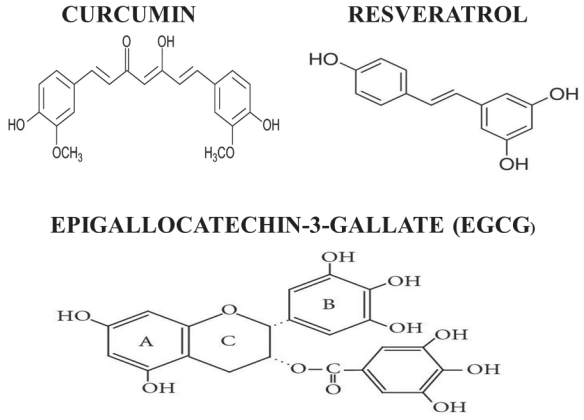
Received 3 December 2024 ♦ **Accepted** 6 December 2024 ♦ **Published** 30 January2025

Citation: Kobakova Y, Moneva-Sakelarieva M, Konstantinov S, Momekov G, Ivanova SA, Atanasova V, Chaneva M, Tododrov R, Bashev N, Atanasov P (2025) Natural products as part of triple negative breast cancer. Pharmacia 72: 1–11. https://doi.org/10.3897/pharmacia.72.e143465

Abstract

Triple negative breast cancer (TNBC) continues to be the breast cancer subtype with the highest recurrence and mortality rates. Treatment of TNBC can be challenging because the disease has different molecular subtypes. Various treatment options are available, such as chemotherapy, immunotherapy, radiation therapy, and surgery. Chemotherapy is the most common of these options. The serious side effects of chemotherapy significantly limit its use. Long-term toxicity can affect the majority of breast cancer survivors, significantly reducing their quality of life. Immunotherapy causes a wide variety of toxic effects called immune-related adverse events (IRAEs). This necessitates the search for alternative methods of treatment for triple negative breast cancer. More and more research in this field is focused on single or combination therapy based on compounds obtained from natural sources. Natural products such as curcumin, resveratrol, and epigallocatechin-3-gallate, with their mechanisms of action and antineoplastic properties, are the subject of numerous studies.

Graphical abstract



Keywords

triple negative breast cancer, therapy, side effects, natural products, curcumin, resveratrol, epigallocatechin-3-gallate

Introduction

Breast cancer represents a significant global challenge as a highly lethal disease affecting women, amid the adverse effects of chemotherapy, radiotherapy and the critical problem of multidrug resistance (MDR). It is the leading cause of death among women, with an estimated 2.3 million new cases in 2020, accounting for 30% of cancers in women alone (Sung et al. 2021; Mandapati and Lukong 2023).

Triple negative breast cancer (TNBC) encompasses a heterogeneous group of fundamentally different diseases with different histological, genomic, and immunological profiles, which are united under this term due to their lack of estrogen receptor (ER), progesterone receptor (PR), and human receptor 2 epidermal growth factor (HER2) (Derakhshan and Reis-Filho 2022; Foulkes et al. 2010). TNBCs represent the most common type of invasive breast cancer developing in the context of patients carrying germline BRCA1 mutations (Stevens et al. 2013). Indeed, >85% of breast cancers developing in the context of germline pathogenic BRCA1 variant carriers show a triple negative phenotype, and 11% to 19% of patients with triple negative disease carry BRCA1 germline or somatic mutations (Mavaddat et al. 2013; Kuchenbaecker et al. 2017). The prevalence of TNBC is increased in young women under 40 years of age of African or Hispanic ancestry. There is also a high prevalence of a first- or second-degree family history of breast or ovarian cancer in patients with this immunohistochemical subtype (Sandoval-Ato et al. 2024).

TNBCs typically resemble basal-like breast cancer (BLBC) with overlapping gene expression characteristics (Yin et al. 2020). Based on gene expression profiles, six TNBC subtypes were identified, each with a different gene expression profile and ontology, which are basal-like 1 (BL-1), basal-like 2 (BL-2), immunomodulatory subtype (IM), mesenchymal subtype (M), mesenchymal stem-like subtype (MSL), and luminal androgen receptor subtype (LAR) (Table 1) (Maqbool et al. 2022; Li et al. 2022b; Lehmann et al. 2011).

Table 1. Molecular subclasses and therapeutic targets in TNBC.

	Molecular subclasses	Candidate therapeutic target
TNBC	Basal-like (BL2)	EGFR, MET, EPHA2, mTOR
	Luminal androgen receptor (LAR)	AR, Hsp90, PI3K, FGFR4
	Mesenchymal stem-like (MSL)	SRC, MEK1/2, mTOR, PI3K, PDGFR, NFkB, IGF1R, FGFR, TGFBRIII
	Immunomodulatory (IM)	STATs, JAK1/2, LYN, IRF1/7/8, BTK, NFkB
	Mesenchymal (M)	SRC, IGF1R, PI3 K and mTOR, PDGFR, FGFR
	Basal-like (BL1)	PARP1, TTK, PLK1, CHEK1, AURKA/B, RAD51
	Unstable (UNS)	PARP1, TTK, CHEK1, PLK1, AURKA/B, RAD51

Therapy

Triple negative breast cancer (TNBC) continues to be the breast cancer subtype with the highest recurrence and mortality rates. The lack of expression of target proteins such as the estrogen receptor and the absence of HER2 amplification has made reliance on cytotoxic chemotherapy necessary for decades (Leon-Ferre and Goetz 2023). Treatment of TNBC can be challenging because the disease has different molecular subtypes. Various treatment options are available, such as chemotherapy, immunotherapy, radiation therapy, and surgery. Chemotherapy is the most common of these options (Obidiro et al. 2023). Traditional treatment guidelines for early TNBC are based on surgery and postoperative adjuvant chemotherapy to prevent disease recurrence (Cardoso et al. 2019a). Adjuvant chemotherapy is based on anthracyclines, taxanes, and alkylating agents (Gupta et al. 2020). In stage II or III TNBC, neoadjuvant chemotherapy is preferred based on different treatment guidelines (Fig. 1) (Gradishar et al. 2022).

Research shows that anthracyclines kill cancer tissues directly and activate the immune system by activating CD8+ T cells (Katz and Alsharedi 2017). Anthracyclines such as doxorubicin and epirubicin have been shown to increase response rates and survival by several months (O'Reilly D et al. 2021). Adverse drug reactions include acute toxicity such as irreversible cardiotoxicity, myelotoxicity, alopecia, nausea, and vomiting (Chowdhury et al. 2021).

The key molecular mechanisms of taxanes include disruption of the mitotic spindle, mitotic escape, and inhibition of angiogenesis (Mosca et al. 2021). Three taxanes have been approved for clinical use: paclitaxel, docetaxel, and cabazitaxel. As a chemotherapy drug, docetaxel (Taxotere®), approved in the 1980s, is one of the most effective drugs for the treatment of cancer, but it can also lead to antibiotic resistance due to its adverse side effects on the normal microbial flora in the body (Catalano et al. 2022).

Platinum-based chemotherapy using carboplatin in the adjuvant or neoadjuvant setting improves long-term disease-free survival (DFS) and overall survival (OS) outcomes in early TNBC, with no evidence of subgroup differences (Mason et al. 2024). According to Feng et al. in a meta-analysis of the effects and safety of platinum compound-based neoadjuvant chemotherapy, it was found that the occurrence of anemia (RR = 8.22, 95% CI, 1.69–40.04, P = 0.009), leukopenia (RR = 1.63, 95% CI = 1.08–2.45, P = 0.02), neutropenia (RR = 2.08, 95% CI, 1.08–4.01, P = 0.03), and thrombocytopenia (RR = 6.01, 95% CI = 2.77–13.07, P < 0.001) was significantly higher in the group treated with platinum-based neoadjuvant chemotherapy compared with the group treated with non-platinum-based neoadjuvant chemotherapy (Feng et al. 2022).

Targeted agents for TNBC include inhibitors of poly (ADP-ribose) polymerase (PARP), epidermal growth factor receptor (EGFR), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), angiogenesis, microtubule, proto-oncogene tyrosine-protein kinase Src (Src kinase), AKT, checkpoint kinase 1 (Chk1), and mammalian target

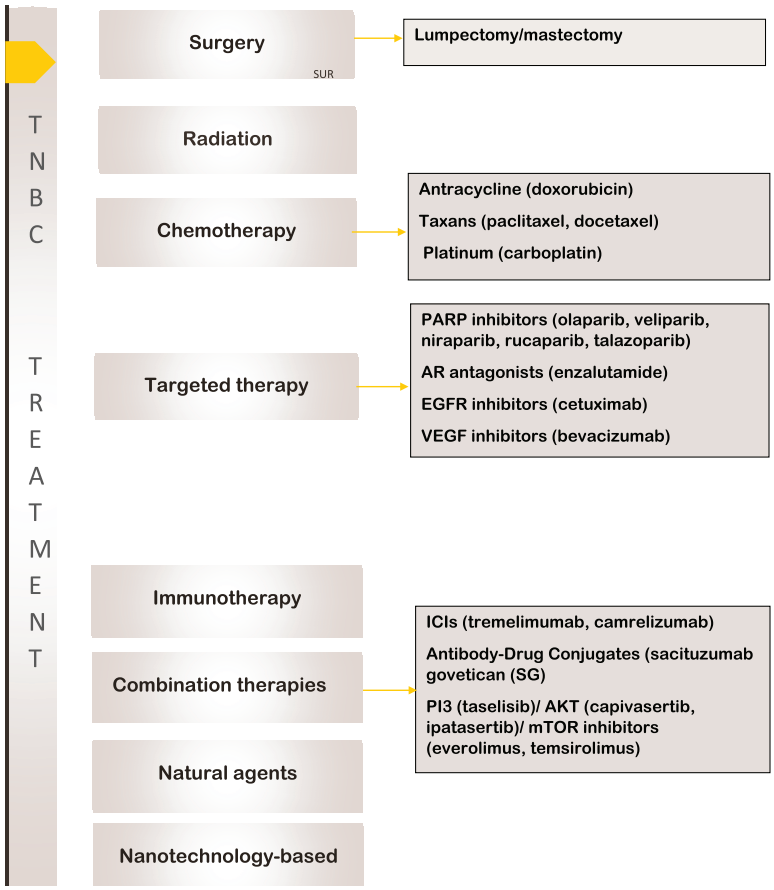


Figure 1. Breast cancer treatment options.

of rapamycin (mTOR). Programmed death receptor-1/programmed death ligand-1 (PD-1/PD-L1) antibodies, androgen receptor blockers, tumor necrosis factor-related apoptosis-inducing ligand receptor agonists, and transforming growth factor antagonists -β also represent targeted agents for TNBC. In addition, signal transducer and activator of transcription 3 (STAT3), EGFR, gamma-butyrobetaine hydroxylase (BBOX1), cyclin-dependent kinases CDK12/CDK13, mammalian transcription factor BACH1, cMET oncogene, and integrin subunit alpha-V gene (ITGAV) are described as potential therapeutic targets for TNBC in the literature (Catalano et al. 2022).

Several types of EGFR-targeted therapies are currently approved for clinical use. EGFR inhibitors include monoclonal antibodies as well as small molecule inhibitors that target the ATP-binding site of the kinase domain (Bhullar et al. 2018). Erlotinib is classified as one of the EGFR-TKIs and has previously been identified as a promising therapeutic target for TNBC. Simultaneous inhibition of EGFR/ERK and PI3K/AKT/mTOR signaling pathways by the combination of monensin and erlotinib showed a synergistic effect on suppressing tumor proliferation and stemness of cancer cells in TNBC. The results show that the combination of monensin with erlotinib synergistically inhibits cell proliferation, migration rate, and invasion ability and reduces the proportion of CSCs (carcinoma stem cells) and the CSC markers SOX2 and CD133 in vivo and in vitro (Fang et al. 2024).

Androgen receptors (ARs) have been shown to play an important role in the growth, invasion, migration, and apoptosis of TNBC cells, both of which contribute to the complications of the disease. Targeting the AR with AR inhibitors may be the most effective therapy for TNBC (Barton et al. 2015). Clinical evidence suggests a role for antiandrogen therapies such as bicalutamide, enzalutamide, and abiraterone, offering an interesting chemotherapy-free alternative for patients who do not respond to chemotherapy and therefore potentially changing current treatment strategies (Gerratana et al. 2018).

PARP inhibitors have emerged as effective treatments in clinical trials for TNBC and BRCA-related sporadic cancers (van Beek et al. 2021; Singh et al. 2021). Two PARP inhibitors are currently approved for triple negative metastatic breast cancer, olaparib and talazoparib, based on two phase III trials that showed a progression-free survival benefit compared to chemotherapy. In addition, other PARP inhibitors such as talazoparib, rucaparib, and veliparib are currently under investigation (Barchiesi et al. 2021).

More recently, immunotherapy has revolutionized the landscape of cancer treatment, particularly immune checkpoint inhibitor (ICI) therapy, with FDA approval for over 20 types of cancer since 2011. Compared to other types of cancer, breast cancer has traditionally been considered immunologically cold; however, TNBC demonstrates the most promising use of immunotherapy, a timely discovery due to the lack of targeted therapy options

(Berger et al. 2021). Combining ICIs with PARP inhibitors may be a great strategy to improve antitumor immunity as well as treatment response. Promising efficacy and safety findings were reported in two single-arm phase 2 studies: TOPACIO and MEDIOLA for niraparib in combination with pembrolizumab and olaparib plus durvalumab, respectively (Domchek et al. 2020; Vinayak et al. 2019).

TNBCs exhibit aberrant initiation of the PI3K pathway through various mechanisms; the PI3K/AKT/mTOR pathway has been explored for therapeutic strategies in TNBC patients (Singh and Yadav 2021). PI3K and PARP inhibitors have been studied in a mouse model for BRCA1-associated tumors and provide synergistic effects in their treatment. The mTOR signaling pathway is an important targeting strategy for TNBC—it causes down-regulation of the PI3K pathway and also down-regulates the TNBC cell line (Singh and Yadav 2021; Ryu and Sohn 2021).

The KEYNOTE-355 trial reported that first-line chemotherapy with pembrolizumab significantly improved PFS compared with chemotherapy in patients with PD-L1-expressing metastatic TNBC (Kulangara et al. 2019).

Side effects

Neo/adjuvant therapy for early-stage breast cancer has become more common over the past few decades, and as a result, the number of breast cancer survivors who often experience debilitating long-term side effects has increased, including fatigue, insomnia, peripheral neuropathy, cognitive impairment, estrogen deprivation, cardiotoxicity, and secondary cancer. Long-term toxicity can affect the majority of breast cancer survivors, significantly reducing their quality of life (Di Nardo et al. 2022).

Based on a comprehensive web-based survey of the presence of long-term side effects of adjuvant breast cancer therapy in 1506 patients who had been diagnosed with primary breast cancer at least 1 year previously, the following data were obtained: fatigue, depression, depressed mood, lack of concentration, pain, changes in the mucosa and skin appendages, and symptoms of peripheral neuropathy are the most commonly reported complaints. Chemotherapies—particularly taxane-based regimens—are associated with increased rates of long-term symptoms, including persistent peripheral neuropathy (Haidinger and Bauerfeind 2019).

Although targeted oncology has improved survival by years for some incurable cancers, such as metastatic breast and lung cancer, only 8% of patients with advanced cancer qualify for targeted oncology drugs, and even fewer benefit. Other limitations include serious adverse events, illustrated by a 20% to 30% incidence of heart attack, stroke, or peripheral vascular events among patients taking ponatinib, which is used to treat chronic myelogenous leukemia. Adverse effects associated with immune checkpoint inhibitor therapy, such as hypothyroidism, are common, and more severe adverse events such as colitis and pneumonitis can be fatal and require immediate intervention. Drug interactions with widely prescribed drugs such as antacids and warfarin are common. In addition, financial toxicity is a concern for cancer patients using costly targeted therapies (Smith and Prasad 2021).

Targeted therapies and immunotherapies are associated with a wide range of dermatological adverse events (dAEs) resulting from common signaling pathways involved in malignant behavior and normal homeostatic functions of the epidermis and dermis. Dermatological toxicity includes damage to the skin, oral mucosa, hair, and nails. Acneiform rash is the most common dAE seen in 25–85% of patients treated with epidermal growth factor receptor (EGFR) and mitogen-activated protein kinase (MAPK) inhibitors (Lacouture and Sibaud 2018).

Immunotherapy hyperactivates the immune system, causing a wide variety of toxic effects called immune-related adverse events (IRAEs). IRAEs can range from mild flu-like symptoms to more serious manifestations, such as pneumonitis, colitis, hepatitis, and endocrinopathies such as type 1 diabetes and adrenal insufficiency, which can lead to the need for lifelong replacement therapies. The incidence of most of these serious events is less than 5%; however, when they do occur, it requires immediate and significant attention. There is wide variation in the severity and time of onset of IRAEs: some may present as a severe event after only one dose, while others develop months later. In addition, there appears to be a higher risk of IRAEs when ICIs are combined with chemotherapy versus monotherapy overall in all disease processes (Ramos-Casals et al. 2020; Yoest 20174; Kanjanapan et al. 2019).

Molecularly targeted anticancer drugs are commonly used in various forms of cancer. A concern is that the risk of serious adverse events (SAEs) and fatal adverse events (FAEs) of molecularly targeted drugs is increasing. An up-to-date meta-analysis of all Phase II/III/IV randomized trials of molecularly targeted anticancer drugs was performed to estimate the increased risk of SAEs and FAEs. There were significant differences in the association of molecularly targeted anticancer drugs with SAE (RR = 1.57, 95% CI = 1.35–1.82, $P < 0.01$, I2 = 81%) and FAE (RR = 1.51, 95% CI = 1.19–1.91, $P < 0.01$, I2 = 0%) compared with placebo. The overall incidence of SAE and FAE was 0.269 (95% CI = 0.262–0.276, $P < 0.01$) and 0.023 (95% CI = 0.020–0.025, $P < 0.01$), respectively. Molecularly targeted anticancer drugs significantly increase the risk of SAEs and FAEs (Wang et al. 2019).

Natural products

The percentage of antitumor drugs derived from natural products is approximately 50%. Chemoprevention and chemotherapy can be achieved with natural products because they inhibit cell proliferation, regulate the cell cycle, and affect several signaling pathways that lead to tumor growth (Naeem et al. 2022). Natural medicinal compounds have been widely studied in cancer models, including breast cancer, for their antineoplastic properties (Mallipeddi et al. 2021). Natural compounds have the potential to be used as therapeutic agents in the treatment of

TNBC. Some natural compounds and potential molecular targets in the TNBC signaling pathway have been identified as anticancer treatments.

Literature evidence is available for six promising compounds, including sulforaphane, curcumin, genistein, resveratrol, lycopene, and epigallocatechin-3-gallate. These compounds have been shown to promote cell cycle arrest and apoptosis in TNBC cells. They can also inhibit epithelial-mesenchymal transition (EMT), which plays an important role in metastasis. Furthermore, these natural compounds were found to inhibit pathways important for CSCs (cancer stem cells), such as NF-KB, PI3K/Akt/mTOR, Notch 1, Wnt/β-catenin, and YAP. Clinical trials conducted on these compounds show varying degrees of effectiveness (Ke et al. 2022).

Curcumin

Curcumin, a polyphenolic compound, is the main pharmacological component extracted from the rhizome of *Curcuma longa* L. (Fig. 2). Modern pharmacological studies have found that curcumin has many types of pharmacological activities, such as anti-inflammatory, anti-tumor, anti-angiogenesis, anti-metastasis, and anti-multidrug resistance (Li et al. 2022a).

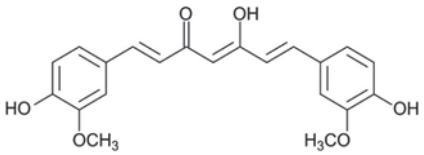


Figure 2. Chemical structure of curcumin ($C_{21}H_{20}O_6$).

Thus, curcumin may play an important role in the initiation and progression of various cancers, including breast, lung, and liver cancer, by affecting multiple signaling and molecular pathways, such as Rb, P53, mitogen-activated protein kinase, phosphatidylinositol 3-K (PI3K)/protein kinase B, and NF-kappaB (nuclear factor kappa B cells, NF-κB) (Fig. 3) (El-Far et al. 2020; Wong et al. 2021; Joshi et al. 2021; Giordano and Tommonaro 2019).

Curcumin exerts its therapeutic potential in TNBC by modulating multiple signaling pathways. It can inhibit the epithelial-mesenchymal transition process by down-regulating the expression of proteins involved in the mTOR and PI3K-Akt signaling pathways, thereby suppressing the motility of TNBC cells. These findings provide experimental evidence to consider curcumin as a potential therapeutic strategy in the treatment of TNBC (Chen et al. 2024).

Although previous studies have shown the ability of curcumin to inhibit cell proliferation and invasion in human TNBC MDA-MB-231 cells, the underlying molecular mechanisms have not yet been fully elucidated. Forty potential targets of curcumin against TNBC have been identified. Of these, STAT3, AKT1, TNF, PTGS2, MMP9, EGFR, PPARG, NFE2L2, EP300, and GSK3B were identified as the top 10 targets of curcumin against TNBC. Deng Z. et al. experimentally confirmed that in vitro CUR and CUR-NP could not only limit the invasion, migration, and proliferation of MDA-MB-231 cells but also induce their apoptosis. In addition, molecular docking showed that CUR could spontaneously bind to the screened top 10 target proteins, and a real-time PCR experiment showed that both CUR and CUR-NP could down-regulate the gene expression levels of the 10 targets. Furthermore, according to the CUR-targets-pathways network, PI3K-Akt, EGFR tyrosine kinase inhibitor resistance, JAK-STAT, Foxo, and HIF-1 signaling pathways were identified as important pathways of CUR effects on TNBC. Among them, the inhibitory effects of CUR and CUR-NPs on the JAK-STAT signaling pathway were further confirmed by Western blot analysis (Deng et al. 2022). Also, curcumin reduced the invasion and migration abilities in stable Gli1-overexpressing MDA-MB-231 cells. Curcumin can inhibit TNBC cell proliferation and metastasis, EMT, and BCSC characteristics through the Hedgehog/Gli1 pathway (Li et al. 2022a).

To improve the sensitivity of resistant TNBC cells to carboplatin, Wang G. et al. administered a combination treatment with curcumin and found it to inhibit proliferation and induce apoptosis. Mechanistically, curcumin exerts its anticancer effect by increasing reactive oxygen species (ROS) production, which down-regulates the DNA repair protein RAD51, leading to up-regulation of γH2AX. As expected, the ROS acceptor NAC reversed the inhibitory effect on the growth and activity of the curcumin-mediated DNA repair pathway. Taken together, our data show that curcumin increases the sensitivity of TNBC to the anticancer effect of carboplatin by increasing ROS-induced DNA damage, thereby providing an effective combination strategy for the treatment of TNBC (Wang et al. 2022).

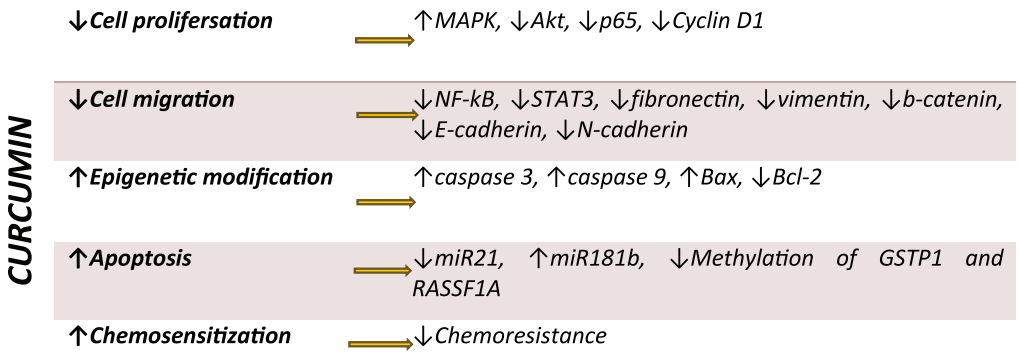


Figure 3. Potential therapeutic effects of curcumin in breast cancer.

Resveratrol

Resveratrol, known as 3,4',5-trihydroxystilbene (Fig. 4), is a phytoalexin belonging to the stilbenol class of compounds that occur naturally in various plants. It was first isolated in 1940 from the roots of white hellebore (Veratrum grandiflorum). The most common sources of resveratrol include red wine (0.1–14.3 mg L–1), white wine (0.1–2.1 mg L–1), grapes (0.16–3.54 μg g–1), blueberries (~32 ng g–1), peanuts (0.02–1.92 μg g–1), pistachios (0.09–1.67 μg g–1), Polygonum cuspidatum (0.524 mg g–1), and Rheum rhaponticum (3.9 mg g–1) (Thapa et al. 2019). This compound serves as a natural phytoalexin released by plants in response to environmental stress (Cragg and Pezzuto 2016; Shen et al. 2017).

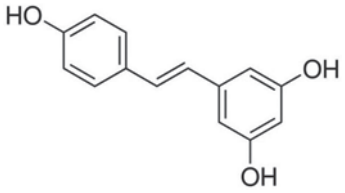


Figure 4. Chemical structure of resveratrol ($C_{14}H_{12}O_3$).

Resveratrol is a powerful antioxidant compound with anti-cancer, anti-angiogenic, anti-inflammatory, and cardiovascular protective effects. It targets various cancer signaling pathways (PI3K/AKT, RAS/RAF/ERK, PKCδ, AMPK, and RhoA/Lats1/YAP, etc.) by stimulating reactive oxygen species (ROS), followed by reduced proliferation and invasion. The antimetastatic effects induced by resveratrol are additionally useful in reducing the side effects of chemotherapy used in the treatment of TNBC (Keshavarz et al. 2020; Khazaei et al. 2020; Bozorgi et al. 2020; Kim et al. 2017).

Resveratrol has been reported to inhibit PARP enzymes, impairing the repair of DNA breaks (Lord and Ashworth 2017; Gao et al. 2015). PARP participates in the BER (base excision repair) pathway, repairing damaged DNA bases (Curtin and Szabo 2013). Inhibition of PARP by resveratrol impairs BER, prevents DNA damage repair, and potentially causes genomic instability and cell death. It can lead to the accumulation of unrepaired DNA damage in cancer cells, triggering cell cycle arrest and apoptosis, effectively inhibiting cancer cell growth (Ahmad et al. 2024). Resveratrol mediates its anticancer activity through various mechanisms such as autophagy, inhibition of tumor cell proliferation, inhibition of tumor cell migration, suppression of tumor progression, and induction of apoptosis, etc. (Avtanski and Poretsky 2018; Yeh et al. 2021; Mohammadhosseinpour et al. 2022). Resveratrol promotes apoptosis in TNBC cells by activating caspases, a family of cysteine proteases that play a central role in programmed cell death. Specifically, resveratrol activated caspase-3, caspase-8, and caspase-9 in TNBC cell lines (MDA-MB-231, MDA-MB-436, and MDA-MB-468) (Zhang et al. 2018).

Resveratrol suppresses the metastatic capacity and enhances the cytotoxic activity of ABT263 in TNBC cells. It can potentially be used as a metastasis repressor or sensitizer to ABT263 for the treatment of TNBC by upregulating CDH1 and CDKN1A through epigenetic mechanisms (Sakamoto et al. 2023).

It increases the secretion of pro-inflammatory cytokines such as interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF-α), which are essential for immune activation and cytotoxicity (Curtin and Szabo 2013). Resveratrol enhances the proliferation and activation of CD4+ and CD8+ T cells, promoting their antitumor functions. It can also increase the production of cytokines such as interferon-gamma (IFN-γ) by T cells, further contributing to antitumor immune responses (Avtanski and Poretsky 2018; Liu et al. 2015).

Sequential administration of resveratrol and FL118 caused accumulation of TNBC cells in the G1 phase and significantly suppressed mRNA and protein levels of N-cadherin, β-catenin, and vimentin, and resveratrol-sensitized TNBC cells to FL118 by facilitating apoptosis, migration, invasion, and EMT and enhancing the intracellular uptake of FL118. Based on this, the possibility of resveratrol as a potential therapeutic agent in advanced breast cancer has been suggested (Yar Saglam et al. 2021).

Nanotechnology offers a promising approach to improve the biopharmaceutical characteristics of resveratrol to achieve clinical efficacy in various cancers. The small size (<200 nm) of the nanotechnology-mediated drug delivery system is useful for improving bioavailability, internalization in TNBC cells, and ligand-specific targeted delivery of loaded resveratrol to the tumor site, including reversal of MDR (multidrug resistance) (Ahmad et al. 2024).

EGCG

The compound (-)-epigallocatechin-3-gallate (EGCG) (Fig. 5) is the main catechin found in green tea [Camellia sinensis L. Ktze. (Theaceae)]. This polyphenolic compound and several related catechins are thought to be responsible for the health benefits associated with green tea consumption. Potential health benefits attributed to green tea and EGCG include antioxidant effects, cancer chemoprevention, improving cardiovascular health, improving weight loss, protecting the skin from damage caused by ionizing radiation, and more (Nagle et al. 2006).

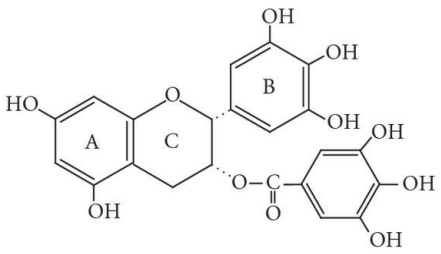


Figure 5. Chemical structure of EGCG ($C_{22}H_{12}O_3$).

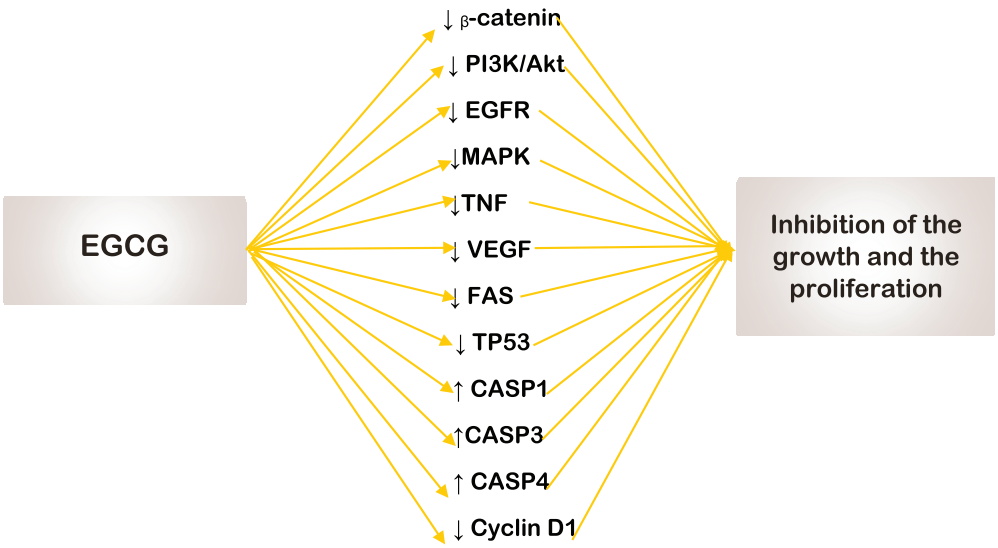


Figure 6. Molecular mechanism underlying the antitumor effect of EGCG in TNBC.

Accumulating studies have confirmed that EGCG can inhibit tumorigenesis and progression by triggering apoptosis, suppressing proliferation, invasion, and migration, altering tumor epigenetic modification, and overcoming chemotherapy resistance. However, its regulatory roles and biomolecular mechanisms in the immune microenvironment, metabolic microenvironment, and immunotherapy remain unclear. Furthermore, EGCG can suppress multiple metabolic reprogramming pathways, including glucose uptake, aerobic glycolysis, glutamine metabolism, fatty acid anabolism, and nucleotide synthesis. Finally, EGCG, as an immunomodulator and immune checkpoint blockade, may improve immunotherapeutic efficacy and may be a promising candidate for antitumor immunotherapy. In conclusion, EGCG plays a multifaceted regulatory role in TME and metabolic reprogramming, which provides new insights and combined therapeutic strategies for cancer immunotherapy (Fig. 6) (Li et al. 2024).

In triple negative breast cancer (TNBC), EGCG was found to inhibit the paracrine cross-talk between adipose-derived MSCs and TNBC cells. For example, on the one hand, evidence suggests that EGCG prevents a proinflammatory and tumor-associated adipocyte-like phenotype (with increased CCL2, CCL5, CXCL8, IL-1β, IL-6, COX2, HIF-1α, and VEGF) induced by the secretome of TNBC in adipose-derived MSCs mainly through the inhibitory effects of EGCG on Smad2 and NF-κB signaling pathways (Gonzalez Suarez et al. 2022). On the other hand, a study revealed that EGCG suppresses the differentiation of MSCs into adipocytes and prevents STAT3-mediated paracrine carcinogenic control of TNBC invasion phenotypes in response to the adipocyte secretome (Gonzalez Suarez et al. 2021).

Steed Kl et al. applied suberoylanilide hydroxamic acid (SAHA), a histone deacetylase (HDAC) inhibitor, in combination with epigallocatechin-3-gallate, a DNA methyltransferase (DNMT) inhibitor isolated from green tea, to triple negative breast cancer (TNBC) cells. The compounds decreased cIAP2 expression while increasing the expression of proapoptotic caspase 7. There were also changes in histone modifications, suggesting a role for epigenetic mechanisms in these changes in cIAP2 expression. These changes lead to an increase in apoptosis. SAHA and EGCG are also able to limit the migration of TNBC cells through the fibronectin (FN) matrix. SAHA and EGCG reduce the metastatic potential of TNBC by inducing the apoptotic pathway (Steed et al. 2020).

Cell proliferation, viability, and apoptosis of MDA-MB-231 cells were impaired by the combination of EGCG and tapentadol. Specifically, the data showed that EGCG and TAP reduced the proliferation of MDA-MB-231 cells by disrupting cell cycle progression ($p < 0.05$). These findings suggest that the combination of these substances may represent a new treatment strategy for patients suffering from triple negative breast cancer (Bimonte et al. 2019).

Conclusion

Natural products of plant origin show high potential as anticancer agents. Limited toxicity, availability, and diversity in mechanisms of action are the main advantages of anticancer natural products. However, low bioavailability, low solubility, and limited stability limit the use of these agents. Natural products are an integral part of the development of innovative anticancer drugs in cancer research, offering the scientific community the opportunity to explore new natural compounds against cancer. It is likely that natural products in combination with other drugs may have great potential to improve the efficacy of TNBC treatment and patient outcomes. The introduction of compounds obtained from natural sources into the therapeutic practice of oncological diseases as agents with minimal side effects correlates with the basic principle in medical ethics, namely "primum non nocere."

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Funding

No funding was reported.

Author contributions

All authors have contributed equally.

Author ORCIDs

Petar Atanasov https://orcid.org/0009-0006-8337-2089

Data availability

All of the data that support the findings of this study are available in the main text.

References

Ahmad J, Ahamad J, Algahtani MS, Garg A, Shahzad N, Ahmad MZ, Imam SS (2024) Nanotechnology-mediated delivery of resveratrol as promising strategy to improve therapeutic efficacy in triple negative breast cancer (TNBC): progress and promises. Expert Opinion on Drug Delivery 21(2): 229–244. https://doi.org/10.1080/17425247.2024.2317194 [Epub 2024 Feb 28; PMID: 38344809]

Avtanski D, Poretsky L (2018) Phyto-polyphenols as potential inhibitors of breast cancer metastasis. Molecular Medicine 24(1): 29. https://doi.org/10.1186/s10020-018-0032-7 [PMID: 30134816; PMCID: PMC6016885]

Barchiesi G, Roberto M, Verrico M, Vici P, Tomao S, Tomao F (2021) Emerging role of PARP inhibitors in metastatic triple negative breast cancer. Current scenario and future perspectives. Frontiers in Oncology 11: 769280. https://doi.org/10.3389/fonc.2021.769280 [PMID: 34900718; PMCID: PMC8655309]

Barton VN, D'Amato NC, Gordon MA, Lind HT, Spoelstra NS, Babbs BL, Heinz RE, Elias A, Jedlicka P, Jacobsen BM, Richer JK (2015) Multiple molecular subtypes of triple-negative breast cancer critically rely on androgen receptor and respond to enzalutamide in vivo. Molecular Cancer Therapeutics14(3): 769–778. https://doi.org/10.1158/1535-7163.MCT-14-0926 [Epub 2015 Feb 23. PMID: 25713333; PMCID: PMC4534304]

Berger ER, Park T, Saridakis A, Golshan M, Greenup RA, Ahuja N (2021) Immunotherapy treatment for triple negative breast cancer. Pharmaceuticals (Basel) 14(8): 763. https://doi.org/10.3390/ph14080763 [PMID: 34451860; PMCID: PMC8401402]

Bhullar KS, Lagarón NO, McGowan EM, Parmar I, Jha A, Hubbard BP, Rupasinghe HPV (2018) Kinase-targeted cancer therapies: progress, challenges and future directions. Molecular Cancer 17(1): 48. https://doi.org/10.1186/s12943-018-0804-2 [PMID: 29455673; PMCID: PMC5817855]

Bimonte S, Cascella M, Barbieri A, Arra C, Cuomo A (2019) Shining a light on the effects of the combination of (-)-Epigallocatechin-3-gallate and Tapentadol on the growth of human triple-negative breast cancer cells. In Vivo 33(5): 1463–1468. https://doi.org/10.21873/invivo.11625 [PMID: 31471393; PMCID: PMC6754998]

Bozorgi A, Khazaei S, Khademi A, Khazaei M (2020) Natural and herbal compounds targeting breast cancer, a review based on cancer stem cells. Iranian Journal of Basic Medical Sciences23(8): 970–983. https://doi.org/10.22038/ijbms.2020.43745.10270 [PMID: 32952942; PMCID: PMC7478260]

Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E, ESMO Guidelines Committee (2019a) Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology 30(8): 1194–1220. https://doi.org/10.1093/annonc/mdz173

Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E, ESMO Guidelines Committee (2019b) Erratum in: Annals of Oncology 30(10): 1674. https://doi.org/10.1093/annonc/mdz189

Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E, ESMO Guidelines Committee (2021) Erratum in: Annals of Oncology 32(2): 284. https://doi.org/10.1016/j.annonc.2020.08.2158 [PMID: 31161190]

Catalano A, Iacopetta D, Ceramella J, Mariconda A, Rosano C, Scumaci D, Saturnino C, Longo P, Sinicropi MS (2022) New Achievements for the treatment of triple-negative breast cancer. Applied Sciences 12(11): 5554. https://doi.org/10.3390/app12115554

Chen Z, Lu P, Li M, Zhang Q, He T, Gan L (2024) Curcumin suppresses metastasis of triple-negative breast cancer cells by modulating EMT signaling pathways: An integrated study of bioinformatics analysis. Medicine (Baltimore) 103(8): e37264. https://doi.org/10.1097/MD.0000000000037264 [PMID: 38394486; PMCID: PMC11309626]

Chowdhury P, Ghosh U, Samanta K, Jaggi M, Chauhan SC, Yallapu MM (2021) Bioactive nanotherapeutic trends to combat triple negative breast cancer. Bioactive Materials 6(10): 3269–3287. https://doi.org/10.1016/j.bioactmat.2021.02.037 [PMID: 33778204; PMCID: PMC7970221]

Cragg GM, Pezzuto JM (2016) Natural products as a vital source for the discovery of cancer chemotherapeutic and chemopreventive agents. Medical Principles and Practice Suppl 2(Suppl 2): 41–59. https://doi.org/10.1159/000443404 [Epub 2015 Dec 17. PMID: 26679767; PMCID: PMC5588531]

Curtin NJ, Szabo C (2013) Therapeutic applications of PARP inhibitors: anticancer therapy and beyond. Molecular Aspects of Medicine 34(6): 1217–1256. https://doi.org/10.1016/j.mam.2013.01.006 [Epub 2013 Jan 29. PMID: 23370117; PMCID: PMC3657315]

Deng Z, Chen G, Shi Y, Lin Y, Ou J, Zhu H, Wu J, Li G, Lv L (2022) Curcumin and its nano-formulations: Defining triple-negative breast

cancer targets through network pharmacology, molecular docking, and experimental verification. Frontiers in Pharmacology 13: 920514. https://doi.org/10.3389/fphar.2022.920514 [PMID: 36003508; PMCID: PMC9393234]

Derakhshan F, Reis-Filho JS (2022) Pathogenesis of triple-negative breast cancer. Annual Review of Pathology 17: 181–204. https://doi.org/10.1146/annurev-pathol-042420-093238 [PMID: 35073169; PMCID: PMC9231507]

Di Nardo P, Lisanti C, Garutti M, Buriolla S, Alberti M, Mazzeo R, Puglisi F (2022) Chemotherapy in patients with early breast cancer: clinical overview and management of long-term side effects. Expert Opinion on Drug Safety 21(11): 1341–1355. https://doi.org/10.1080/14740338.2022.2151584 [Epub 2022 Dec 5. PMID: 36469577]

Domchek SM, Postel-Vinay S, Im SA, Park YH, Delord JP, Italiano A, Alexandre J, You B, Bastian S, Krebs MG, Wang D, Waqar SN, Lanasa M, Rhee J, Gao H, Rocher-Ros V, Jones EV, Gulati S, Coenen-Stass A, Kozarewa I, Lai Z, Angell HK, Opincar L, Herbolsheimer P, Kaufman B (2020) Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study. The Lancet Oncology 21(9): 1155–1164. https://doi.org/10.1016/S1470-2045(20)30324-7

El-Far AH, Darwish NHE, Mousa SA (2020) Senescent colon and breast cancer cells induced by doxorubicin exhibit enhanced sensitivity to curcumin, caffeine, and thymoquinone. Integrative Cancer Therapies 19: 1534735419901160. https://doi.org/10.1177/1534735419901160 [PMID: 32054357; PMCID: PMC7025418]

Fang T, Hu S, Song X, Wang J, Zuo R, Yun S, Jiang S, Guo D (2024) Combination of monensin and erlotinib synergistically inhibited the growth and cancer stem cell properties of triple-negative breast cancer by simultaneously inhibiting EGFR and PI3K signaling pathways. Breast Cancer Research and Treatment 207(2): 435–451. https://doi.org/10.1007/s10549-024-07374-y [Epub 2024 Jul 3. PMID: 38958784]

Feng W, He Y, Xu J, Zhang H, Si Y, Xu J, Li S (2022) A meta-analysis of the effect and safety of platinum-based neoadjuvant chemotherapy in treatment of resectable triple-negative breast cancer. Anticancer Drugs 33(1): e52–e60. https://doi.org/10.1097/CAD.0000000000001196 [PMID: 34371505; PMCID: PMC8670346]

Foulkes WD, Smith IE, Reis-Filho JS (2010) Triple-negative breast cancer. The New England Journal of Medicine 363(20): 1938–1948. https://doi.org/10.1056/NEJMra1001389 [PMID: 21067385]

Gao Q, Yuan Y, Gan HZ, Peng Q (2015) Resveratrol inhibits the hedgehog signaling pathway and epithelial-mesenchymal transition and suppresses gastric cancer invasion and metastasis. Oncology Letters 9(5): 2381–2387. https://doi.org/10.3892/ol.2015.2988 [Epub 2015 Feb 26. PMID: 26137075; PMCID: PMC4467343]

Gerratana L, Basile D, Buono G, De Placido S, Giuliano M, Minichillo S, Coinu A, Martorana F, De Santo I, Del Mastro L, De Laurentiis M, Puglisi F, Arpino G (2018) Androgen receptor in triple negative breast cancer: A potential target for the targetless subtype. Cancer Treatment Reviews 68: 102–110. https://doi.org/10.1016/j.ctrv.2018.06.005 [Epub 2018 Jun 11. PMID: 29940524]

Giordano A, Tommonaro G (2019) Curcumin and cancer. Nutrients 11(10): 2376. https://doi.org/10.3390/nu11102376 [PMID: 31590362; PMCID: PMC6835707]

Gonzalez Suarez N, Fernandez-Marrero Y, Torabidastgerdooei S, Annabi B (2022) EGCG prevents the onset of an inflammatory and cancer-associated adipocyte-like phenotype in adipose-derived mesenchymal stem/stromal cells in response to the triple-negative breast cancer secretome. Nutrients 14(5): 1099. https://doi.org/10.3390/nu14051099 [PMID: 35268073; PMCID: PMC8912398]

Gonzalez Suarez N, Rodriguez Torres S, Ouanouki A, El Cheikh-Hussein L, Annabi B (2021) EGCG inhibits adipose-derived mesenchymal stem cells differentiation into adipocytes and prevents a STAT3-mediated paracrine oncogenic control of triple-negative breast cancer cell invasive phenotype. Molecules 26(6): 1506. https://doi.org/10.3390/molecules26061506 [PMID: 33801973; PMCID: PMC7998295]

Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, Anderson B, Burstein HJ, Chew H, Dang C, Elias AD, Giordano SH, Goetz MP, Goldstein LJ, Hurvitz SA, Isakoff SJ, Jankowitz RC, Javid SH, Krishnamurthy J, Leitch M, Lyons J, Mortimer J, Patel SA, Pierce LJ, Rosenberger LH, Rugo HS, Sitapati A, Smith KL, Smith ML, Soliman H, Stringer-Reasor EM, Telli ML, Ward JH, Wisinski KB, Young JS, Burns J, Kumar R (2022) Breast cancer, Version 3.2022, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network 20(6): 691–722. https://doi.org/10.6004/jnccn.2022.0030 [PMID: 35714673]

Gupta GK, Collier AL, Lee D, Hoefer RA, Zheleva V, Siewertsz van Reesema LL, Tang-Tan AM, Guye ML, Chang DZ, Winston JS, Samli B, Jansen RJ, Petricoin EF, Goetz MP, Bear HD, Tang AH (2020) Perspectives on triple-negative breast cancer: Current treatment strategies, unmet needs, and potential targets for future therapies. Cancers (Basel) 12(9): 2392. https://doi.org/10.3390/cancers12092392 [PMID: 32846967; PMCID: PMC7565566]

Haidinger R, Bauerfeind I (2019) Long-term side effects of adjuvant therapy in primary breast cancer patients: Results of a web-based survey. Breast Care (Basel) 14(2): 111–116. https://doi.org/10.1159/000497233 [Epub 2019 Feb 15. PMID: 31798383; PMCID: PMC6886114]

Joshi P, Joshi S, Semwal D, Bisht A, Paliwal S, Dwivedi J, Sharma S (2021) Curcumin: An insight into molecular pathways involved in anticancer activity. Mini-Reviews in Medicinal Chemistry 21(17): 2420–2457. https://doi.org/10.2174/1389557521666210122153823 [PMID: 33480345]

Kanjanapan Y, Day D, Butler MO, Wang L, Joshua AM, Hogg D, Leighl NB, Razak ARA, Hansen AR, Boujos S, Chappell M, Chow K, Sherwin B, Stayner LA, Soultani L, Zambrana A, Siu LL, Bedard PL, Spreafico A (2019) Delayed immune-related adverse events in assessment for dose-limiting toxicity in early phase immunotherapy trials. European Journal of Cancer 107: 1–7. https://doi.org/10.1016/j.ejca.2018.10.017 [Epub 2018 Dec 7. PMID: 30529898]

Katz H, Alsharedi M (2017) Immunotherapy in triple-negative breast cancer. Medical Oncology 35(1): 13. https://doi.org/10.1007/s12032-017-1071-6 [PMID: 29255938]

Ke DYJ, El-Sahli S, Wang L (2022) The potential of natural products in the treatment of triple-negative breast cancer. Curr Cancer Drug Targets 22(5): 388–403. https://doi.org/10.2174/1568009622666211231140623 [PMID: 34970954]

Keshavarz G, Jalili C, Pazhouhi M, Khazaei M (2020) Resveratrol effect on adipose-derived stem cells differentiation to chondrocyte in three-dimensional culture. Advanced Pharmaceutical Bulletin 10(1): 88–96. https://doi.org/10.15171/apb.2020.011 [Epub 2019 Dec 11. PMID: 32002366; PMCID: PMC6983992]

Khazaei MR, Rashidi Z, Chobsaz F, Niromand E, Khazaei M (2020) Inhibitory effect of resveratrol on the growth and angiogenesis of human endometrial tissue in an in vitro three-dimensional model of endometriosis. Reproductive Biology 20(4): 484–490. https://doi.org/10.1016/j.repbio.2020.07.012 [Epub 2020 Sep 28. PMID: 32896495]

Kim YN, Choe SR, Cho KH, Cho DY, Kang J, Park CG, Lee HY (2017) Resveratrol suppresses breast cancer cell invasion by inactivating a RhoA/YAP signaling axis. Experimental & Molecular Medicine 49(2): e296. https://doi.org/10.1038/emm.2016.151 [PMID: 28232662; PMCID: PMC5336560]

Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips K-A, Mooij TM, Roos-Blom M-J, Jervis S, van Leeuwen FE, Milne RL, Andrieu N, Goldgar DE, Terry MB, Rookus MA, Easton DF, Antoniou AC [BRCA1 and BRCA2 Cohort Consortium] (2017) Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 317(23): 2402–2416. https://doi.org/10.1001/jama.2017.7112

Kulangara K, Zhang N, Corigliano E, Guerrero L, Waldroup S, Jaiswal D, Ms MJ, Shah S, Hanks D, Wang J, Lunceford J, Savage MJ, Juco J, Emancipator K (2019) Clinical utility of the combined positive score for programmed death Ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. Archives of Pathology & Laboratory Medicine 143(3): 330–337. https://doi.org/10.5858/arpa.2018-0043-OA [Epub 2018 Jul 20. PMID: 30028179]

Lacouture M, Sibaud V (2018) Toxic side effects of targeted therapies and immunotherapies affecting the skin, oral mucosa, hair, and nails. Am American Journal of Clinical Dermatology 19(Suppl 1): 31–39. https://doi.org/10.1007/s40257-018-0384-3 [PMID: 30374901; PMCID: PMC6244569]

Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, Pietenpol JA (2011) Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. Journal of Clinical Investigation 121(7): 2750–2767. https://doi.org/10.1172/JCI45014 [PMID: 21633166; PMCID: PMC3127435]

Leon-Ferre RA, Goetz MP (2023) Advances in systemic therapies for triple negative breast cancer. BMJ 381: e071674. https://doi.org/10.1136/bmj-2022-071674 [PMID: 37253507]

Li D, Cao D, Sun Y, Cui Y, Zhang Y, Jiang J, Cao X (2024) The roles of epigallocatechin gallate in the tumor microenvironment, metabolic reprogramming, and immunotherapy. Frontiers in Immunology 15: 1331641. https://doi.org/10.3389/fimmu.2024.1331641 [PMID: 38348027; PMCID: PMC10859531]

Li M, Guo T, Lin J, Huang X, Ke Q, Wu Y, Fang C, Hu C (2022a) Curcumin inhibits the invasion and metastasis of triple negative breast cancer via Hedgehog/Gli1 signaling pathway. Journal of Ethnopharmacology 283: 114689. https://doi.org/10.1016/j.jep.2021.114689 [Epub 2021 Sep 28]

Li M, Guo T, Lin J, Huang X, Ke Q, Wu Y, Fang C, Hu C (2023) Erratum in: Journal of Ethnopharmacology 312: 116524. https://doi.org/10.1016/j.jep.2023.116524 [PMID: 34592340]

Li Y, Zhang H, Merkher Y, Chen L, Liu N, Leonov S, Chen Y (2022b) Recent advances in therapeutic strategies for triple-negative breast cancer. Journal of Hematology & Oncology 15(1): 121. https://doi.org/10.1186/s13045-022-01341-0 [PMID: 36038913; PMCID: PMC9422136]

Liu Q, Kim C, Jo YH, Kim SB, Hwang BY, Lee MK (2015) Synthesis and biological evaluation of resveratrol derivatives as melanogenesis inhibitors. Molecules 20(9): 16933–16945. https://doi.org/10.3390/molecules200916933 [PMID: 26393543; PMCID: PMC6332419]

Lord CJ, Ashworth A (2017) PARP inhibitors: Synthetic lethality in the clinic. Science 355(6330): 1152–1158. https://doi.org/10.1126/science.aam7344 [Epub 2017 Mar 16. PMID: 28302823; PMCID: PMC6175050]

Mallipeddi H, Thyagarajan A, Sahu RP (2021) Implications of Withaferin-A for triple-negative breast cancer chemoprevention. Biomedicine & Pharmacotherapy 134: 111124. https://doi.org/10.1016/j.biopha.2020.111124 [Epub 2021 Jan 9. PMID: 33434782]

Mandapati A, Lukong KE (2023) Triple negative breast cancer: approved treatment options and their mechanisms of action. Journal of Cancer Research and Clinical Oncology 149(7): 3701–3719. https://doi.org/10.1007/s00432-022-04189-6 [Epub 2022 Aug 17. PMID: 35976445; PMCID: PMC10314854]

Maqbool M, Bekele F, Fekadu G (2022) Treatment strategies against triple-negative breast cancer: An updated review. Breast Cancer (Dove Med Press) 14: 15–24. https://doi.org/10.2147/BCTT.S348060 [PMID: 35046722; PMCID: PMC8760999]

Mason SR, Willson ML, Egger SJ, Beith J, Dear RF, Goodwin A (2024) Platinum chemotherapy for early triple-negative breast cancer. Breast 75: 103712. https://doi.org/10.1016/j.breast.2024.103712 [Epub 2024 Mar 12. PMID: 38492276; PMCID: PMC10959715]

Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, Evans DG, Izatt L, Eeles RA, Adlard J, Davidson R, Eccles D, Cole T, Cook J, Brewer C, Tischkowitz M, Douglas F, Hodgson S, Walker L, Porteous ME, Morrison PJ, Side LE, Kennedy MJ, Houghton C, Donaldson A, Rogers MT, Dorkins H, Miedzybrodzka Z, Gregory H, Eason J, Barwell J, McCann E, Murray A, Antoniou AC, Easton DF [on behalf of EMBRACE] (2013) Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. Journal of the National Cancer Institute 105(11): 812–822. https://doi.org/10.1093/jnci/djt095 [Epub 2013 Apr 29. PMID: 23628597]

Mohammadhosseinpour S, Ho LC, Fang L, Xu J, Medina-Bolivar F (2022) Arachidin-1, a prenylated stilbenoid from peanut, induces apoptosis in triple-negative breast cancer cells. International Journal of Molecular Sciences 23(3): 1139. https://doi.org/10.3390/ijms23031139 [PMID: 35163062; PMCID: PMC8835363]

Mosca L, Ilari A, Fazi F, Assaraf YG, Colotti G (2021) Taxanes in cancer treatment: Activity, chemoresistance and its overcoming. Drug Resist Updates 54: 100742. https://doi.org/10.1016/j.drup.2020.100742 [Epub 2021 Jan 9. PMID: 33429249]

Naeem A, Hu P, Yang M, Zhang J, Liu Y, Zhu W, Zheng Q (2022) Natural products as anticancer agents: Current status and future perspectives. Molecules 27(23): 8367. https://doi.org/10.3390/molecules27238367 [PMID: 36500466; PMCID: PMC9737905]

Nagle DG, Ferreira D, Zhou YD (2006) Epigallocatechin-3-gallate (EGCG): chemical and biomedical perspectives. Phytochemistry 67(17): 1849–1855. https://doi.org/10.1016/j.phytochem.2006.06.020 [Epub 2006 Jul 31. PMID: 16876833; PMCID: PMC2903211]

Obidiro O, Battogtokh G, Akala EO (2023) Triple negative breast cancer treatment options and limitations: Future outlook. Pharmaceutics 15(7): 1796. https://doi.org/10.3390/pharmaceutics15071796 [PMID: 37513983; PMCID: PMC10384267]

O'Reilly D, Sendi MA, Kelly CM (2021) Overview of recent advances in metastatic triple negative breast cancer. World Journal of Clinical Oncology 12(3): 164–182. https://doi.org/10.5306/wjco.v12.i3.164 [PMID: 33767972; PMCID: PMC7968109]

Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, Lambotte O, Mariette X, Prat A, Suárez-Almazor ME (2020) Immune-related adverse events of checkpoint inhibitors. Nature Reviews Disease Primers 6(1): 38. https://doi.org/10.1038/s41572-020-0160-6 [PMID: 32382051; PMCID: PMC9728094]

Ryu WJ, Sohn JH (2021) Molecular targets and promising therapeutics of triple-negative breast cancer. Pharmaceuticals (Basel) 14(10): 1008. https://doi.org/10.3390/ph14101008 [PMID: 34681231; PMCID: PMC8540846]

Sakamoto T, Tanimoto K, Eguchi H, Sasaki S, Tsuboi K, Hayashi SI, Ichihara S (2023) Resveratrol exhibits diverse anti-cancer activities through epigenetic regulation of E-cadherin and p21 in triple-negative breast cancer cells. Breast Cancer 30(5): 727–738. https://doi.org/10.1007/s12282-023-01465-2 [Epub 2023 May 11. PMID: 37166625]

Sandoval-Ato R, Coral-Gonzales P, Coronel-Arias S, Espinoza-Mantilla L, Terrones-Chaparro G, Serna-Alarcón V (2024) Clinical and radiological manifestations associated with triple-negative breast cancer in women from northern Peru. A case-control study. ecancer 18: 1720. https://doi.org/10.3332/ecancer.2024.1720 [PMID: 39021537; PMCID: PMC11254400]

Shen J, Zhou Q, Li P, Wang Z, Liu S, He C, Zhang C, Xiao P (2017) Update on phytochemistry and pharmacology of naturally occurring resveratrol oligomers. Molecules 22(12): 2050. https://doi.org/10.3390/molecules22122050 [PMID: 29186764; PMCID: PMC6149893]

Singh DD, Parveen A, Yadav DK (2021) Role of PARP in TNBC: Mechanism of inhibition, clinical applications, and resistance. Biomedicines 9(11): 1512. https://doi.org/10.3390/biomedicines9111512 [PMID: 34829741; PMCID: PMC8614648]

Singh DD, Yadav DK (2021) TNBC: Potential targeting of multiple receptors for a therapeutic breakthrough, nanomedicine, and immunotherapy. Biomedicines 9(8): 876. https://doi.org/10.3390/biomedicines9080876 [PMID: 34440080; PMCID: PMC8389539]

Smith CEP, Prasad V (2021) Targeted cancer therapies. American Family Physician 103(3): 155–163. [PMID: 33507053]

Steed KL, Jordan HR, Tollefsbol TO (2020) SAHA and EGCG promote apoptosis in triple-negative breast cancer cells, possibly through the modulation of cIAP2. Anticancer Research 40(1): 9–26. https://doi.org/10.21873/anticanres.13922 [PMID: 31892549; PMCID: PMC7032656]

Stevens KN, Vachon CM, Couch FJ (2013) Genetic susceptibility to triple-negative breast cancer. Cancer Research 73(7): 2025–2030. https://doi.org/10.1158/0008-5472.CAN-12-1699 [Epub 2013 Mar 27. PMID: 23536562; PMCID: PMC3654815]

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians 71(3): 209–249. https://doi.org/10.3322/caac.21660 [Epub 2021 Feb 4. PMID: 33538338]

Thapa SB, Pandey RP, Park YI, Sohng JK (2019) Biotechnological advances in resveratrol production and its chemical diversity. Molecules 24(14): 2571. https://doi.org/10.3390/molecules24142571

van Beek L, McClay É, Patel S, Schimpl M, Spagnolo L, Maia de Oliveira T (2021) PARP power: A structural perspective on PARP1, PARP2, and PARP3 in DNA damage repair and nucleosome remodelling. International Journal of Molecular Sciences 22(10): 5112. https://doi.org/10.3390/ijms22105112 [PMID: 34066057; PMCID: PMC8150716]

Vinayak S, Tolaney SM, Schwartzberg L, Mita M, McCann G, Tan AR, Wahner-Hendrickson AE, Forero A, Anders C, Wulf GM, Dillon P, Lynce F, Zarwan C, Erban JK, Zhou Y, Buerstatte N, Graham JR, Arora S, Dezube BJ, Telli ML (2019) Open-label clinical trial of niraparib combined with pembrolizumab for treatment of advanced or metastatic triple-negative breast cancer. JAMA Oncology 5(8): 1132–1140. https://doi.org/10.1001/jamaoncol.2019.1029 [PMID: 31194225; PMCID: PMC6567845]

Wang G, Duan P, Wei Z, Liu F (2022) Curcumin sensitizes carboplatin treatment in triple negative breast cancer through reactive oxygen species induced DNA repair pathway. Molecular Biology Reports 49(4): 3259–3270. https://doi.org/10.1007/s11033-022-07162-1 [Epub 2022 Jan 25. PMID: 35076853]

Wang Z, Yang X, Wang J, Wang S, Mao X, Li M, Zhao Y, Wang W, Qi X, Wu T (2019) Risk of serious adverse event and fatal adverse event with molecular target anticancer drugs in cancer patients: A meta-analysis. Journal of Cancer Research and Therapeutics 15(7): 1435–1449. https://doi.org/10.4103/jcrt.JCRT_577_18 [PMID: 31939421]

Wong SC, Kamarudin MNA, Naidu R (2021) Anticancer mechanism of curcumin on human glioblastoma. Nutrients 13(3): 950. https://doi.org/10.3390/nu13030950 [PMID: 33809462; PMCID: PMC7998496]

Yar Saglam AS, Kayhan H, Alp E, Onen HI (2021) Resveratrol enhances the sensitivity of FL118 in triple-negative breast cancer cell lines via suppressing epithelial to mesenchymal transition. Molecular Biology Reports 48(1): 475–489. https://doi.org/10.1007/s11033-020-06078-y [Epub 2021 Jan 3. PMID: 33389483]

Yeh SJ, Hsu BJ, Chen BS (2021) Systems medicine design for triple-negative breast cancer and non-triple-negative breast cancer based on systems identification and carcinogenic mechanisms. International Journal of Molecular Sciences 22(6): 3083. https://doi.org/10.3390/ijms22063083

Yin L, Duan JJ, Bian XW, Yu SC (2020) Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Research 22(1): 61. https://doi.org/10.1186/s13058-020-01296-5 [PMID: 32517735; PMCID: PMC7285581]

Yoest JM (2017) Clinical features, predictive correlates, and pathophysiology of immune-related adverse events in immune checkpoint inhibitor treatments in cancer: a short review. ImmunoTargets and Therapy 6: 73–82. https://doi.org/10.2147/ITT.S126227 [PMID: 29067284; PMCID: PMC5644546]

Zhang Z, Liu Z, Chen J, Yi J, Cheng J, Dun W, Wei H (2018) Resveratrol induces autophagic apoptosis via the lysosomal cathepsin D pathway in human drug-resistant K562/ADM leukemia cells. Experimental and Therapeutic Medicine 15(3): 3012–3019. https://doi.org/10.3892/etm.2018.5742 [Epub 2018 Jan 12. PMID: 29456707; PMCID: PMC5795814]