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Phytochemicals in breast cancer therapy: Decoding molecular pathways and pioneering therapeutic strategies

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ABSTRACT

Background: Breast cancer constitutes a global health crisis, affecting millions worldwide and contributing significantly to cancer-related mortality. Its development, progression, and persistence are driven by complex molecular signaling networks, including the PI3K/Akt/mTOR, MAPK/ERK, NF-κB, TNF, and apoptotic pathways. Phytochemicals such as curcumin, genistein, resveratrol, and EGCG have demonstrated therapeutic potential by modulating these critical pathways, thereby inhibiting cancer cell proliferation, inducing apoptosis, suppressing metastasis, and potentially overcoming drug resistance, offering a promising basis for developing targeted and less toxic breast cancer therapies.

Purpose: This review aims to examine the phytochemical composition of medicinal plants and elucidate the molecular pathways involved in their therapeutic effects against breast cancer. It also seeks to compile evidence from in vitro and in vivo studies, providing updated references for molecular targets suitable for phytochemical-based interventions.

Methods: A comprehensive search of PubMed, Web of Science, ScienceDirect, and CNKI up to September 2024 used keywords on breast cancer, molecular pathways, natural active ingredients, and pharmacological activity. Eligible studies examined phytochemicals' molecular mechanisms or therapeutic effects in breast cancer, while non-peer-reviewed, duplicate, or unrelated studies were excluded.

Results: Decoding signaling pathways allows for the development of an individualized molecular profile for each patient, guiding the selection of optimal treatments while minimizing adverse effects. Assessing mutation status and protein expression within these pathways can help predict prognosis and evaluate therapeutic effectiveness. Phytochemicals, in particular, can inhibit cancer cell growth by targeting key signaling cascades that regulate the cell cycle, such as the PI3K/Akt and MAPK pathways. When used in combination with conventional therapies, these compounds may enhance treatment efficacy and reduce drug resistance. This review highlights the molecular pathways through which plant-derived phytochemicals act against breast cancer in both in vitro and in vivo settings, and elucidates their pharmacological effects at the molecular level. The findings provide a valuable reference for future research into molecularly targeted therapies and the development of breast cancer drugs from herbal sources.

Abbreviations: AKT, Also known as Protein Kinase B; ATM, Ataxia-telangiectasia mutated; AP1, Activator protein 1; BRCA, Breast Cancer gene; CDH1, Cadherin-1; CHK, Checkpoint Kinase 2.; DISC, Death-inducing signaling complex; DSBs, Double-strand breaks; EGCG, Epigallocatechin gallate; EMT, Epithelial-mesenchymal transition; ER, Estrogen Receptor; FADD, Fas-Associated protein with Death Domain; FKBP12, FK506 Binding Protein 12; GSK-3β, Glycogen Synthase Kinase-3 Beta; HUVECs, Human Umbilical Vein Endothelial Cells; HDGC, Hereditary diffuse gastric cancer; Her2, Human Epidermal Growth Factor Receptor 2; MAPK, Mitogen-Activated Protein Kinase; MAPKK, MAPK Kinase; MDA, Malondialdehyde; mTOR, Mammalian Target of Rapamycin; PARP, Poly ADP-ribose polymerase; PALB2, Partner and Localizer of BRCA2.; PI3K, Phosphatidylinositol 3-Kinase; PI3KCA, Phosphoinositide 3-kinase catalytic subunit alpha; PI3KCB, Phosphoinositide 3-kinase catalytic subunit beta; PI3KCD, Phosphoinositide 3-kinase catalytic subunit delta; PI3KKCG, Phosphoinositide 3-kinase catalytic subunit gamma; PTEN, Phosphatase and Tensin Homolog; RAD51C, RAD51 paralog C; ROS, Reactive oxygen species; S6K1, Ribosomal Protein S6 Kinase 1; SOD, Superoxide dismutase; TRADD, TNFR-Associated Death Domain.; TNF, Tumor Necrosis Factor; TNBC, Triple-negative breast cancer; VEGF, Vascular Endothelial Growth Factor.

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1. Introduction

Worldwide, breast cancer is the prevailing kind of malignant tumor among women (Łukasiewicz et al., 2021). According to recent GLOBOCAN statistics, breast cancer has become the most frequently diagnosed cancer worldwide, with approximately 2.3 million new cases reported in 2020 which is representing 11.7 % of all cancer diagnoses (Arnold et al., 2022; Filho et al., 2024; Sedeta et al., 2023; Sung et al., 2021). That same year, the disease caused around 685,000 deaths, making it the leading cause of cancer-related mortality among women and accounting for 6.9 % of all cancer deaths globally (Arnold et al., 2022; Filho et al., 2024; Sedeta et al., 2023; Sung et al., 2021). Incidence rates vary markedly across regions, ranging from fewer than 40 cases per 100,000 women in parts of Asia and Africa to over 80 per 100,000 in Australia/New Zealand, North America, and some European countries. Mortality patterns also differ geographically, with the highest rates observed in Melanesia, Polynesia, and Western Africa, and the lowest in Eastern Asia and Australia/New Zealand (Arnold et al., 2022; Filho et al., 2024). While high-income countries record higher incidence rates, low- and middle-income countries bear a disproportionately high mortality burden, largely due to limited access to early detection and effective treatment (Bellanger et al., 2018; DeSantis et al., 2015; Sharma, 2021; Sung et al., 2021). Projections indicate that by 2040, breast cancer could affect >3 million individuals annually and cause approximately 1 million deaths, driven by global population growth and aging. These figures underscore the urgent need for strengthened cancer control measures, particularly in transitioning nations facing rapidly rising incidence and mortality (Arnold et al., 2022; Bellanger et al., 2018; DeSantis et al., 2015; Sung et al., 2021).

The global incidence of breast cancer is increasing, largely driven by lifestyle factors such as poor diet, smoking, chronic stress, and physical inactivity (Łukasiewicz et al., 2021). Although the exact causes of carcinogenesis are not fully understood, several established risk factors contribute to breast cancer development (Feng et al., 2018). Hormonal influences are particularly important, including the timing and duration of estrogen exposure, reproductive history such as number of children, age at first childbirth, and breastfeeding practices (Jefferson et al., 2012). Age also plays a critical role, with rising breast cancer rates observed worldwide across all age groups, especially among women under 50 (Wilkinson and Gathani, 2022). Molecular subtypes such as HER2-positive and basal-like (triple-negative) breast cancers are commonly identified. As a hormone-dependent tumor, breast cancer risk increases with higher and prolonged estrogen exposure (Al-Shami et al., 2023). Epidemiological data link both endogenous and exogenous estrogen exposure to elevated breast cancer risk, particularly among postmenopausal women with high circulating estrogen levels (Yue et al., 2010). However, the effects of external estrogen remain a subject of ongoing scientific debate (Albers et al., 2023).

Breast cancer arises from abnormal cell growth within breast tissue, typically triggered by genetic mutations that can be inherited or occur spontaneously (Geyer et al., 2009; Laconi et al., 2020).These mutated cells evade normal regulatory controls, leading to uncontrolled proliferation and the formation of tumors, which may be benign or malignant (Brown et al., 2023). Malignant cells can invade surrounding tissues and spread through the circulatory or lymphatic systems to distant organs, a process known as metastasis—the primary cause of breast cancer mortality (Hinck and Näthke, 2014; Leong et al., 2022). Risk factors include genetics, age, hormonal history, lifestyle, and environmental influences (Seyfried and Huysentruyt, 2013). Early detection via self-exams, mammography, and medical check-ups significantly improves prognosis (Kösters and Gøtzsche, 2003). Treatment options vary based on cancer stage and patient health, encompassing surgery, chemotherapy, radiation, hormone therapy, and targeted molecular therapies (Debela et al., 2021).

This narrative review aims to elucidate key molecular pathways involved in breast cancer and highlight advances in phytochemical applications from herbal plants. We systematically summarize phytochemicals' pharmacological effects and dissect their mechanisms at the molecular level, offering valuable insights for future research on herbal-based breast cancer therapies.

2. Literature Review methodology

A systematic and rigorous literature search was conducted to identify high-quality scientific studies exploring the molecular mechanisms of phytochemicals in breast cancer. Multiple reputable databases such as PubMed, Web of Science, Scopus, ScienceDirect, and CNKI were utilized to ensure comprehensive coverage of both international and regional research.

The search strategy combined controlled vocabulary and free-text keywords, using Boolean operators to refine results. Core search terms included "breast cancer" or "breast neoplasm" in combination with "phytochemicals," "natural compounds," "herbal extracts," or "plant-derived compounds," along with terms such as "molecular pathways," "signaling pathways," "molecular mechanisms," and "pharmacological activity." Additional filters targeted therapeutic outcomes, including "anticancer activity," "apoptosis," "cell proliferation," and "metastasis," as well as specific phytochemicals such as curcumin, genistein, resveratrol, EGCG, sulforaphane, and kaempferol. Searches were limited to peer-reviewed original research, reviews, and clinical trials published in English or Chinese up to September 2024.

Studies were included if they investigated molecular mechanisms of phytochemicals in breast cancer through in vitro, in vivo, or clinical models, with a focus on key signaling pathways such as PI3K/Akt, MAPK/ERK, and NF-κB, and reported pharmacological or therapeutic outcomes. Exclusion criteria comprised studies without molecular detail, abstracts lacking full text, duplicate publications, non-peer-reviewed sources, and research unrelated to breast cancer or phytochemicals. For each eligible study, data on the phytochemical compounds, molecular targets, experimental models, mechanisms of action, and available clinical evidence were systematically extracted. The methodological quality, particularly for clinical trials was evaluated based on study design, sample size, control measures, and outcome assessments to ensure reliability and scientific rigor.

3. Genes involved in the development of breast cancer

Gene expression in breast cancer varies considerably depending on the tumor subtype, stage of progression, and underlying biological mechanisms. Despite this variability, distinct gene expression profiles are frequently observed, offering important insights into the disease's origins, molecular characteristics, and clinical behavior.

3.1. *Her2*

Overexpression of the HER2 gene in breast cancer is marked by an abnormal increase in the production or activity of the HER2 protein within tumor cells. This overexpression typically arises from HER2 gene amplification, a process in which multiple copies of the gene are present, leading to excessive protein synthesis (Iqbal and Iqbal, 2014). Although HER2 amplification occurs in only about 20–25 % of breast cancer cases (Goddard et al., 2012). it has profound implications for disease progression and treatment strategies. The increased gene copies result in heightened expression of HER2 receptors on the surface of cancer cells (Gutierrez and Schiff, 2011). These receptors play a key role in promoting cell growth and division, and their overabundance can drive more aggressive tumor proliferation. HER2-positive tumors represent one of the four major molecular subtypes of breast cancer, alongside luminal A, luminal B, and triple-negative breast cancer. HER2 status is routinely evaluated using immunohistochemistry (IHC) or in situ hybridization (ISH) techniques (Bilous et al., 2012). Understanding the HER2 signaling pathway is essential, as it underpins the action of

targeted therapies and reveals mechanisms of treatment resistance. For example, the truncated p95HER2 isoform lacks the extracellular trastuzumab-binding domain, enabling the activation of alternative receptor tyrosine kinases such as IGF1-R and C-Met, which continue downstream signaling despite HER2 inhibition. Similarly, PTEN mutations or deletions can lead to persistent activation of the PI3K pathway (Fig. 1). HER2 testing outcomes directly influence therapeutic decision-making, guiding the use of targeted agents such as trastuzumab (Herceptin) and pertuzumab (Cao et al., 2023). These drugs effectively suppress excessive HER2 activity, thereby slowing tumor growth and improving treatment efficacy (Swain et al., 2023). The recognition of HER2 overexpression has transformed breast cancer management by enabling more precise, personalized treatment approaches (Harbeck et al., 2019) Widespread implementation of HER2 screening, coupled with targeted therapies, has significantly improved prognosis and survival rates for many patients with HER2-positive breast cancer (Situmorang et al., 2025).

3.2. ER

The estrogen receptor (ER) plays a pivotal role in breast cancer through its complex interaction with the estrogen hormone (Miziak et al., 2023). ER is a protein located in breast cancer cells that regulates their growth and activity. When estrogen binds to ER on the cell surface, the receptor becomes activated and translocates into the nucleus, where the estrogen–ER complex binds to hormone response elements (HRE) on DNA to modulate the transcription of genes involved in cell cycle regulation and proliferation (Fuentes and Silveyra, 2019). In ER-positive breast cancer, accounting for approximately 70–80 % of cases of cancer cells exploit estrogen signaling to drive uncontrolled growth (Chen et al., 2022; Yoon et al., 2022). Standard treatment involves hormone therapy aimed at blocking or reducing ER activity, such as tamoxifen, which antagonizes ER in breast tissue, or aromatase inhibitors, which lower estrogen levels (Bekes and Huober, 2023; Yao et al., 2020). Although initially effective, resistance can develop through genetic or epigenetic changes that alter the tumor's response to therapy. Understanding the molecular mechanisms of ER signaling and resistance has been critical in advancing more precise and effective therapeutic strategies for ER-positive breast cancer (Sarvari et al., 2022).

3.3. BRCA

BRCA expression in breast cancer is closely associated with pathogenic alterations in the BRCA1 or BRCA2 genes. These tumor suppressor genes maintain genomic stability by repairing DNA damage (Gorodetska et al., 2019). Mutations in BRCA1 or BRCA2, whether inherited or arising sporadically in somatic cells disrupt their normal function, increasing susceptibility to breast and ovarian cancers (Somasundaram, 2010). Carriers of these mutations face a lifetime breast cancer risk as high as 70–80 %, compared with approximately 12 % in the general population (Testa et al., 2020)(Nitschke et al., 2023).

In addition to structural mutations, altered expression or regulation of BRCA1/2 can influence tumor behavior, therapeutic response, and prognosis (Caputo et al., 2023). Genetic testing for BRCA mutations is now a key component of care for individuals with relevant family histories or clinical indicators of hereditary risk (Lynch et al., 2015). Results from such testing inform genetic counseling and guide treatment decisions. Notably, patients with BRCA1/2 mutations may benefit from targeted therapies such as PARP (poly ADP-ribose polymerase) inhibitors, which exploit the DNA repair vulnerabilities caused by BRCA deficiency (Smith and Isaacs, 2011). Grasping the role of BRCA gene expression in breast cancer has greatly improved disease prevention,

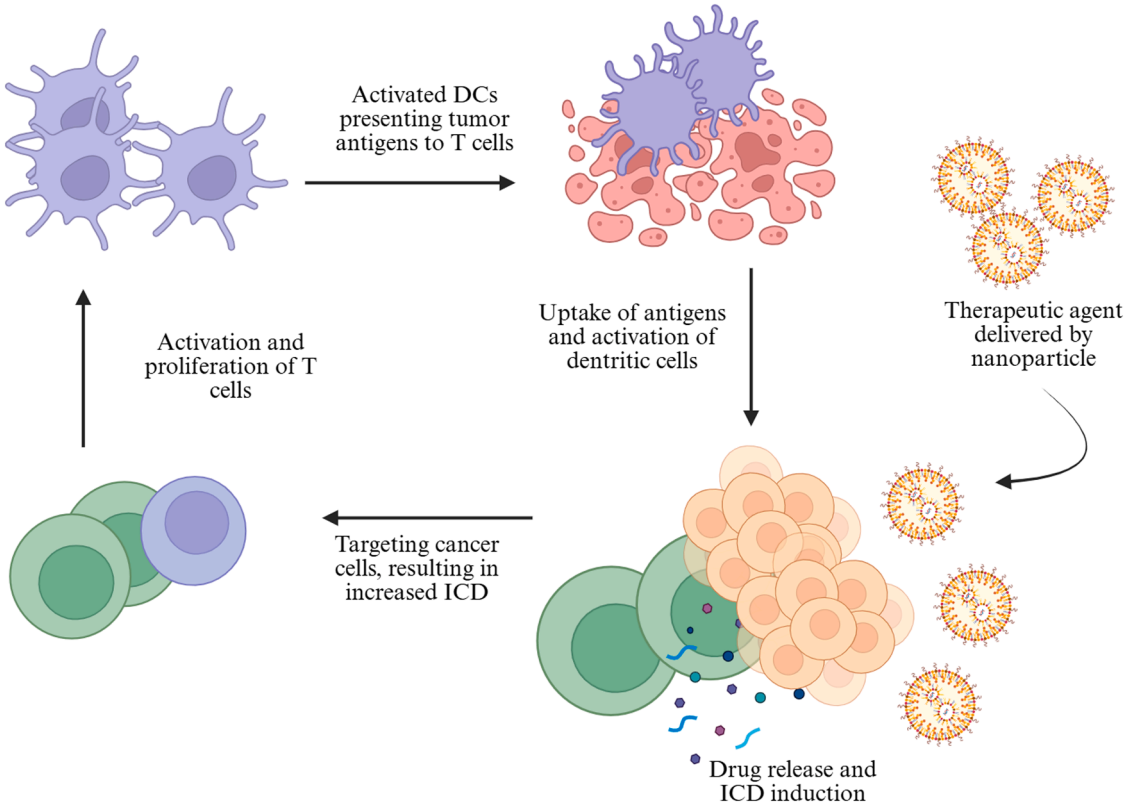

Fig. 1. The HER2 extracellular domain does not have any identified ligands and is activated through the creation of homo- or heterodimers. These pairs of molecules induce the addition of phosphate groups to certain amino acid residues called tyrosine kinases in the interior region of the cell. These residues operate as locations where other proteins can attach and trigger the activation of signaling pathways known as PI3K and MAPK. These pathways are responsible for promoting the development of the cell cycle and cell proliferation.

facilitated earlier detection, and refined precision treatment strategies, highlighting the essential contribution of genetic research to personalized oncology (Godet and Gilkes, 2017).

3.4. PTEN

PTEN (Phosphatase and Tensin Homolog) is a critical tumor suppressor gene that regulates cell growth and prevents malignant transformation (Wang et al., 2021). In breast cancer, loss or disruption of PTEN function significantly increases cancer susceptibility. As a phosphatase enzyme, PTEN inhibits cell cycle progression and proliferation by blocking growth-promoting signaling pathways, particularly the AKT (protein kinase B) pathway, which is central to cell survival and development (Leslie and Downes, 2004).

Mutations or deletions in PTEN—frequent in breast cancer—impair its tumor-suppressive role, enabling unchecked proliferation and malignant progression (Miricescu et al., 2020) (Fedorova et al., 2022). Without PTEN's regulation, the PI3K/AKT/mTOR signaling cascade becomes hyperactivated, driving excessive growth, resistance to apoptosis, and enhanced tumor cell survival. This loss not only fuels tumor aggressiveness but can also reduce responsiveness to both targeted and conventional therapies, including chemotherapy.

Given these implications, genetic testing for PTEN mutations or altered expression is essential for diagnosis, prognosis, and treatment planning (Carbognin et al., 2019). In particular, therapies targeting the PI3K/AKT/mTOR pathway are being actively explored for PTEN-deficient breast cancers (Hayama et al., 2023). As understanding of PTEN biology continues to evolve, it offers valuable opportunities for developing more precise, effective therapeutic strategies.

3.5. STK11

STK11, also known as LKB1, is a tumor suppressor gene essential for regulating cell proliferation and maintaining genomic stability (Hu et al., 2023). Mutations in STK11 disrupt normal cellular regulatory pathways, contributing to the development of multiple cancers, including breast cancer. As a kinase enzyme, STK11/LKB1 governs key processes such as cell growth, division, and energy metabolism, largely through activation of AMP-activated protein kinase (AMPK)—a central regulator of cellular energy homeostasis and the cell cycle (Zheng et al., 2024; Hardie, 2011). In its tumor-suppressive role, STK11 limits cancer cell proliferation by modulating signaling pathways that control metabolism, proliferation, and stress responses (Shackelford and Shaw, 2009). Loss or mutation of STK11 removes this regulatory brake, enabling uncontrolled cell growth and increasing susceptibility to malignant transformation (Pons-Tostivint et al., 2021). TK11 mutations are also linked to Peutz-Jeghers syndrome (PJS), a rare hereditary condition that significantly elevates lifetime breast cancer risk along with other malignancies (Thakur et al., 2006). Although less common than BRCA1/2 alterations, STK11 mutations can profoundly impact breast cancer biology by altering pathways critical for tumor cell proliferation and differentiation (Olopade et al., 2008). Currently, no targeted therapies exist for STK11-mutant breast cancer; however, ongoing research is exploring combination strategies, including AMPK-targeting approaches, to develop more effective treatments for this subset of patients. Analysing the role of STK11 in breast cancer remains a promising avenue for advancing precision oncology.

3.6. P53

The p53 gene encodes a protein often described as the "guardian of the genome" for its central role in safeguarding DNA integrity (Ozaki and Nakagawara, 2011). It detects DNA damage and directs the cell toward repair or, if the damage is irreparable, initiates apoptosis. Through these mechanisms, p53 maintains genomic stability and prevents the malignant transformation of cells (Zhou et al., 2023).

Mutations in p53 are common in breast cancer and typically abolish its tumor-suppressive activity. Loss of function leads to uncontrolled proliferation of genetically damaged cells, contributing to aggressive tumor behavior and poor clinical outcomes (Marvalim et al., 2023) Such mutations are also associated with metastasis, therapy resistance, and enhanced invasiveness (Shahbandi et al., 2020).

Beyond regulating the cell cycle and apoptosis, p53 integrates with multiple signaling networks involved in proliferation, differentiation, and stress response (Gülow et al., 2023). Disruption of these pathways fosters a cellular environment favorable to cancer progression (Alvarado-Ortiz et al., 2020). Clinically, p53 mutations can compromise the efficacy of both chemotherapy and targeted treatments (Hientz et al., 2017). Ongoing studies are focused on restoring p53 function or exploiting its loss to develop novel therapeutic approaches for breast cancer.

3.7. CDH1

The CDH1 gene encodes E-cadherin, a key cell adhesion protein critical for maintaining epithelial tissue structure and function. Inherited CDH1 mutations are associated with hereditary diffuse gastric cancer (HDGC) syndrome and significantly increase the risk of invasive lobular breast cancer, while somatic mutations can also occur sporadically in breast tumors (Van der Post et al., 2015). Loss or reduction of E-cadherin function—through genetic mutation, promoter hypermethylation, or histone modifications such as deacetylation—disrupts cell–cell adhesion and facilitates tumor progression (Caldeira et al., 2006; Serrano-Gomez et al., 2016). Functionally, this loss promotes epithelial–mesenchymal transition (EMT), a process in which epithelial cells gain mesenchymal properties, enhancing motility, invasiveness, and metastatic potential (Liu et al., 2014). E-cadherin serves as an adhesive protein for epithelial cells, and the absence of E-cadherin activity can lead to reduced cell adhesion, enabling the dissemination and metastasis of cancer cells (Loh et al., 2019). E-cadherin loss also influences multiple signaling pathways, notably activating Wnt/β-catenin signaling, which supports tumor development (Stockinger et al., 2001). In clinical study, reduced E-cadherin expression correlates with poorer prognosis in breast cancer due to its association with aggressive, invasive phenotypes (Fernandez-Ferreira et al., 2021). Research is ongoing to develop therapeutic strategies targeting downstream pathways affected by E-cadherin loss and to explore epigenetic interventions aimed at restoring its expression.

3.8. CHK2

The CHK2 or CHEK2 gene is crucial for DNA damage response and cell cycle regulation. Genetic mutations in the CHEK2 gene can elevate the susceptibility to various types of cancer, including breast cancer (Cybulski et al., 2004). CHEK2 operates as a serine/threonine kinase that becomes active when DNA damage occurs, particularly in the case of double-strand breaks (DSBs) (Zannini et al., 2014). In Fig. 2. Upon activation, CHEK2 controls a range of subsequent targets that are crucial for halting the cell cycle and facilitating the repair of DNA. The p53 protein, which governs apoptosis (programmed cell death) and DNA repair, is a primary focus of investigation (Zannini et al., 2014). CHEK2 plays a role in causing cell cycle arrest at the G1/S and G2/M checkpoints, hence inhibiting the proliferation of cells with DNA damage. Germline mutations in the CHEK2 gene, namely the c.1100delC mutation, have been identified as being linked to a higher susceptibility to breast cancer (van Jaarsveld et al., 2020). This genetic mutation leads to the lack of CHEK2 kinase activity, which hampers the ability to respond to DNA damage. CHEK2 somatic mutations can also manifest in breast cancer cells (Chrisanthar et al., 2008). The occurrence of somatic mutations can lead to the inactivation of CHEK2, hence playing a role in the development of cancer. Disabling CHEK2 diminishes the capacity of cells to halt the cell cycle and mend DNA that has been harmed, resulting

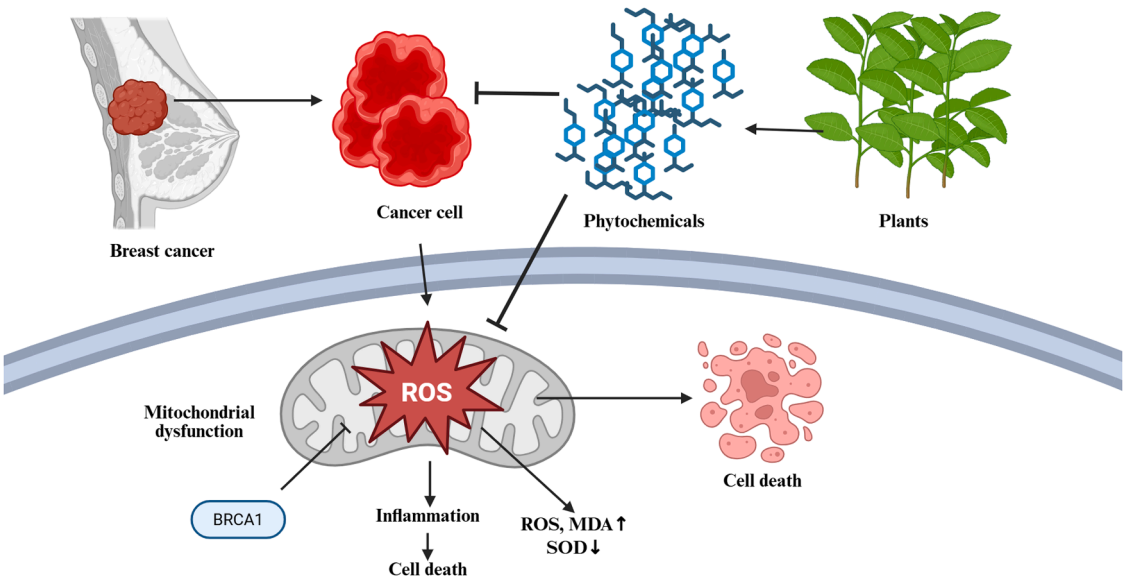

Fig. 2. CHK2 regulates cell cycle arrest at the G1/S and G2/M checkpoints, thereby suppressing cell proliferation that leads to DNA damage. Inactivation of CHK2 hinders p53 activation, resulting in a decrease in programmed cell death and promoting the survival and reproduction of cells with DNA damage.

in the buildup of mutations and damage to the genome (Stolarova et al., 2020). When CHEK2 is deactivated, the activation of p53 is hindered, which decreases the occurrence of programmed cell death and enables cells with DNA damage to survive and multiply (Hirao et al., 2000). ATM (ataxia-telangiectasia mutated) activates CHEK2 in response to DNA damage. The ATM/CHEK2 pathway and the ATR (ATM and Rad3-related) pathway interact with each other and both play a role in responding to DNA damage (Helt et al., 2005). CHEK2 interacts with the BRCA1 and BRCA2 proteins, both of which play a role in DNA repair. Disruption of BRCA1/BRCA2 function may occur due to inactivation of CHEK2, leading to an elevated risk of breast cancer. CHEK2 mutations frequently correlate with a poorer prognosis in breast cancer patients, primarily because cancer cells can persist despite DNA damage. Therapies that focus on response pathways to DNA damage are currently in development. PARP inhibitors are a type of medication that has been effective in treating malignancies with DNA repair defects, such as in individuals with CHEK2 mutations.

3.9. PALB2

PALB2 acts as a mediator in the DNA double-strand break (DSB) repair process by facilitating homologous recombination (HR). PALB2 forms a connection and attracts BRCA2 to specific locations where DNA has been damaged (Wu et al., 2020). PALB2 contributes to the process of DNA repair, which is crucial for preserving the stability of the genome and preventing the occurrence of cancer (Park et al., 2014). PALB2 engages in interactions with many proteins implicated in DNA repair, such as BRCA1, BRCA2, and RAD51. PALB2 germline mutations are linked to a heightened susceptibility to breast cancer (Le et al., 2021). These mutations can result in the loss of PALB2′s functionality, which disrupts the processes involved in repairing DNA. Somatic mutations in the PALB2 gene can also arise in breast cancer cells, playing a role in the advancement of cancer in a similar manner as inherited mutations (Pauty et al., 2017). Disruption of PALB2 function leads to impairments in the repair of DNA damage through homologous recombination, resulting in an elevated build-up of DNA damage and mutations (Bleuyard et al., 2017). Cells with PALB2 mutations, due to their diminished DNA repair capacity, exhibit increased vulnerability to genomic instability, hence potentially initiating the onset of cancer. may impact the control of the cell cycle, enabling cells with DNA damage to multiply (Tuppurainen et al., 2024). PALB2 acts as an intermediary between BRCA1 and BRCA2 during the process of repairing DNA. Disruption of PALB2 results in the inactivation of this DNA repair complex (Fig. 3). PALB2 mutations frequently result in a poorer prognosis among breast cancer patients, mostly because they are linked to deficiencies in DNA repair and instability in the genome (Sy et al., 2009). Efforts are underway to create therapies that specifically target the processes involved in repairing DNA. PARP inhibitors are a type of medication that is effective in treating malignancies with DNA repair defects, such as in individuals with PALB2 mutations.

3.10. RAD51C

The RAD51C gene, also known as RAD51 homolog C, is a member of the RAD51 gene family. This gene family is crucial for the DNA repair process, namely through a mechanism called homologous recombination (HR). RAD51C is a crucial component in the process of homologous recombination, which is a method used to fix breaks in the DNA double helix (Jing et al., 2019). RAD51C facilitates the identification of DNA counterparts that are similar and facilitates the replacement of impaired DNA strands with intact DNA strands. RAD51C plays a crucial role in facilitating the creation and durability of RAD51 filaments at locations of DNA damage, which is vital for the process of DNA repair. Germline mutations in the RAD51C gene are linked to a higher susceptibility to developing breast and ovarian cancer. This mutation can lead to the impairment of RAD51C function, hence affecting the process of DNA repair (Somyajit et al., 2010). Somatic mutations in the RAD51C gene can also arise in breast cancer cells and have a role in the development of cancer through a similar mechanism. Disruption of RAD51C function leads to a failure in the repair of DNA damage by homologous recombination (Longo et al., 2023). This leads to a higher buildup of DNA damage and mutations. Cells carrying RAD51C mutations have diminished DNA repair capacity, rendering them more vulnerable to genomic instability, hence increasing the risk of cancer formation (Hopkins et al., 2022). Cells lacking RAD51C may exhibit reduced viability when exposed to DNA-damaging chemicals, as they are unable to effectively repair such damage. RAD51C functions in conjunction with BRCA1, BRCA2, PALB2, and RAD51 proteins to facilitate DNA repair via homologous recombination (Orhan et al., 2021). RAD51C, in conjunction with BRCA2, facilitates the interaction between RAD51 and damaged DNA, a crucial process for precise DNA repair. The presence of RAD51C mutations in breast cancer patients is frequently linked to a poorer

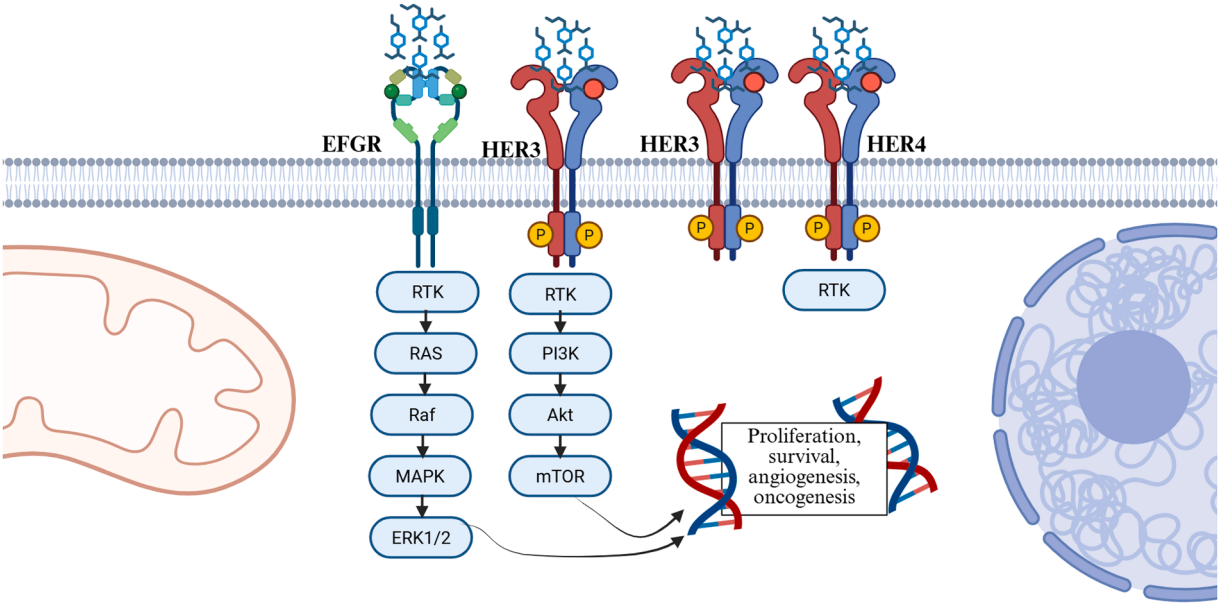

Fig. 3. PALB2 serves as the vital connector between BRCA1 and BRCA2, helping them work together to repair damaged DNA. By bringing these proteins into close cooperation, PALB2 ensures that DNA double-strand breaks are fixed accurately, protecting the cell's genetic stability.

prognosis. This is because these mutations are associated with a failure in DNA repair and an increased risk of genomic instability. Efforts are underway to create therapies that specifically target DNA repair pathways (Dawson et al., 2020). PARP inhibitors are a type of treatment that has been proven effective in malignancies with DNA repair deficits, such as in individuals with RAD51C mutations (Dawson et al., 2020). PARP inhibitors function by impeding the mending of DNA single-strand breaks (SSBs), leading to the buildup of double-strand breaks that cannot be adequately repaired in cells lacking homologous recombination (HR), ultimately culminating in the demise of cancer cells.

4. Role of phytochemicals in breast cancer

Phytochemicals are biologically active substances that are present in plants and possess a range of health advantages, such as the ability to potentially prevent and treat breast cancer. Flavonoids consist of quercetin, kaempferol, and epigallocatechin gallate (EGCG) (Ullah et al., 2020). Flavonoids possess antioxidant and anti-inflammatory characteristics that can impede the proliferation of cancer cells. Resveratrol, which is present in red grapes and berries, exhibits anti-cancer properties via promoting apoptosis and suppressing the development of cancer cells (Kursvietiene et al., 2023). Carotenoids, including Beta-carotene, are present in carrots, pumpkin, and green leafy vegetables. Beta-carotene possesses immunomodulatory effects and exhibits antioxidant characteristics. Lycopene, which is included in tomatoes and tomato products, possesses potent antioxidant qualities and has the potential to lower the likelihood of developing breast cancer (Imran et al., 2020). Isoflavones, such as Genistein, are present in soybeans. Genistein has the ability to impede the proliferation of breast cancer cells by specifically targeting estrogen receptors and triggering apoptosis (Kim, 2021). Daidzein, which is present in soybeans, possesses anti-cancer capabilities that are comparable to those of genistein (Alshehri et al., 2021). Orange peel and other citrus fruits contain terpenoid compounds, including Limonene. Limonene possesses anti-cancer characteristics that can trigger apoptosis and impede the growth of cancer cells (Maqbool et al., 2023). Beta-caryophyllene is present in a variety of spices and fragrant plants. It possesses anti-inflammatory characteristics and has the ability to impede the proliferation of cancer cells (Fidyt et al., 2016). An example of an alkaloid phytochemical is Berberine. Berberine, which is present in plants like goldenseal and barberry, possesses anti-cancer characteristics by impeding cell proliferation and triggering apoptosis (Behl et al., 2022). Camptothecin and its derivatives, which are derived from the Camptotheca acuminata plant, are employed in cancer therapy due to their capacity to suppress topoisomerase I. Diosgenin, which is present in wild yam, exhibits anti-cancer effects by promoting apoptosis and suppressing the multiplication of cancer cells. Lignans are present in flax seeds, sesame seeds, and various other types of seeds. Lignans have the ability to act as anti-estrogens by binding to estrogen receptors, hence decreasing the likelihood of developing breast cancer (Sethi et al., 2018).

Phytochemicals possessing antioxidant capabilities aid in counteracting free radicals and diminishing oxidative harm to DNA, hence inhibiting mutations that result in cancer. Several phytochemicals have the ability to induce apoptosis, a process of programmed cell death, in cancer cells, hence aiding in the reduction of tumor growth (George et al., 2021). Phytochemicals have the ability to affect many cellular signaling pathways that play a role in the growth and progression of cancer, including the NF-κB, MAPK, and PI3K/Akt pathways. Phytochemicals possessing anti-inflammatory qualities have the ability to diminish chronic inflammation, which is recognized as a risk factor for the development of cancer. Certain phytochemicals have the ability to affect the way genes are expressed by using epigenetic mechanisms like DNA methylation and histone changes (Barreca et al., 2023). Fig. 4 demonstrates that phytochemicals have the ability to effectively decrease the levels of reactive oxygen species (ROS) and malondialdehyde (MDA) when administered in low quantities. Nevertheless, elevated concentrations of flavonoids effectively induce cell death by causing oxidative stress, as demonstrated by the increased expression of reactive oxygen species (ROS) and malondialdehyde (MDA), as well as the decreased activity of superoxide dismutase (SOD). The processes responsible for this increased cell death were shown to be apoptosis, cell cycle arrest, buildup of mitochondrial superoxide, poor mitochondrial activity, and reduced ATP generation. BRCA1 overexpression

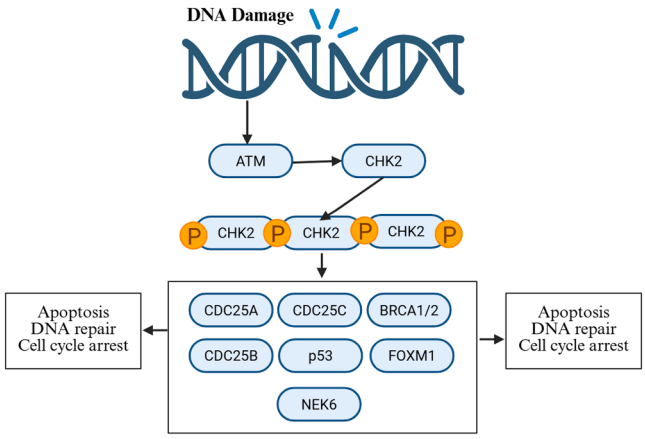

Fig. 4. Phytochemicals decreased the levels of reactive oxygen species (ROS) and malondialdehyde (MDA). Nevertheless, significant amounts of resulted in a pronounced induction of cellular apoptosis. BRCA1 overexpression effectively reduces oxidative stress and inflammation while inhibiting ATP generation, potentially by repairing DNA damage. This highlights the crucial role of BRCA1 in the treatment involving plant phytochemicals.

significantly reduced oxidative stress and inflammation while inhibiting ATP generation, potentially by repairing DNA damage (Jurcău et al., 2022). This highlights the crucial role of BRCA1 in protecting against oxidative damage and inflammatory responses triggered by external stimuli.

5. The role of antioxidants in breast cancer

The involvement of antioxidants in breast cancer is a multifaceted and contentious subject. Antioxidants are compounds that have the ability to impede the process of oxidation and counteract the harmful effects of free radicals on cells and DNA. Antioxidants, such as vitamin C, vitamin E, selenium, and polyphenols, have the ability to counteract free radicals and minimize oxidative harm to DNA, lipids, and proteins (Griñan-Lison et al., 2021). Oxidative damage can lead to genetic alterations, which have the potential to induce the development of cancer. Antioxidants possess anti-inflammatory characteristics that can aid in the reduction of chronic inflammation, a recognized risk factor for cancer. Antioxidants can, in certain instances, shield cancer cells from harm inflicted by cancer treatments like radiation and chemotherapy, which seek to eliminate cancer cells by generating free radicals (Didier et al., 2023). Some studies have found a correlation between the consumption of large amounts of antioxidant supplements and a higher likelihood of developing certain types of cancer. Certain antioxidants have the ability to induce apoptosis, which is the process of programmed cell death, in cancer cells (Yang et al., 2023). Antioxidants have the ability to regulate cellular signaling pathways that are implicated in the formation and advancement of cancer, such as the NF-κB, MAPK, and PI3K/Akt pathways. Antioxidants enhance the cellular capacity to mend DNA damage, hence mitigating the occurrence of cancer-causing mutations (Herdiana et al., 2023).

It is advisable to consume a well-rounded diet that includes ample amounts of fruits, vegetables, whole grains, and foods that naturally contain antioxidants. In addition, this diet offers a diverse range of essential nutrients that promote general well-being (Liu, 2013). In order to decrease the likelihood of developing breast cancer, it is crucial to adopt a health-conscious way of life, which involves keeping a healthy body weight, engaging in regular physical activity, refraining from smoking, and limiting alcohol intake. In general, while antioxidants may have the ability to provide protection against breast cancer, their usage should be approached with care and should be supported by robust scientific data and medical advice.

6. Moleculer pathways

6.1. The role of phytochemicals in the estrogen receptor (ER) pathway in breast cancer

Estrogen induces cellular alterations through multiple ways. Estrogen receptor (ER) interacts with estrogen, which then permeates into the cell nucleus. The nuclear estrogen-ER complex subsequently attaches to estrogen response element sequences either directly or by means of protein interactions with activator protein 1 (AP1) or SP1 sites in the promoter regions of estrogen-responsive genes (Liu, 2013). This leads to the enlistment of coregulator proteins (coactivators or corepressors) to the promoter, subsequently amplifying or reducing mRNA levels and the production of related proteins, ultimately leading to a physiological response (Rigalli et al., 2021). The estrogen receptor (ER) is a protein that serves the purpose of regulating genes and attaching to estrogen. Estrogen exerts its effects by acting on two types of estrogen receptors, specifically ERα and ERβ. ERα is located at the 6q25.1 chromosomal locus, while Erβ is located at the 14q23–24 chromosomal locus (Szukiewicz, 2023). Both ERα and Erβ consist of four distinct sections. The protein consists of four regions: Region A/B at the N-terminal, Region C containing DHF, Region D, and Region E/F at the C-terminal, which contains LBF (Yaşar et al., 2017). Estrogen and its receptor (ER) have the ability to impact the progression of several diseases, such as breast cancer. Estrogen, when binding to the ER, promotes the proliferation of breast cells and augments the cell count in the respective tissue. The pathway responsible for signal transduction between the endoplasmic reticulum (ER) and estrogen is known as the classical pathway. Estrogen acts as a ligand by binding to receptors in the nucleus. If the ER is in an inactive state, it will form a complex with heat shock proteins. Upon ligand binding, the receptor releases the heat shock protein and undergoes dimerization as a result of hyperphosphorylation of the resin and tyrosine. The estrogen response element (ERE) will be occupied by a receptor-ligand complex and interact with other complex response elements to bind additional transcription factors (Klinge, 2001). Breast cancer is the leading cause of cancer-related mortality worldwide. Indonesia and the world have the highest incidence of breast cancer among women. Cellular and genetic abnormalities have an impact on the biological functioning and therapeutic response of breast cancer. The occurrence of breast cancer is influenced by factors such as age, family history, and amount of differentiation (Feng et al., 2018). Breast cancer is classified into three types based on the status of hormone receptors. The initial set of tumors exhibited positive expression of estrogen receptor (ER) or progesterone receptor (PR), the second set had positive expression of human epidermal growth factor receptor 2 (HER2), and the third set consisted of triple-negative breast cancer (TNBC) cancers (Yoon et al., 2020).

In the initial hypothesis, the proliferation of breast cells can be enhanced through the activation of estrogen receptors, which stimulate their growth. Consequently, the likelihood of errors occurring during cell division and DNA synthesis is heightened, leading to disruptions in essential cellular processes such as DNA repair, apoptosis, and cell growth due to genetic mutations (Clusan et al., 2023). In the second hypothesis, DNA may undergo damage as a result of byproducts generated during estrogen metabolism, leading to the occurrence of point mutations (Ayala et al., 2014). Both ideas propose that estrogen has a function in initiating or hastening the development of breast cancer. Phytochemicals are a natural source for the creation of anti-cancer medicines. Phytochemicals are utilized due to their non-toxic nature, safety, and accessibility. Up to 70 % of anti-cancer chemicals

can be derived from medicinal plants (Shrihastini et al., 2021). Some examples of plants are Piper longum, Nigella sativa, and curcuma longa. This natural substance can provide protection against breast malignancy by acting through many pathways associated with breast cancer, so serving as a preventive measure against the development of breast cancer (McGrowder et al., 2020). Various phytochemicals derived from plant extracts have been discovered to possess anti-cancer properties, which can help mitigate the adverse effects of anti-cancer treatment (Dehelean et al., 2021). Phytochemicals are present in vegetables, fruits, seeds, and other plant components. Phytochemicals serve not only as a source of energy but also exert beneficial effects on processes related to inflammation, control of the cell cycle, and cell signaling (Muscolo et al., 2024). Phytoestrogens are substances that have estrogenic action. This phytochemical is utilized because to its minimal adverse effects and exceptional safety profile, making it suitable for pharmaceutical applications targeting the estrogen receptor (ER) pathway (Lecomte et al., 2017). Nevertheless, the scarcity of these phytochemicals in comparison to other artificial medications has posed a challenge for their utilization in clinical practice. Table 1 demonstrates the function of different phytochemical substances in the estrogen receptor (ER) pathway in breast cancer.

6.2. *The Role of phytochemicals in the TNF signaling pathway in breast cancer*

Breast cancer commonly develops in an inflammatory milieu characterized by chronic inflammation, which involves the presence of many types of immune cells like neutrophils, macrophages, B lymphocytes, plasma cells, and CD4 Th1 lymphocytes (Li et al., 2021). Furthermore, this milieu is abundant in growth factors, mediator proteins like perforin and granzymes, and pro-inflammatory cytokines such as TNF-α. TNF-α, also known as Tumor necrosis factor-alpha, is a protein that promotes inflammation and is frequently present in the tumor microenvironment (TME) (H. Zhao et al., 2021).

The TME plays a role at every stage of breast cancer progression, including cell proliferation, tumor cell survival, epithelial to mesenchymal transition (EMT), and metastasis. The activation of molecular pathways by TNF-α in breast cancer cells is significant for the

Table 1
Role of Phytochemicals in the ER Pathway in Breast Cancer.

Target	Compound	Types of Study	Mechanism of action	Cell line(s)/animal model(s)	References
ER	Curcumin	In Vitro	Curcumin effectively decreases the expression of Erα, Erβ, and leptin, hence inhibiting the growth of breast cancer cells.	MCF-7 cells	(Nejati-Koshki et al., 2014)
ER	Kaempferol	In Vivo	Kaempferol inhibits the proliferation of MCF-7 cells that have been stimulated by nongenomic ER signaling pathways involving 17β-estradiol or triclosan-associated IGF-1R by degrading.	MCF-7 cells	(Kim et al., 2016)
ER	Apigenin	In Vitro	Apigenin results in T47D gene expression downregulation, which in turn causes tumor cell proliferation.	T47D cells	(Ashrafizadeh et al., 2020a)
ER	Caffeic Acid	In Vitro	Caffeic acid's ability to attach to two hydroxyl groups on its ring allows it to inhibit ER function and inhibit the proliferation of breast cells by binding to ER protein amino acids Arg-394 and Glu-353.	MCF-7 cells	(Alam et al., 2022)
ER	Genistein	In Silico	Genistein is a reversible competitive inhibitor that blocks E2 binding, induces apoptosis, inhibits EGFRI, stops the cell cycle in the G2-M phase, and prevents angiogenesis.	T47D cells	(Sharifi-Rad et al., 2021)
ER	Furanodienone	In Vitro	Furodionone reduces cell cycle and growth by activating E2-ERE, which hinders reporter plasmid activity and loses c-Myc, Bcl-2, and cyclin D1 expression in MCF-7 cells.	MCF-7 cells, T47D cells, and MDA-MB-231	(Caldon et al., 2009)
ER	Germacrone	In Vitro	Blocks transcription in MCF-7 breast cancer cells to fight cancer.	MCF-7 cells	(San-Millan et al., 2023)
ER	Calcitriol	In Vitro	Caltriol decreases aromatase expression in estrogen-responsive and estrogen-resistant breast cancer cells. Using vitamin D response elements, aromatase transcription is directly suppressed.	MCF-7 cells	(Krishnan et al., 2010)
ER	Decursin	In Vitro	Decursin in MCF-7 reduces mRNA, protein, and estrogen-induced gene activity.	MCF-7 and MDA MB-231 cells.	(Jiang et al., 2007)
ER	Berberin	In Vitro	Berberine can downregulate the EGFR gene, while EGRF mediates signaling to enhance ER-36 production by binding to AP-1 from its promoter. Berberine can diminish ER-36 expression through transcriptional regulation.	MCF7-TAM and BT-474 cells	(Wang et al., 2016)
ER	3-(3-chloropropoxy)-2-(4-methoxyphenyl)-4H-chromen-4-on (TF4)	In Vitro	The crystal structure of 3ERT is linked to 4-OH, a SERM that inhibits coactivator binding to the receptor and signals breast cancer cell proliferation.	MCF-7 cells	(Jordan et al., 2015)
ER	EGCG	In Vitro	The proliferation of MDA-MB-231 and MDA-MB-436 is inhibited by EGCG through its inhibition of Er-α36.	T47D, MDA-MB-231, MDA-MB-436 cells	(Marín et al., 2023)
ER	Sulforaphane	In Vitro	By reducing mRNA transcription and enhancing degradation through a proteasome-mediated mechanism, sulforaphane partially suppresses the production of Erα protein.	MCF-7 cells	(Ramirez and Singletary, 2008)
ER	Triptolide	In Vtro	Its expression was successful at the mRNA Level and Protein Level in a dose-dependent manner in MCF-7 cells	MCF-7 cells	(Chang et al., 2017)
ER	Resveratrol	In Vitro	Resveratrol inhibits highly invasive ER negative MDA-MB-435 breast cancer cells more than MCF-7.	MCF-7, T47D, MDA-MB-231 and MDA-MB-435 cells	(Ci et al., 2016)
ER	Piperine	In Vitro	Piperine reduces the number of TNBC cells (MDA-MB-468 and MDA-MB-231) and ER-expressing cells (MCF-7 and T47D in the G2 phase of the cell cycle and inhibits growth in vitro in p53-deficient cells	MCF-7, T47D, MDA-MB-231 and MDA-MB-435 cells	(Ali et al., 2024)
ER	Cyanidin-3-o-Glucoside	In Vitro	Inhibiting Erα−36 and EGFR/Akt signaling led to enhanced apoptotic cell death in MDA-MB-231, MDA-MB-436, and BT20 cells.	MDA-MB-231, MDA-MB-436 and BT20 cells	(Thiebaut et al., 2020)
ER	Calycosin	In Vitro and In Vivo	Although less effective than on ER+ breast cancer cells, calycosin can decrease the proliferation of ER- breast cancer cells.	MCF-7, T47D, and mouse animal models	(Li et al., 2022)

progression and metastasis of tumors, as well as for the resistance to treatment. TNF-α production is mediated by many receptors, including the T cell receptor. The expression of TNF-α mRNA is controlled by nuclear factor kappa B (NF-κB) and nuclear factor of activated T cells (Parameswaran and Patial, 2010). TNF-alpha exerts its effects by binding to two distinct receptors, TNF-α receptor I (also referred to as p55 or p60) and TNF-α receptor II (also known as p75 or p80). While TNF-α receptor I is ubiquitous throughout all cell types in the body, TNF-α receptor II is only expressed on endothelial cells and immune system cells (Jang et al., 2021).

Phytochemical substances are non-nutritive secondary metabolites that are present in plants and are derived from a variety of sources including vegetables, fruits, cereals, beverages, and medicinal plants (A. Kumar et al., 2023). A few instances of bioactive phytochemicals are polyphenols, carotenoids, organosulfur compounds, and alkaloids. Phytochemicals, whether in their pure form or combined in whole plant diets, exhibit a diverse array of biological functions. These activities encompass antioxidant, immunomodulatory, antibacterial, anti-inflammatory, and anticancer effects (Huang et al., 2016). Table 2 depicts the involvement of different phytochemical substances in the TNF pathway in breast cancer.

6.3. Role of phytochemicals in the mapk/erk pathway in breast cancer

The MAPK/ERK pathway is a protein kinase signaling pathway that is composed of serine or threonine residues. This collection of proteins is responsible for transmitting signals by being activated through different external stimuli that are received by the receptor (Cargnello and Roux, 2011). The activation of this pathway occurs when mitogens or growth factors, such as Epidermal Growth Factor, bind to receptors in the basement membrane layer. This binding triggers a series of kinase molecules, starting with the earliest kinase called MAPKKK. MAPKKK then activates MAPKK in response to GTP signals from RAS. MAPKK, in turn, phosphorylates and activates a single MAPK molecule, which is located in the nucleus and can interact with transcription factors during the cell proliferation process (Katz et al., 2007). Breast cancer is a malignancy that arises from the abnormal and unregulated activation of certain genes, such as HER2 (Hormonal Epidermal Receptor). HER2 belongs to a group of enzymes called tyrosine kinases, which can stimulate cell division and facilitate the growth of cells (Iqbal and Iqbal, 2014). The presence of alterations in the MAPK signaling pathway, triggered by unregulated gene expression, will have a significant correlation with the progression and maturation of breast cancer. It is crucial to examine the kinase components of the MAPKinase pathway that are targeted and search for kinase inhibitors in breast cancer therapy, as this route has been demonstrated to be associated with invasion, metastasis, resistance, and prognosis in breast cancer caused by HER2 expression (Rocca et al., 2022). Phytochemical substances are now in development and are highly regarded as prospective medication candidates for the prevention and treatment of breast cancer. Various categories of secondary metabolite chemicals are thought to possess multi-target actions in suppressing the growth of breast cancer. Table 3 presents the involvement of different phytochemical substances in the MAPK/ERK pathway in breast cancer.

Table 4

6.4. Role of phytochemicals in the PI3K/AKT/mTOR pathway in breast cancer

The PI3K/Akt/mTOR intracellular signaling pathway is activated in response to shortages in nutrients, hormones, and growth factors, which ultimately contribute to the growth of metastatic tumors. The PI3K/Akt/mTOR pathway is extensively researched and plays a crucial role in the progression of several forms of human cancer (Miricescu et al., 2020). Every core node in this route exhibits significant activity in the majority of malignancies. P13K is classified into three categories based on its structure and substrate specificity, with class 1 being the most extensively researched. Currently, there have been four isoforms of class 1A PI3K discovered and labeled as PI3KCA, PI3KCB, PI3KCD, and PI3KKCG (Thorpe et al., 2015). These isoforms are responsible for measuring inositol phosphorylation at the 3′ position. The serine/threonine protein kinase AKT is the primary molecule that inhibits PI3K molecules. There are three subtypes of AKT isoforms. AKT1 is present in the majority of major blood arteries, whereas AKT2 is found in blood vessels that have limited responsiveness to insulin, such as the esophagus, pancreas, and liver (Basu and Lambring, 2021). AKT3 is expressed in the esophagus and testis. AKT is triggered by the retraction imposed by PIP2 and PIP3 on the plasma membrane.

The PI3K/Akt/mTOR pathway is the most frequently affected in breast cancer subtypes. Breast cancer is an epithelial malignancy that mostly affects the mammary glands, namely the ducts and lobules. Malignant tumors are the primary etiology of the majority of breast cancer cases, but sarcomas such as phyllodes tumor and angiosarcoma are few. Breast cancer is a malignancy that has the potential to metastasize to other organs in the body, such as the heart, lungs, and brain, so affecting a significant portion of the body (Esperança-Martins et al., 2023). The PI3K/Akt/mTOR pathway plays a role in the development of resistance to trastuzumab in breast cancer cases when there is an overexpression of the HER2 gene. Research indicates that compounds that block this route may have a combined effect with trastuzumab on cells that are resistant to treatment (Dong et al., 2021).

Phytochemicals are plant-derived compounds that are classified as secondary metabolites. Examples of these compounds include triterpenoids, flavonoids, catechol, sulfated polysaccharides, and tannins (Al-Khayri et al., 2023). Various types of cancer can be combated by the anticancer properties of natural substances present in plant extracts, herbs, vegetables, and fruits. Additionally, numerous phytoconstituents have demonstrated preventive properties in that regard. Plants synthesize phytochemicals, also known as secondary metabolites, which are chemical compounds that are not essential for nutrition and are created through several biochemical routes (Ali Abdalla et al., 2022). Ongoing research is being conducted to explore the biological importance of phytochemicals, leading to the discovery of several active constituents in plants. Phytochemicals possess diverse and significant attributes, including antioxidant, antibacterial, and anticancer capabilities.

6.5. Role of phytochemicals in the apoptotic pathway in breast cancer

Apoptosis is a crucial biological mechanism that enables the body to remove cells that are either damaged or pose a potential threat, such as cancer cells. Several phytochemicals, such as polyphenols, flavonoids, and isoflavones, have been studied for their ability to trigger apoptosis in breast cancer cells (Pfeffer and Singh, 2018). Curcumin, a phytochemical, has been extensively researched for its ability to trigger apoptosis in MCF-7 cells by upregulating the production of caspase-3 and caspase-9. Curcumin decreases the growth of MCF-7 cells by lowering the amounts of nitric oxide and reactive oxygen species (ROS) (G et al., 2021). When curcumin was combined with the ECM proteins fibronectin or collagen, a synergistic anti-proliferative action was seen. Furthermore, the chemical increased the expression of Bax and decreased the expression of Bcl-2 in MDA-MB-231 cells, resulting in the suppression of cell growth and the initiation of programmed cell death (Gabr et al., 2022).

Apoptosis, often known as programmed cell death, encompasses two primary routes that function differently but are interconnected: the extrinsic pathway and the intrinsic pathway (Situmorang and ilyas., 2018). The initiation of the extrinsic route occurs through the activation of death receptors, including as TNF-α/TNFR1 and FasL/FasR (Elmore, 2007). Upon activation of these receptors, adapter proteins such as FADD and TRADD participate in the formation of the death-inducing signaling complex (DISC), thereby triggering the activation of caspase-8. The intrinsic pathway, however, is associated with the

Table 2
Phytochemical compounds in the TNF pathway in breast cancer.

Target	Compund	Types of Study	Mechanism of action	Cell line(s)/animal model(s)	References
TNF Signaling	Curcumin	In vitro	Curcumin inhibits the TNF-α-activated NFκB signaling pathway, preventing cancer cell proliferation.	MCF-7 cells	(Yang et al., 2022)
TNF Signaling	Celastrol	In vitro	Celastrol suppresses a TNF-α-activated protein that prevents cell death. Celastrol modulates activity of caspase-8, caspase-3, and PARP cleavage produced by TNF-α.	MCF-7 Cell line dan MDA-MB-231	(Cascão et al., 2017)
TNF Signaling	Piperlongumine	In vitro	Piperlongumine reduces TNF-α-induced NFκB activation and regulates non-coding RNA expression.	MDA-MB-468, MDA-MB-231, MCF-7, and T-47D Cell	(Awasthee et al., 2022)
TNF Signaling	Apigenin	In vitro	Apigenin inhibits TNF-α-induced CCL2 release, limiting inflammatory cell movement and penetration into tissue. Inflammation and tumor growth can decrease.	MDA-MB-231	(Bauer et al., 2017)
TNF Signaling	Berberine	In vivo	Berberine lowers TNF-α production in breast cancer. High IL-1B levels are linked to breast cancer. Berberine also decreased NFκB, IL1B, and IL-6 levels.	Female Sprague Dawley rats	(Zhao and Zhang, 2020)
TNF Signaling	Sulforaphane	In Vitro	Sulforaphane suppresses NFκB activation by reducing TNF-α-stimulated IκBα phosphorylation and downregulating gene products implicated in cell proliferation and anti-apoptosis.	MCF-7 cells	(Hung et al., 2014)
TNF Signaling	Scutelarin	In vivo	Scutellarin prevents TNF-α-induced reduction in endothelial functional proteins.	Nude (Balb/c) female mice and normal (Balb/c) female mice	(Mei et al., 2022)
TNF Signaling	Genistein	In vitro	Genistein dramatically decreases tumor necrosis factor receptor (TNFRSF1A or TNFR1). TNFRSF1A binds to TNF-a to induce apoptosis.	MCF-7 cells	(Deng et al., 2019)
TNF Signaling	Thymoquinone	In vitro	Thymoquinone controls TNBC cell growth, TNF-α-stimulated TNB cell viability, and proinflammatory cytokine release.	MDA-MB-231 and MDA-MB-468	(Adinew et al., 2023)
TNF Signaling	Puerarin	In vitro	Puerarin inhibits breast cancer cell migration, invasion, and adhesion. In addition, puerarin dramatically decreased TNF-α and IL-6 production. In breast cancer cells, puerarin suppresses NF-κB activation by reducing p65 and IκBα phosphorylation.	MCF-7 cells	(Liu et al., 2017)
TNF Signaling	Baicalin	In vitro	Baicalin decreases NF-kB activation, p-IkBa, and p65 expression, and hinders translocation. Baicalin targets EMT proteins to affect epithelial-to-mesenchymal transition (EMT). Baicalin inhibits NF-kB activation and downstream effects by targeting critical pathway components. This inhibits breast cancer cell growth, migration, and invasion and increases chemotherapy sensitivity.	MDA-MB-231 and MDA-MB-453	(Zeng et al., 2020)
TNF Signaling	Crocin	In vitro	Exposure to crocin lowers inflammatory cytokines including TNF-α and IL-1β. Crocin dramatically suppresses cancer cell growth. Crocin reduces the expression of protein kinase C theta (PRKCQ), a regulator of NF-κB activation, promoting apoptosis and suppressing cell growth. Crocin reduces PRKCQ expression, inhibiting the NF-κB pathway that promotes cancer cell growth.	MDA-MB-231, MDA-MB-468, BT-549, and MCF-7, and breast epithelial cell line MCF-10A	(Xu et al., 2022)
TNF Signaling	Chrysophanol	In vitro	Chrysophanol targets NF-kB/Bcl-2 signaling to activate caspase-3 and PARP and suppress breast cancer cell growth. Chysophanol also regulates cell cycle proteins by lowering cyclin D1 and cyclin E and raising p27 mRNA and protein. Additionally, chrysophanol boosted apoptosis and reduced NF-κB activation.	MCF-7 and MDA-MB-231	(Ren et al., 2018)
TNF Signaling	Sanguinarine	In vitro	Research indicates that inhibiting TNF-α-induced signaling pathways in triple-negative breast cancer (TNBC) cells by reducing CCL2 expression is crucial for tumor angiogenesis and dissemination.	MDA-MB- 231 and MDA-MB-468 cells	(Messeha et al., 2022)
TNF Signaling	Rosmaniric Acid	In vitro	RA inhibits the NF-κB pathway, resulting in reduced release of pro-inflammatory cytokines. Inhibited NF-κB activation lowers VEGF expression, linked to breast cancer.	Female Swiss Albino Mice	(Wang et al., 2015)
TNF Signaling	Oridonin	In vitro	Oridonin reduces development of breast cancer by lowering TNF-α and IL-10 levels, which contribute to its etiology. Oridonin could potentially decrease breast cancer cell growth by drastically inhibiting TNF-α and IL-10, as shown by molecular docking studies.	MCF-7 cells	(Y. Zhao et al., 2021)
TNF Signaling	Honokiol	In vitro	Honokiol synergistically induces breast cancer cell death. Honokiol effectively inhibits TNF-α, IKK, and JNK activation responsible for reducing Nur77 expression produced by TNF-α.	MCF-7 and MDA-MB-231	(Xie et al., 2016)

Table 3
Role of Phytochemicals in the MAPK/ERK Pathway in Breast Cancer.

Target	Compunds	Types of Study	Mechanism of action	Cell line(s)/animal model(s)	References
MAPK/ ERK	Curcumin	In Vitro	Curcumin has demonstrated its ability to inhibit the phosphorylation of ERK 1/2 and p38 MAPK, which are first activated by TGF (a growth factor). This inhibition occurs by preventing TGF from binding to its receptor, which in turn prevents the stimulation of tyrosine phosphorylation of ERK1/2.	*Cell line* MDA-MB-231	(Farghadani and Naidu, 2021)
MAPK/ ERK	Sulforaphane	In Vitro	Sulforaphane can bind ARAF, BRAF, and CRAF to restraining their phosphorylation, forming three bonds with CRAF and targeting serine/ threonine RAF to stop ERK signaling and form actin stress fibers to prevent breast cancer cell migration.	*Cell line* TNBC (*Triple Negative Breast Cancer*)	(Zhang et al., 2022)
MAPK/ ERK	Kaempferol	In vitro	Kaempferol activates ERK by phosphorylating MEK1, a kinase involved in pro-apoptosis. ERK then interacts with transcription factors to regulate genes involved in apoptosis and proliferation.	*Cell line* MDA-MB-231 and *Cell line* MCF-7	(Almatroudi et al., 2023)
MAPK/ ERK	α-mangostin	In-Vitro	Inducing c-Raf dephosphorylation at Ser259 activates MEK1 and MEK2, which activate ERK ½, promoting pro-apoptosis and reducing transcription factors like NF-κB p65 and c-Rel expression, inhibiting proliferation and inflammation.	MDA-MB-468, AU565, SKBR3 and T47D	(McCubrey et al., 2007)
MAPK/ ERK	Silymarin	In-Vitro	Silymarin inhibits breast cancer cell proliferation and promotes apoptosis. MAPK signaling increased p-JNK expression in MDA MB 231 and MCF 7 cells, which can induce apoptosis and inhibit cancer cell proliferation, and decreased p-ERK1/2 expression by inhibiting RAS and RAF phosphorylation, which prevents ERK1/2 from localizing in the nucleus and interacting with transcription factors.	MDA-MB 231 dan MCF-7 cells	(Kim et al., 2021)
MAPK/ ERK	Benzyl Isothiocyanate (BIC)	In-Vitro	BIC hinders breast cancer growth by enhancing ERK1/2 pathway phosphorylation of MAPKK and MAPK (ERK ½), which interacts with p53, the tumor protein. Increased ERK phosphorylation modulates p53, suppressing breast cancer development. BITC inhibits breast cancer growth via boosting ERK phosphorylation and p53 gene expression.	MCF-7 cells	(Hu et al., 2019)
MAPK/ ERK	Celastrol	In-Vitro	Celastrol prevents the dimerization of EGFR (Epidermal Growth Factor Receptor) with the EGF mitogen, which activates and phosphorylates MEK, which is localized and interacts with growth and transcription factors, including AREG. Celastrol reduces AREG expression, which prevents breast cancer cell proliferation.	T47D, ZR75–1, HCC1143, and HCC1806 cells	(Lin et al., 2021)
MAPK/ ERK	Flavopiridol	In-Vitro	Reduces ERK phosphorylation on fibronectin substrates, affecting other MAPK pathways including p38. Reduced phosphorylation prevents MEK from becoming localized ERK1/2 and is connected with growth factors that cause cancer cell proliferation, suppressing cancer cell proliferation. Research shows flavopiridol inhibits ERK.	MCF-7 and T-47D cells	(Martínez-Limón et al., 2020)
MAPK/ ERK	Quercetin	In-Vitro	Quercetin increases miR-146a expression, which regulates proliferation and apoptosis. This regulates the expression of cleaved caspase-3 when ERK1/2 interacts with transcription factors in the nucleus, causing apoptosis. MiR-146a also affects MEK phosphorylation and decreases NF-κB expression.	MDA-MB-231 *and MCF-7*	(Maugeri et al., 2023)
MAPK/ ERK	Fisetin	In-Vitro	Fisetin has been shown to reduce the expression of MMP-9 (Metalloproteinase-9), which prevents breast cancer cell migration. Reducing ERK1/2 phosphorylation can prevent interactions with transcription factors and enzymes in the nucleus, proving that Fisetin may be an anti-proliferative agent.	*Cell line* TNBC (*Triple Negative Breast Cancer*) and MDA-MB-468 cells	(Rahmani et al., 2022)
MAPK/ ERK	Nobiletin	In-Vitro	Nobiletin inhibits cancer growth by activating the p38 protein kinase, which regulates the apoptosis pathway in cells. This is shown by its ability to stimulate the phosphorylation of the MAPK pathway protein kinase, which interacts with MMP genes (MMP-9) via AP −1 (transcription factor) by binding to its promoter.	MCF-7 cells	(Ashrafizadeh et al., 2020b)
MAPK/ ERK	Gallic acid	In-Vitro	Galiic acid inhibits cancer by phosphorylating ERK1/2, JNK, and p38, allowing ERK ½ to connect with c-jun (AP-1) and bind to the promoter of Caspase-9 and Caspase-3 genes, causing apoptosis in cells. Either by activating p38, which phosphorylates p53 and increases ROS to limit cancer cell motility and induce death.	TNBC HCC1806 and MDA-MB-468 cells	(Lin et al., 2022)
MAPK/ ERK	*Cis*-Guggulsterone	In-Vitro	AP-1-regulated MAPK signaling suppresses MMP-9 gene expression. Cis-guggulsterone inhibits the binding of ERK/JNK/p38 kinase to AP-1 by blocking c-Fos, c-Jun activation, so the activator protein cannot control MMP 9 in cancer cell proliferation.	MCF-7 cells	(Mittelstadt and Patel, 2012)
MAPK/ ERK	Delphinidin	In-Vitro	Demonstrates promise for the ERK 1/2 pathway, reducing MEK/ MAPKK phosphorylation to limit ERK ½ activation, controlling proliferation genes (MMP-9), and preventing signaling. ERK ½ regulates apoptosis and anti-migration in HCC1806 and MDA468 TNBC cells.	TNBC HCC1806, MDA231, MDA468, SKBR3, MDA453, BT474 and MCF-7 cells	(Martin-Vega and Cobb, 2023)
MAPK/ ERK	Chrysosplenol d	In-Vitro	Stimulates the phosphorylation of threonine-202/tyrosine-204, which affects GTP-RAS, which activates the RAF/MEK kinase and activates ERK1/2, which localizes in the nucleus, binds AP-1, and regulates the Caspease 8 gene, which induces pro-apoptosis in cancer cells and increases lysosome size and number, which activate In TNBC cancer cells, boosting ERK 1/2 activity inhibits mitochondrial respiration, induces membrane permeability, and induces cytochrome c.	TNBC and MDA-MB-231 cells	(Olea-Flores et al., 2019)

(*continued on next page*)

Table 3 (*continued*)

Target	Compunds	Types of Study	Mechanism of action	Cell line(s)/animal model(s)	References
MAPK/ ERK	Timosaponin AIII (TAIII)	In-Vitro	TAIII activates apoptosis and induces G2 cell cycle suppression by phosphorylating MAPK p-38, addressing G2/M cell cycle arrest in cancer cells and accelerating cell aging. MAPK signaling also phosphorylates Ser1981, which regulates the p53 gene, which suppresses tumor development and promotes breast cancer cell pro-apoptosis.	MDA-MB-231 and MCF-7 cells	(Zhang et al., 2020)

Table 4
Role of Phytochemicals in the PI3K/AKT/mTOR Pathway in Breast Cancer.

Target	Compunds	Types of Study	Mechanism of action	Cell line(s)/animal model(s)
PI3/Akt/ mTOR	Curcumin	In Vitro	In MDA-MB-231 cells, curcumin reduced Akt phosphorylation time- and dose-dependently. Curcumin had a more complex influence on Akt phosphorylation in MCF-7 cells. Lower curcumin concentrations promoted Akt activation, while greater quantities decreased Akt phosphorylation.	MCF-7 and MDA-MB-231 cells
PI3/Akt/ mTOR	Luteolin	In Vitro	Luteolin dramatically lowered MCF-7 IGF-1R and IGF-1-dependent Akt phosphorylation without changing ERK. Luteolin delays cell cycle and causes apoptosis in breast cancer cells via inhibiting PI3K/Akt and activating FOXO3a.	MCF-7 and MDA-MB-231 cells
PI3/Akt/ mTOR	Delphinilin	In Vitro	Delphinidin dramatically reduced HER2, Akt, and Erk2 phosphorylation, inhibiting HER2 signaling. Delphinidin inhibits Erk2 phosphorylation and HER2 signaling in breast cancer cells that overexpress HERS2 and triple-negative breast cancer cells.	Triple-negative breast cancer cells.
PI3/Akt/ mTOR	Isorhamnetin	In Vitro	Isorhamnetin inhibits the PI3K/Akt/mTOR pathway in breast cancer, reducing cell proliferation and arresting cell cycle in G2/M.	S-605,240 (S1410) and nocodazole
PI3/Akt/ mTOR	Epigallocationchin-3-Gallate	In Vitro	Apoptosis is induced by epigallocatechin-3-gallate inhibiting PI3K/Akt and MEK/ERK signaling pathways in T47D human breast cancer cells.	T47D cells.
PI3/Akt/ mTOR	Piperine	In Silico	Piperine enhanced the protein expression of Bax, Bad, Cyto C, PARP cleavage, and caspase-3 and decreased Bcl-2, Bcl-xl, PI3k, and PAkt. Piperine partially inhibited the Akt/mTOR/MMP-9 signaling pathway, preventing DU145 cell metastasis.	Ligand Proteins
PI3/Akt/ mTOR	Eugenol	In Silico	Eugenol topically can alleviate or reduce breast precancerous situations by inducing apoptosis and arresting the cell cycle in S phase via the HER2/PI3K-AKT pathway.	Ligand Proteins
PI3/Akt/ mTOR	Celastrol	In Vitro	Celastrol inhibits ubiquitin-dependent mTOR phosphorylation to inhibit mTOR signaling.	MG132 cells
PI3/Akt/ mTOR	Apigenin	In Vitro	Apigenin blocks the PI3K/Akt pathway to stop breast cancer cell growth.	MDA-MB-231 cells
PI3/Akt/ mTOR	Berberin	In Vitro	Berberine inhibits Cyclin D and Cyclin E, reduces HER2 expression via the PI3K/AKT pathway, and decreases luminal B cell VEGFR2, MMP2, and MMP9 expression via the AKT/ERK pathway.	MDA-MB-468 cells
PI3/Akt/ mTOR	Silibinin	In Vitro	Silibinin inhibits AKT and Mitogen-activated protein kinases and arrests cell cycles, among other anticancer actions. EGFR mRNA, a key component of the PAM signaling pathway, and downstream genes like PI3K, AKT-1, PTEN, and mTOR mRNA were lowered by silibinin in cancer cells. Blocking effect	MCF-7 cells
PI3/Akt/ mTOR	Genistein	In Vitro	Genestein inhibits MCF-7 breast cancer Akt. Suppressing apoptosis with PI3K/Akt pathway activation is known to promote cell survival. By inhibiting the PI3K/Akt signaling pathway, genistein reduces downstream target expression and breast cancer cell proliferation.	MCF-7 cells
PI3/Akt/ mTOR	Kaempferol	In Vitro	HUVECs' PI3K/AKT/mTOR signaling and AKT kinase activity are altered by kaempferol. The concentration-dependent decrease in PI3K protein, AKT, and mTOR phosphorylation was significant. PI3K/AKT/mTOR signaling helps kaempferol promote angiogenic effects in VEGF-stimulated HUVECs.	Cell Culture HUVECs
PI3/Akt/ mTOR	Quercetin-3-metil eter	In Vitro	Quercetin-3-methyl ether dramatically reduced phosphorylated PI3K, AKT, and mTOR in MCF-7 and T47D breast cancer cells. This drug effectively inhibited IGF-1-induced PI3K/Akt/mTOR signaling pathway activation and phosphorylation of PI3K, Akt, and GSK-3β in breast cancer cells. There is growing evidence that the PI3K/Akt pathway and Notch signaling combine to cause cancer.	MCF-7, T47D and MDA-MB-23
PI3/Akt/ mTOR	Calycosin	In Vitro	The ERβ-mediated PI3K/Akt signaling impacts the activity of poly(ADP-ribose) polymerase 1 and caspase-3 In MG-63 OS cells, calycosin suppresses proliferation and causes cell death by inhibiting the ERβ-dependent PI3K/Akt pathway.	MG-63 cells
PI3/Akt/ mTOR	Eupafolin	In Vitro	Eupafolin dramatically decreased p-PI3K, Akt, and mTOR protein levels. This chemical modulates the PI3K/Akt/mTOR pathway to impact EO771 cell proliferation and death.	EO771 cells
PI3/Akt/ mTOR	Cardamonin	In Vitro	Cardamonin inhibits mTOR and S6K1 in breast cancer cells to regulate metabolism. Unlike rapamycin, cardamonin suppresses mTOR without FKBP12. Previously, cardamonin reduced Raptor protein levels to block the mTORC1 signaling pathway.	MCF-7 Cells
PI3/Akt/ mTOR	Eriodictyol	In Vitro	Eriodictyol reduced PI3K/Akt signaling pathway and caused a decrease in circ_0007503 in breast cancer cells and carcinogenesis ($P < 0.01$). Eriodictyol's cytotoxic effects and PI3K/Akt pathway inhibition in breast cancer cells were considerably reduced when a plasmid overexpressing circ_0007503 was transfected.	MCF-7, MDA-MB-231 and MCF10A cells

internal state of the cell, particularly malfunctioning of the mitochondria (Gnesutta and Minden, 2003). Dysfunctions in mitochondria lead to the liberation of intramembrane proteins, such as cytochrome c, which subsequently initiates the activation of caspase-9. Caspase-3, as the primary executor caspase, has a pivotal function in starting and executing the last stage of apoptosis (Situmorang et al., 2024). This mechanism is crucial for maintaining cellular balance and has substantial significance in the development of therapeutic methods for breast cancer. Comprehensive knowledge of the apoptotic pathway and the function of phytochemical substances is crucial for the advancement of more potent cancer treatments. The well-established anti-inflammatory and anti-cancer characteristics of this substance, together with its

minimal side effects and low toxicity towards healthy cells, make it a highly appealing option for the treatment of breast cancer (Shrihastini et al., 2021).

Phytochemicals such as curcumin, resveratrol, epigallocatechin gallate (EGCG), genistein, quercetin, kaempferol, apigenin, luteolin, sulforaphane, and thymoquinone have demonstrated the ability to inhibit breast cancer by affecting several signal transduction pathways, genes, and gene products (Younas et al., 2018). These phytochemicals have the ability to cause programmed cell death and decrease the growth of breast cancer cells by affecting several targets. Table 5 provides a detailed account of the function of several phytochemical substances in the apoptotic pathway specifically related to breast cancer.

7. Role of nanoparticles in breast cancer

Leveraging nanotechnology to deliver phytochemical combinations in breast cancer treatment offers improved therapeutic precision and effectiveness. Nanoparticles protect these compounds from enzymatic degradation, boost their absorption, and enhance stability by preventing oxidative and hydrolytic damage during storage and transport (Li et al., 2015). Nanoparticles can be engineered to selectively target breast cancer cells by altering their surface with ligands that bind to specific markers on cancer cells. Nanoparticles selectively target cancer cells, minimizing harm to healthy cells and mitigating undesirable side effects. Nanoparticles can be precisely engineered to deliver phytochemicals in a controlled and sustained manner within the tumor microenvironment, ensuring therapeutic levels are maintained over time. They induce apoptosis in cancer cells through multiple mechanisms, most notably via reactive oxygen species (ROS) generation, as well as protein regulation, immune modulation, transcriptional inhibition, and targeted cytotoxicity, often working in interconnected ways to trigger cell death. Additionally, nanoparticles play a vital role in activating the immune system against cancer by encapsulating tumor antigens and adjuvants, attaching targeting ligands to their surface, and stimulating dendritic cells (DCs). This activation leads to antigen presentation to T cells, which then release cytotoxic molecules such as Perforin-1, granzyme B, and IFN-γ, promoting cancer cell death and further antigen release that amplifies immune response within the tumor microenvironment (Fig. 5).

Certain nanoparticles can be engineered to react to particular conditions, such as the acidic pH found in the tumor microenvironment (Raju et al., 2022). This allows them to selectively release the medicine only at the site of the tumor. Nanoparticles have the ability to transport numerous phytochemicals at the same time, taking advantage of the combined effects between these compounds to enhance the efficiency of treatments (Chavda et al., 2023). For instance, the synergistic use of quercetin and curcumin yields more potent anticancer effects compared to their individual administration. Various cellular signaling pathways in cancer cells can be targeted by different combinations of phytochemicals, hence boosting the overall anti-cancer effect (Talib et al., 2022). By bypass the efflux pumps utilized by cancer cells for drug expulsion, it can be enhancing drug accumulation within cancer cells. Utilizing various combinations of phytochemicals that specifically target numerous resistance mechanisms can potentially decrease the probability of cancer cells acquiring resistance to therapy (Talib et al., 2021). Nanoparticles containing phytochemicals like resveratrol and curcumin exhibit potent antioxidant properties, effectively mitigating oxidative harm and impeding the proliferation of cancerous cells (Zhang et al., 2015).

Genistein and berberine also have the ability to trigger apoptosis in breast cancer cells, hence decreasing the development of cancerous cells (G. Kumar et al., 2023). Phytochemicals like sulforaphane and limonene have the ability to decrease chronic inflammation, a significant contributing component in the progression of cancer (Nair et al., 2010). Epigallocatechin gallate (EGCG), can hinder the development of new blood vessels that are essential for the growth of tumors (Yıldırım et al., 2023). Studies indicate that nanoparticles containing curcumin have the ability to decrease the development and spread of breast cancer cells by enhancing the availability and anticancer properties of curcumin (Sohn et al., 2021). Combination of resveratrol and quercetin exhibit improved effectiveness against cancer by specifically targeting multiple signaling pathways and promoting apoptosis (Inchingolo et al., 2022). Another study reported that phytochemical-loaded liposomal nanoparticles have been effectively employed to transport medications to breast cancer cells, resulting in enhanced treatment effectiveness in preclinical models. Prior to clinical application, it is crucial to assess the toxicity and safety of nanoparticles (Ganesan et al., 2021). Nanoparticles must be engineered to possess non-toxic properties and avoid inducing severe adverse reactions. Prior to its application in patient treatment, nanoparticles containing phytochemicals must undergo meticulous clinical trials and secure approval from regulatory organizations (Xuan et al., 2023).

For example, natural polysaccharide-based nanoparticles, particularly dextran and its derivatives, have gained attention for their biocompatibility, biodegradability, and modifiability, enhancing the efficacy of anticancer drugs in breast cancer treatment and imaging, while minimizing toxicity (Khan et al., 2023). Additionally, mitochondria-targeting nanoparticles, such as functionalized liposomes, are being explored to deliver therapies directly to these critical organelles involved in cancer metabolism, offering a novel and precise approach for treating breast and other cancers (Khan et al., 2024).

8. Challenges and limitations

Despite their promising potential in breast cancer therapy, the clinical translation of phytochemicals remains constrained by significant limitations and challenges. A major hurdle lies in their poor bioavailability and unfavorable pharmacokinetic profiles. Compounds such as curcumin, resveratrol, and epigallocatechin-3-gallate (EGCG) often suffer from low solubility, rapid metabolic breakdown, and limited systemic absorption, resulting in subtherapeutic tumor concentrations and reduced in vivo efficacy. For example, curcumin's modulation of the PI3K/Akt pathway varies with dose and cell type, underscoring the difficulty of achieving consistent therapeutic levels. Inter-patient variability further complicates clinical application. Genetic polymorphisms, metabolic differences, and tumor heterogeneity can significantly alter pharmacodynamics and molecular responses. Studies have shown that compounds like genistein and EGCG can modulate apoptotic and proliferative pathways differently depending on patient-specific factors and cancer subtypes, making dose optimization and outcome prediction challenging. The multitarget nature of phytochemicals is a double-edged sword. While their ability to act on pathways such as NF-κB, PI3K/Akt/mTOR, and MAPK/ERK can enhance therapeutic efficacy, it also increases the risk of off-target effects, drug interactions, and unpredictable cellular responses. This highlights the need for more detailed mechanistic research and safety profiling. Translational progress is also hampered by limitations in clinical trial design. Many studies remain small-scale or preliminary, lacking standardized formulations, consistent dosing regimens, and long-term safety data that weaken the evidence base for clinical recommendations. Large, well-structured randomized controlled trials are essential to validate efficacy, determine optimal dosing, and establish safety profiles.

Regulatory and quality control issues present another barrier. Variations in plant sources, extraction techniques, and formulation processes lead to inconsistent phytochemical content, making standardization and reproducibility difficult. Without robust manufacturing standards and regulatory guidelines, clinical adoption will remain limited. Overcoming these barriers will require advanced drug delivery technologies such as nanoformulations to improve bioavailability and tumor targeting, as well as personalized treatment strategies that account for molecular and metabolic differences among patients. Establishing standardized preparations, coupled with rigorous clinical evaluation,

Table 5
Role of Phytochemicals in the Apoptotic Pathway in Breast Cancer.

Target	Compunds	Types of Study	Mechanism of action	Cell line(s)/animal model (s)	References
Apoptosis	CurCumin	In vitro	Curcumin induces apoptosis in MCF-7 cells through increasing the expression of caspase-3 and caspase-9. Upregulation of Bax and downregulation of Bcl-2 expression in MDA-MB-231 cells, leading to growth inhibition and induction of apoptosis. Inhibition of fatty acid synthase by curcumin also results in apoptosis of breast cancer cells	MDA-MB-361 and MCF7 cells	(Younas et al., 2018)
Apoptosis	Epigallo catechin gallate (EGCG)	In vitro	EGCG stimulates p53, which raises pro-apoptotic proteins and reduces Bcl-2, killing breast cancer cells and decreasing tumor growth.	MCF-7 cells	(Marín et al., 2023)
Apoptosis	Genistein	In vitro	Genistein increases Bax expression to promote apoptosis in breast cancer cells and p21WAF1 to regulate the cell cycle in MDA-MB-231.	MDA-MB-231 cells	(Sharifi-Rad et al., 2021)
Apoptosis	Resvera trol	In vivo	Resveratrol promotes breast cancer apoptosis by modulating Bcl-2 and Bax expression, activating caspases, suppressing NF-kB, and influencing PI3K/Akt and MAPK activity.	DMBA-induced rats	(Jang et al., 2022)
Apoptosis	Kuersetin	In vitro	Apoptosis is induced by decreased Bcl-2 expression and increased Bax expression. In addition, inhibiting the PI3K-Akt pathway, which is crucial to cell survival and growth, might enhance pro-apoptotic effects and facilitate programmed cell death.	MCF-7, HCC1937, SK-Br3, 4T1, MDA-MB-231 cells	(Qian et al., 2022)
Apoptosis	Kaempferol	In vitro	The G2/M phase of the cell cycle is stopped by kaempferol, which inhibits breast cancer cell development and increases cell death.	MDA-MB-453 cells	(Almatroudi et al., 2023)
Apoptosis	Apigenin	In vivo	Apigenin activates caspase-8, −9, and −3 and cleaves ADP-ribose and PARP, causing apoptosis.	DMBA-induced rats	(Seo et al., 2012)
Apoptosis	Luteolin	In vitro	In MCF-7 cells, luteolin induces forkhead box O3 (FOXO3a) and DNA damage to decrease PI3K/Akt phosphorylation and initiate the mitochondrial apoptotic cascade.	MCF-7 cells	(Raina et al., 2021)
Apoptosis	Sulforaphane	In vitro	Sulforaphane activates PARP, caspase-3, and caspase-9 cleavage but not caspase-8, lowers Bcl-2 expression, and releases cytochrome c from mitochondria to the cytoplasm.	MDA-MB-468 cells	(Lin et al., 2017)
Apoptosis	Thymoquinone	In vitro	Thymoquinone increases ROS, inhibits PI3K/Akt, activates p53, and caspase, and promotes apoptosis in MDA-MB-468 and T47D breast cancer cells.	MDA-MB-468, T47D cells	(Asaduzzaman Khan et al., 2017)
Apoptosis	Beta-carotene	In vitro	Beta carotene induces apoptosis via PPAR-γ activation and ROS generation. Beta carotene activates PPAR-γ, leading to enhanced production of apoptosis-regulating genes. Increased ROS production from PPAR-γ activation can lead to oxidative stress, which triggers the apoptotic pathway. In breast cancer cells, PPAR-γ activation and elevated ROS generate an environment that promotes programmed cell death.	MCF-7 cells	(Cui et al., 2007)
Apoptosis	Pterostilbene	In vivo	Pterostilbene prevents tumor microenvironment metastatic cancer stem cell development. This is achieved via reducing NF-κB activity, which decreases cancer cell survival genes, and modulating microRNA 448, which promotes pro-apoptotic gene expression. This combination induces breast cancer cell apoptosis, stopping cancer growth.	MDA-MB-231 carrier NOD/SCID mice	(Shin et al., 2020)
Apoptosis	Myricetin	In vitro	Myricetin reduces matrix metalloproteinase (MMP) enzyme production and downregulates metastasis-promoting signaling pathways. Programmed death reduces cancer cells' ability to spread and invade other tissues.	MCF-7, MDA Mb-231 cells	(Felice et al., 2022)
Apoptosis	Gingerol	In vitro	Gingerol releases cytochrome c from mitochondria to the cytosol, activating caspase-9 and caspase-3 and initiating intrinsic apoptosis. Gingerol blocked the NF-κB pathway in MDA-MB-231 cells, reducing anti-apoptotic gene expression and cancer cell proliferation. Gingerol inhibited the cancer-promoting PI3K/Akt pathway in MCF-7 cells. Apoptosis is enhanced by inhibiting this mechanism, which decreases cancer cell growth and survival signals.	MDA-MB-231, MCF-7 cells	(Choi et al., 2022)
Apoptosis	Ginsenosida	In vitro	Ginsenoside causes mitochondrial apoptosis. This chemical reduces cancer cell proliferation by inhibiting ERK and Akt. Ginsenoside also reduces apoptosis by inhibiting p53 mutation and NF-κB activation. This inhibition enhances mitochondrial membrane permeability, releasing cytochrome c and activating caspases to kill cells and limit cancer growth.	MDA-MB 231 cells	(Li et al., 2023)
Apoptosis	Isoliquiritigenin	In vitro	Isoliquiritigenin reduces VEGF expression by targeting HIF-1α for proteasomal degradation. This suppresses VEGF/VEGFR-2, which forms new blood vessels (neoangiogenesis) to nourish the tumor. Tumor growth is suppressed and more cancer cells undergo apoptosis, preventing breast cancer.	MCF-7MDA MB-231HUVEC cells	(Wang et al., 2013)
Apoptosis	α-Mangostin	In vitro	α-Mangostin causes organized cancer cell killing. This chemical also decreases Bcl-2 and enhances Bax. α-Mangostin activates the JNK pathway, controlling apoptosis in response to cellular stress. Finally, α-Mangostin prevents NF-κB activation, which can lead to breast cancer cell apoptosis resistance.	SKBR3, MCF-7, MDA-MB-231 cells	(Lee et al., 2017)
Apoptosis	Allicin	In vitro	Allicin modulates the regulation of certain genes in breast cancer cells. Allicin enhances the expression of A1BG and THBS1 in MDA-MB-231 cells. These proteins are involved in suppressing the development of cancer cells by disrupting angiogenesis and cell-cell interactions. In contrast, allicin induced a downregulation of A1BG, THBS1, and TPM4 expression in MCF-7 cells, demonstrating its capacity to impede cellular proliferation and metastasis.	MCF-7, MD-MBA-231 cells	(Maitisha et al., 2021)
Apoptosis	Fisetin	In vitro	Fisetin regulates the PI3 kinase/AKT signaling pathway, a crucial system involved in controlling cell growth and survival. Fisetin has the ability to	MCF-7 cells	(Hassan et al., 2022)

(*continued on next page*)

Table 5 (*continued*)

Target	Compunds	Types of Study	Mechanism of action	Cell line(s)/animal model (s)	References
Apoptosis	Lycopene	In vitro	modify signaling in this route, which results in the inhibition of cell growth and the promotion of apoptosis, also known as programmed cell death. Lycopene mitigates oxidative stress, a process that can inflict harm on DNA and initiate the development of cancer. Lycopene upregulates the transcription of pro-apoptotic genes, including Bax and P53, while downregulating the expression of anti-apoptotic genes, such as Bcl-2. This leads to the liberation of cytochrome c from mitochondria and the activation of caspase-9 and caspase-3, which are enzymes involved in the regulation of apoptosis. Furthermore, lycopene hinders the activity of the transcription factor NF-κB, which is involved in the growth and survival of cells, therefore promoting the demise of cancer cells.	MCF-7 cells	(Trejo-Solís et al., 2013)

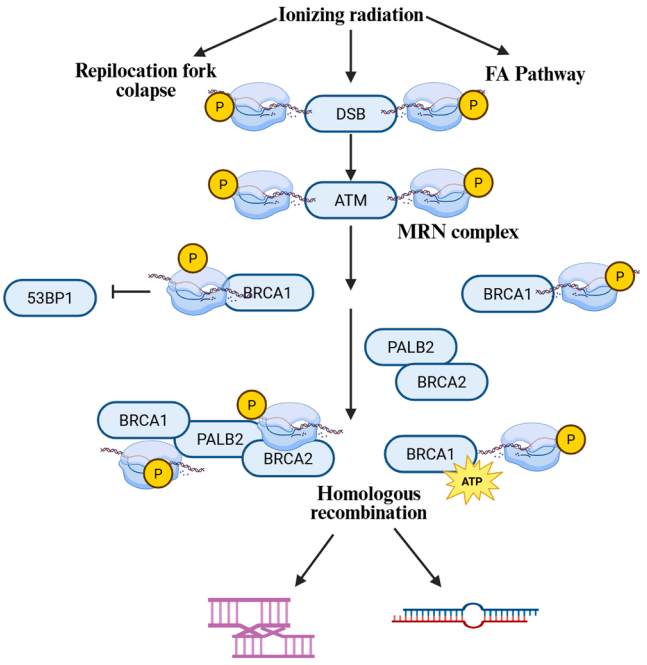

Fig. 5. The encapsulation of antigens and immunostimulatory molecules within nanoparticles, along with their efficient distribution by antigen-presenting cells (APCs), can greatly enhance B-cell responses as compared to using soluble antigens and adjuvants.

will be critical to unlocking the full therapeutic potential of phytochemicals in breast cancer management.

9. Discussion

A deep understanding of the molecular signaling pathways driving breast cancer is essential for uncovering the mechanisms that govern tumor initiation, growth, and metastasis. Such insights not only reveal the biological underpinnings of the disease but also open opportunities for developing more precise therapeutic strategies, including the use of phytochemicals. Mapping these pathways allows researchers to identify highly specific molecular targets, enabling interventions tailored to the tumor's profile—much like the use of trastuzumab to inhibit the HER2 pathway in HER2-positive breast cancer. Targeted approaches such as kinase inhibitors against EGFR or PI3K exemplify how pathway knowledge translates into effective drug design.

Understanding these networks is also critical for addressing treatment resistance, a frequent challenge in oncology. Cancer cells can bypass inhibited pathways by activating compensatory routes for instance, PI3K blockade may lead to MAPK activation. By elucidating these resistance mechanisms, researchers can design combination therapies or alternative inhibitors to outmaneuver tumor adaptation. Moreover, decoding pathway alterations enables the creation of a patient's molecular profile, which guides optimal therapy selection, minimizes adverse effects, and aids in prognosis prediction.

Phytochemicals such as curcumin, genistein, and EGCG have demonstrated the ability to selectively interfere with cancer-promoting pathways. Curcumin and genistein induce apoptosis through the p53 and Bcl-2 pathways, while EGCG inhibits the Akt pathway to suppress tumor growth. Compounds like sulforaphane and curcumin also disrupt angiogenesis by targeting VEGF signaling, cutting off the tumor's blood supply. In many cases, phytochemicals enhance conventional treatments like curcumin combined with chemotherapy can improve cancer cell killing and reduce drug resistance, while also protecting healthy cells, as seen with resveratrol's antioxidant protection during chemotherapy.

Advances in nanotechnology further enhance the potential of phytochemicals by improving their bioavailability, specificity, and controlled release at tumor sites. This targeted delivery maximizes local therapeutic effects while minimizing systemic toxicity. Key breast cancer pathways such as PI3K/Akt/mTOR, which regulates cell growth, proliferation, and survival, remain central to these strategies, as their dysregulation is a hallmark of tumor progression and a prime target for intervention.

10. Conclusion

Phytochemicals such as curcumin, genistein, resveratrol, and EGCG offer a unique advantage in breast cancer therapy by acting on multiple fronts. They influence key molecular pathways like PI3K/Akt/mTOR, MAPK/ERK, NF-κB, apoptotic, and estrogen receptor signaling to slow cancer growth, trigger cell death, block metastasis, and even help overcome drug resistance. Clinical studies are beginning to confirm these benefits, showing that phytochemicals can work alongside conventional treatments to improve outcomes, ease side effects, and influence important epigenetic changes. Bringing these plant-derived compounds into mainstream cancer care could lead to treatments that are not only more effective but also gentler on patients. To get there, we need carefully designed clinical trials to define safe and effective doses, understand how these compounds behave in the body, and evaluate their long-term benefits. Deeper insights into the molecular pathways they target will help us discover new treatment opportunities, tackle resistance, and personalize therapy. Combining phytochemicals with modern delivery technologies like nanocarriers may further boost their precision and potency, opening the door to safer, smarter, and more holistic breast cancer treatments.

AI statement

Artificial intelligence tools were used only to assist in the preparation of this manuscript. BioRender was utilized for creating scientific illustrations and graphical figures. QuillBot was used to improve sentence clarity and paraphrasing without altering the scientific meaning. Grammarly was employed to check for grammatical errors and

typographical consistency. The authors confirm that no AI tools were used for data analysis, result generation, or interpretation of scientific findings. All intellectual and scientific contributions were made by the authors.

Data availability

Data are available upon reasonable request from the corresponding author

CRediT authorship contribution statement

Putri cahaya Situmorang: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Data curation, Conceptualization. **Denny Satria:** Writing – review & editing, Writing – original draft, Visualization, Validation, Conceptualization. **Syafruddin Ilyas:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Kaniwa Berliani:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Nursahara Pasaribu:** Writing – review & editing, Software, Resources, Funding acquisition. **Nik Mohd Afizan Nik Abd Rahman:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Investigation. **Alexander Patera Nugraha:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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