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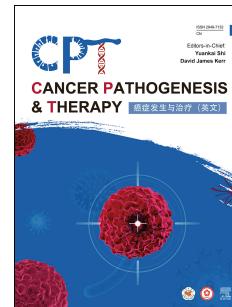
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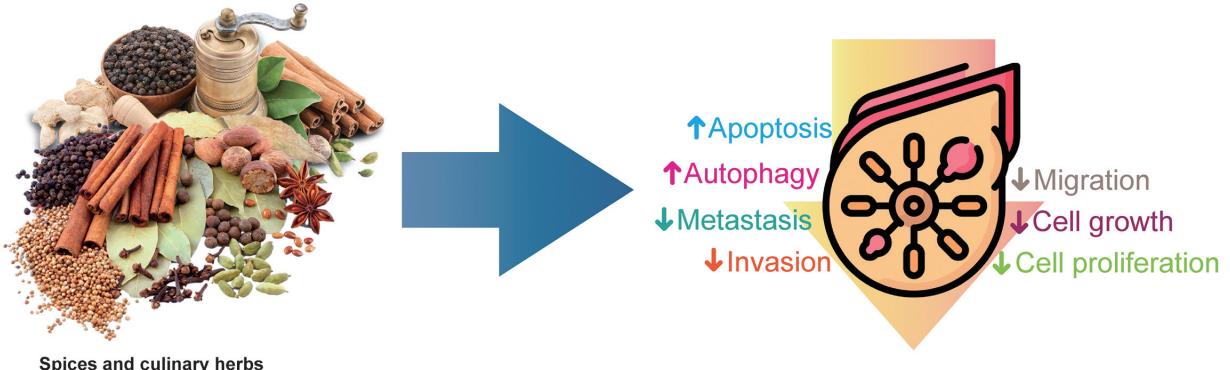
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**Spices and culinary herbs**

Turmeric • Garlic • Ginger • Clove • Black pepper • Onion • Red pepper • Fenugreek • Fennel • Rosemary • Coriander
 Cumin • True cardamom • Caraway • Nutmeg • Parsley • Chili pepper • Ajwain • Peppermint • Basil
 Anise • Star anise • Mustard • Oregano • True cinnamon

This review centers on investigating the chemopreventive and therapeutic impacts, as well as the mechanisms of action, of different spices and culinary herbs in combating breast cancer.

Review Article

Spices and culinary herbs for the prevention and treatment of breast cancer: A comprehensive review with mechanistic insights

Md. Liakot Ali^{1,2}, Fabiha Noushin^{1,2}, Qurratul Ain Sadia^{1,2}, Afroz Fathema Metu^{1,2}, Jannatul Naima Meem^{1,2}, Md. Tanvir Chowdhury^{1,2}, Md. Hossain Rasel^{1,2}, Khurshida Jahan Suma^{1,2}, Md. Abdul Alim^{1,2}, Muhammad Abdul Jalil^{1,2}, Md. Jahirul Islam Mamun^{1,2}, Md. Mahmudul Hasan^{1,2}, Neamul Hoque^{1,2}, Eva Azme^{1,2}

¹Department of Pharmacy, University of Chittagong, Chattogram 4331, Bangladesh;

²Department of Cancer Therapeutics, Research Center of Natural Products, Chattogram 4331, Bangladesh.

Correspondence to: Md. Liakot Ali, Department of Pharmacy, University of Chittagong, Chattogram 4331, Bangladesh

Department of Cancer Therapeutics, Research Center of Natural Products, Chattogram 4331, Bangladesh

E-Mail: liakotpranto@gmail.com

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Highlights

- Breast cancer is the most prevalent cancer among women globally
- Spices and culinary herbs demonstrate strong pharmacological activities against various diseases
- Spices and culinary herbs exhibit preventive and therapeutic effects against breast cancer
- Spices and culinary herbs are safe and effective and may serve as valuable additions in the treatment of breast cancer

Abstract

Breast cancer (BC) continues to be the primary malignant neoplasm affecting women. For many years, traditional approaches such as chemotherapy, hormone therapy, radiation, and surgical interventions have been employed to treat BC. However, these therapies often fall short due to considerable adverse effects and the development of multidrug resistance or tolerance. Spices and culinary herbs that have been utilized in culinary practices for millennia have also demonstrated therapeutic effects in traditional medicinal practices serving to both prevent and treat BC. This review aims to comprehensively explore the roles and underlying mechanisms through which spices and culinary herbs exert anti-BC properties. These natural ingredients exhibit diverse anti-BC effects that encompass diverse mechanisms, including the inhibition of BC cell proliferation, migration, metastasis, and angiogenesis, as well as the induction of cell cycle arrest and apoptosis. These actions are achieved by targeting signaling pathways such as phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR), notch signaling, Hedgehog signaling, nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), and Wingless/int (Wnt)/ β -catenin signaling pathways that are predominantly overexpressed in breast tumors or are exploited by them to promote cancer progression. Additionally, compounds such as curcumin, allicin, gingerol, zerumbone, diosgenin, capsaicin, piperine, quercetin, malabaricone C, eugenol, cardamomin, carnosol, cinnamaldehyde, sinigrin present in these spices and herbs may be more effective with reduced side effects against BC compared to conventional chemotherapeutic drugs. This review presents a concise overview of the potential contributions of spices, culinary herbs, and their potent bioactive constituents against BC, with particular emphasis on elucidating their mechanisms of action.

Keywords: Spice; Breast cancer; Antineoplastic agents; Phytochemicals; Complementary therapies

Introduction

Breast cancer (BC) accounts for the majority of cancer-related deaths among females globally and is the most frequently diagnosed type of cancer in women.^[1] In 2021, it was projected that over two million new cases of BC would be diagnosed globally, with the United States (US) alone accounting for >250,000 new cases. Moreover, mortality rates for men exhibited a dramatic increase compared to women in 2018, reaching 9.09% for men and 1.87% for women.^[2] BC is typically classified based on estrogen receptor (ER) status, with ER-positive types including Michigan Cancer Foundation-7 (MCF-7) as well as T47D cell lines, whereas MDA-MB-231, MDA-MB-453, MDA-MB-468, and SKBR3 cell lines are ER-negative. Molecular markers like progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) are also used to classify BC into distinct molecular subtypes, such as luminal A, luminal B, basal-like, and HER2-positive subtypes.^[3] Luminal A represents the most common subtype of BC, accounting for approximately 40% of all cases. Conversely, basal-like subtype also known as triple-negative breast cancer (TNBC), is the most aggressive form, typically affecting younger women.^[4] The designation “triple negative” indicates the absence of ER, PR, and HER2 receptors, thereby rendering hormone therapy less effective in its treatment.^[5] Non-genetic risk factors include age, obesity, hormone replacement therapy after menopause, chest radiation therapy, excessive alcohol consumption, not having children or not breastfeeding, exposure to diethylstilbestrol, use of birth control, and contraceptives.^[6] Genetic predispositions, such as mutations in the BC susceptibility genes *BRCA1* and *BRCA2*, account for 5%–10% of all BC cases.^[7] Current treatment options for early-stage BC include radiotherapy, surgical resection, hormone therapy, and adjuvant chemotherapy.^[8] Nevertheless, the presence of various subtypes characterized by unique pathologies complicates the treatment of this disease. Additionally, the emergence of therapy resistance, as well as considerable detrimental outcomes has diminished the effectiveness of these therapies.^[9] Therefore, the need for research on novel approaches for the prevention and treatment of BC that are more effective, with fewer side effects is crucial. Throughout history, people have utilized natural plant-based remedies to address a range of ailments, often yielding promising results.^[2] An expanding body of evidence, bolstered by numerous studies, affirms the feasibility of utilizing plant-derived extracts or compounds to target multiple cancer hallmarks for the treatment of BC.^[10] Therefore, further research is essential to discover natural remedies with enhanced chemopreventive and therapeutic properties, and greater tolerability, with the potential

to add significant value in combating BC. Such findings would constitute a valuable addition to the arsenal against this disease.

A spice is a fragrant or spicy plant-based substance used to enhance the flavor of food. Typically, dried seeds, fruits, roots, barks, or vegetables are primarily employed for their sensory appeal.^[11] A significant portion of scientific and commercial literature fail to differentiate between culinary herbs and spices, as some plants are categorized as both. However, an alternative definition provided by the US National Arboretum distinguishes spices as dried flavorings, often originating from tropical regions, while culinary herbs encompass fresh or dried leaves from plants used for flavoring in food preparation.^[12] Both spices and herbs serve to enhance the flavor of bland foods, stimulate appetite, and promote the secretion of gastric juices. Consequently, they are commonly regarded as food enhancers or additives, devoid of any medicinal properties.^[13] However, historical records reveal that herbs and spices were utilized as medicinal substances in ancient civilizations such as Egypt and Assyria. Furthermore, contemporary research suggests that they demonstrate a variety of beneficial characteristics such as anticancer, anti-inflammatory, antioxidant, and antimicrobial effects.^[14,15] A plethora of spices and culinary herbs exhibit anti-BC potential including turmeric (*Curcuma longa*), ginger (*Zingiber officinale*), clove (*Syzygium aromaticum*), fenugreek (*Trigonella foenum-graecum*), rosemary (*Salvia rosmarinus*) garlic (*Allium sativum*), coriander (*Coriandrum sativum*), onion (*Allium cepa*), black pepper (*Piper nigrum*), nutmeg (*Myristica fragrans*), and fennel (*Foeniculum vulgare*). These spices and herbs are believed to exert anti-BC effects by influencing various pathways, including rat sarcoma virus (Ras)/rapidly accelerated fibrosarcoma (Raf), mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR), Wingless/int (Wnt)/β-catenin, Hedgehog, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and Notch signaling pathways.^[16,17] Despite the existence of numerous studies indicating the chemopreventive and therapeutic effects of spices and culinary herbs regarding BC, a comprehensive and focused review that consolidates these research findings and outlines future research directions concerning the chemopreventive and therapeutic aspects of spices and culinary herbs along with their possible mechanism of action in relation to BC is lacking. Therefore, this review aims to provide a critical assessment encompassing a basic overview of BC pathophysiology, along with an examination of the existing experimental data

derived from *in vitro*, *in vivo*, and clinical trials regarding the chemopreventive and therapeutic potentials of spices and culinary herbs.

Brief Overview of Breast Cancer: From Initiation to Metastasis

BC typically begins with ductal hyperplasia, progressing to benign tumors, and potentially advancing to metastatic cancer under the influence of diverse carcinogens.^[2] BC is not a single entity, but rather encompasses a highly diverse array of diseases, making it particularly challenging to identify the precise initiating factors. Both environmental influences and genetic mutations have been implicated in the development of breast tumors. Research has confirmed that *BRCA1/2* germline mutations lead to early-onset BC.^[18] The primary models explaining BC initiation include the sporadic clonal evolution (SCE) model and the cancer stem cell (CSC) model.^[19] The SCE hypothesis proposes that tumor initiation occurs when a single cell undergoes multiple random mutations, granting it a selective growth advantage over neighboring normal cells. As the tumor develops, genetic instability and unregulated proliferation facilitate the generation of cells with further mutations, leading to the acquisition of new characteristics such as invasiveness, and resistance to apoptosis or therapy.^[20,21] The alternative CSC model suggests that a tiny fraction of tumor cells comprise CSCs with the ability to both self-renew endlessly and differentiate. Every type of tumor cell is produced by their self-renewal and differentiation processes. It is widely accepted that normal breast stem or progenitor cells give rise to CSCs.^[22] These two hypotheses are not mutually exclusive, and it was previously suggested that stem cells may undergo clonal evolution, creating a constantly evolving connection between both hypotheses.^[23]

BC progresses through specific pathological and clinical stages, beginning with ductal hyperproliferation and evolving into invasive and *in situ* carcinomas before ultimately progressing to metastatic disease.^[19] Two different models have been proposed for the ductal and lobular subtypes of BC. According to the traditional model of ductal type BC progression, neoplastic evolution begins in normal epithelium, develops into atypical ductal hyperplasia, ductal carcinoma *in situ*, and finally leads to invasive ductal carcinoma. The lobular BC model suggests a multi-step, sequential progression involving stages from normal epithelium, through atypical lobular hyperplasia, to lobular carcinoma *in situ*, ultimately leading to invasive lobular carcinoma.^[20] Hence, BC progresses sequentially through distinct stages, beginning with hyperproliferation of the epithelium and terminating with *in situ*, invasive, and metastatic carcinomas.^[24] When *in situ*

ductal carcinoma transforms into invasive ductal carcinoma, collapse of the basement membrane and myoepithelial cell layer is crucial.^[25] The tumor's microenvironment, which includes macrophages and the influence of the stroma, plays a critical role in the advancement of BC. Macrophages possess the ability to create a mutagenic inflammatory microenvironment that promotes angiogenesis and allows cancerous cells to evade the immune system.^[26]

For patients with BC, metastasis is the primary cause of mortality. BC can metastasize to the brain, liver, lung, and bone. The process of metastasis involves a series of sequential steps.^[6] Cells from the initial tumor locally infiltrate the surrounding host tissue, thereby initiating metastasis. This progresses until the tumor cells enter the blood or lymphatic circulation and begin to proliferate. The tumor cells travel through blood or lymphatic systems to distant organs.^[27] Cadherin, particularly N- and E-cadherin, is important for BC metastasis. E-cadherin plays a significant role in the growth of metastatic BC cells, particularly in lobular breast carcinoma which often exhibits E-cadherin mutations.^[28] Additionally, by aiding in invasion and intravasation into the bloodstream and triggering proteases involved in the degradation of the extracellular matrix (ECM), which is predominantly conducted by matrix metalloproteinases (MMPs), as well as the urokinase plasminogen activator (uPA) system, epithelial-to-mesenchymal transition (EMT) is pivotal in tumor advancement.^[29,30] Once tumor cells successfully infiltrate a secondary location, they begin to adapt to the new surroundings, altering inflammatory patterns, dampening immune responses, promoting blood vessel formation, impacting growth, and ultimately leading to the emergence of clinically detectable metastases at the secondary site.^[31]

PI3K-Akt-mTOR, Wnt/β-catenin, Notch, Hedgehog, and NF-κB signaling pathways are crucial in the development, advancement, and spread of BC. While these pathways are carefully controlled in healthy cells, tumor cells manipulate or hijack them to promote cancer proliferation, invasion, and treatment resistance.^[32,33] The PI3K/Akt/mTOR pathway is a complex intracellular pathway that serves a crucial role in BC via cellular growth and tumor proliferation and has been linked to endocrine resistance in BC.^[34] In BC, this pathway is activated via mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) or AKT serine/threonine kinase 1 (AKT1) and loss of phosphatase and tensin homolog (PTEN).^[35-37] PI3K activation triggers the important downstream mediators Akt and mTOR, which in turn promote cell cycle progression, anti-apoptosis, increased growth, and translation 2.^[38,39] The Wnt/β-catenin

signaling pathway, which is vital for embryonic morphogenesis, is detected as dysregulated and excessively expressed in BC, particularly in TNBC.^[40] This pathway is autocrinely activated in BC.^[6] Approximately 50% of BC cases exhibit elevated levels of β-catenin.^[41,42] Notch signaling comprises five Notch ligands including Delta-like 1, 3, 4, and Jagged (JAG) 1, 2, and there are four Notch transmembrane receptors: Notch1–4. There is a statistically significant correlation between the basal/TN subtype and the increased expression of Notch ligands/receptors.^[32] Patients with BC who overexpress Notch signaling tend to exhibit lower overall survival rates.^[43] Primary human BC has demonstrated high-level expression of JAG-1 and Notch-1.^[43–45] Moreover, it has been reported that in primary BC and BC cell line-derived tumorspheres, Notch 3 and Jag1 are crucial regulators of CSC.^[46] Also, Notch 3 is necessary for the proliferation of *HER2*-negative BC cells.^[47] NF-κB is one of the important transcription factors that connects inflammation with cancer and also notably impacts tumorigenesis and endocrine therapy resistance in BC. When NF-κB is activated, it promotes transcription of cyclin D1, B cell lymphoma-extra large (Bcl-XL), and inhibitors of apoptosis proteins (IAPs), thereby influencing anti-apoptotic signaling in BC.^[48] The proliferation of breast tumor stem cells and heterotypic signals supporting vasculogenesis and tumor-associated macrophages (TAMs) are both mediated by NF-κB. These pathways may play a role in NF-κB-dependent carcinogenesis of breast tissue.^[49]

Anti-Breast Cancer Effects of Spices and Culinary Herbs

Besides their culinary applications, spices and culinary herbs have been found to possess chemotherapeutic and chemopreventive properties which may be attributable to their antioxidative, anti-inflammatory, and anti-tumor activities.^[50] These serve as significant sources of potent compounds [Figures 1 and 2], with the dual advantage of effectiveness and safety compared to conventional cytotoxic drugs used in BC treatment, providing advantages for effectively combating BC.^[16] We therefore explore the effects of spices and culinary herbs and their potential mechanisms of action against BC.

Turmeric (Curcuma longa)

Experimental and clinical studies have demonstrated that turmeric, as well as its primary compound curcumin (1) possess significant anti-cancer attributes, particularly in the context of BC

[Figure 3].^[51] Turmeric extract exhibited potent anti-proliferative effects against MCF-7 and MDA-MB-231 (TNBC) BC cells by decreasing the production of intracellular reactive oxygen species (ROS), inhibiting cell migration, inducing morphological alterations in cells and nuclei, and in cell cycle arrest at the synthesis (S) and gap 2 (G2)/mitosis (M) phases, leading to cell apoptosis.^[52,53] Another study by Anggia Paramita *et al*^[54] reported that *C. longa* extracts exerted dose-dependent cytotoxic effects on MDA-MB-231 through caspase-3-dependent apoptosis due to p53 and survivin. It also inhibited cell cycle progression and triggered apoptosis in T47D BC cells.^[55] Moreover, turmeric extract was reported to exert an anti-telomerase effect on T47D and MCF-7 BC cell lines.^[56,57]

Several studies reported that curcumin (1), the active ingredient of *C. longa*, exhibited anti-BC effects through various pathways.^[58] Curcumin (1) was shown to decrease the viability of several BC cell lines, such as HER2-overexpressed BT-474 (ER-positive, HER2-positive), MDA-MB-231 (ER-negative, HER2-negative), HERceptin-resistant SK-BR-3-hr (ER-negative, HER2-positive), and MCF-7 (ER-positive, HER2-negative). BT-474 and SK-BR-3-hr cells treated with curcumin displayed dose- and time-dependent reductions in HER2 oncoprotein, p-Akt, p-MAPK, and NF-κB. A BT-474 xenograft model showed a notable decrease in tumor size with curcumin (1) therapy.^[59] Curcumin (1) exhibited dose- and time-dependent growth inhibitory effects on BT-20, T47D, SK-BR3, and MCF-7 BC cell lines, and was also correlated with ornithine decarboxylase suppression.^[60] In ER-positive MCF-7 cells, curcumin (1) suppressed the expression of ER downstream genes, such as *pS2* and *TGF-β*, and also exerted potent anti-invasive effects *in vitro* on ER-negative MDA-MB-231 BC cells whereby curcumin (1) may prevent MDA-MB-231 cells from invasion and metastasis by targeting Gli1 in the Hedgehog/Gli1 signaling pathway.^[61,62] In both MCF-7 and MDA-MB-231 BC cells, curcumin (1) is reported to decrease cell growth and induce apoptosis by regulating the β-catenin pathway in which disheveled proteins (Dvl), β-catenin, cyclin D1, and slug expressions were inhibited by curcumin (1).^[63,64] Survival of these two cell lines is also diminished by curcumin (1) via the lowering of hypoxia-inducible factor (HIF)-1α and -2α protein levels in hypoxia.^[65,66] Curcumin inhibited cell proliferation in MCF-7 cells in a dose-dependent manner by arresting the G2/M phase cell cycle and forming aberrant, monopolar mitotic spindles.^[67,68] By downregulating the expression of human telomerase reverse transcriptase (hTERT) that occurs in the c-myc-independent pathway, curcumin (1) suppressed telomerase activity in MCF-7 BC cells resulting in cell apoptosis.^[69] In the aforementioned cell

line, curcumin counteracted insulin-like growth factor-1 (IGF-1) induced resistance to apoptosis, and inhibited IGF-1 driven cell proliferation.^[70] Curcumin (1) exerted anti-proliferative and apoptotic effects on the HER2 overexpressing human BC cell line, SK-BR-3, caused by interference with several cell growth regulatory pathways, including G2/M arrest, cyclin D1 level reduction, and induction of p21.^[71,72] Moreover, curcumin inhibited histone deacetylase (HDAC), which results in cell cycle arrest and apoptosis through the upregulation of p21 in MDA-MB-231 and MCF-7 BC cell lines.^[73] In MDA-MB-435/β4-integrin transfectants and MDA-MB-231 BC cell lines, curcumin also significantly reduced α6β4-dependent BC cell mobility, as well as cell invasion, in a dosage-dependent manner without altering apoptosis; however, it also enhanced apoptosis and blocked fatty acid synthase (FAS) activity, expression, and messenger ribonucleic acid (mRNA) levels in a dose-dependent manner.^[74,75] Curcumin (1) caused G2/M arrest to suppress MDA-MB-231 cell growth in a dose-dependent manner by enhancing the expression of the proteins p21 and Bcl-2-associated X protein (Bax). In contrast, the protein expression of p53 and Bcl-2 was downregulated, and a time- and dose-dependent anti-proliferative effect on MDA-MB-231 and BT-483 cells via down-regulation of cyclin D, NF-κB, and MMP-1 transcription.^[76,77] Curcumin (1) triggered apoptosis and deoxyribonucleic acid (DNA) damage in TNBC cells along with enhanced BRCA1 protein expression, phosphorylation, and cytoplasmic retention.^[78] Curcumin (1) suppressed the growth of MDA-MB-435 cells in conjunction with the down-regulation of the enhancer of zeste homolog 2 (EZH2) expression via the MAPK pathway. It increased the cytotoxic effect of NK-92 on MDA-MB-231 by activating the signal transducer and activator of transcription (Stat) 4 and Stat5 proteins in NK-92.^[79,80] Curcumin (1) induced apoptosis and produced a dose-dependent cytotoxic effect on ZR-75-1 BC cells.^[81] Curcumin (1) inhibited TPA-induced MMP-9 production and cell invasion in MCF-7 cells by suppressing the MAPK, protein kinase C alpha (PKC α), as well as NF-κB/activating protein-1 (AP-1) pathway and downregulating uPA protein expression through NF-κB activation. Here, the suppression of LPS-induced EMT by reducing NF-κB-Snail signaling has also been observed.^[82-85] Curcumin (1) inhibited NF-κB signaling and microRNA (miR)-182-96-183 cluster expression, which prevented autocrine GH-triggered invasion-metastasis and EMT activation and thus promoted apoptotic cell death in T47D cells by modifying members of the Bcl-2 family.^[86] Dietary curcumin (1) demonstrated the ability to reduce chemotherapy-induced apoptosis by suppressing ROS formation and blocking c-Jun N-terminal kinase (JNK) activity in MCF-7, MDA-MB-231, and

BT-474 cells. Moreover, curcumin significantly impeded cyclophosphamide-induced tumor regression in an *in vivo* model of human BC.^[87] Curcumin (1) inhibited the production of key MMPs by downregulating AP-1 transcriptionally and reducing NF-κB activation which resulted in a noticeably decreased number of lung metastases in immunodeficient mice.^[88] It also significantly reduced PKC- α and - ζ expression in MCF-7 and MDA-MB-231 cells. Furthermore, curcumin (1) downregulated PKC, NF-κB, and HDAC in a mouse model to enhance the effects of cyclophosphamide and paclitaxel (PTX).^[84] Further, curcumin (1) significantly prolonged tumor-free survival and decreased tumor multiplicity in BALB-neuT transgenic mice bearing the neu oncogene, both in the early and advanced stages of mammary carcinogenesis,^[89] and also hindered angiogenesis in an *in vivo* mouse model of BC.^[90] Curcumin increased γ-H2A histone family member X (H2AX) levels in MDA-MB-231 cells and suppressed the development of Rad51 foci, a crucial step in the homologous recombination (HR) pathway. In MDA-MB-231 BC cells, curcumin (1) directly lowered HR and resulted in cell death when combined with a poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. Moreover, along with PARP inhibitor, curcumin (1) reduced the growth of breast tumors in xenograft mice, which was mediated by HR signaling pathway inhibition.^[91] Curcumin substantially lowered the viability of MDA-MB-231 cells and decreased tumor volume and cell proliferation *in vivo*.^[92] By lowering the deleted in liver cancer 1 (DLC1) promoter's hypermethylation to increase DLC1 expression, curcumin (1) exerted growth inhibitory effects in MDA-MB-361 cells both *in vitro* and *in vivo*.^[61] Dendrosomal curcumin (1) prevented 4T1 cells from migrating and adhering, and significantly decreased tumor incidence, size, and weight in female BALB/c mice along with the inhibition of the breast tumor's expression of NF-κB p105 and several of its downstream genes.^[93] By decreasing colon cancer-associated transcript-1 (CCAT1) and inactivating the PI3K/Akt/mTOR pathway, curcumin was able to activate autophagy, which resulted in sensitizing of cisplatin-resistant multidrug resistant (MDR) BC cells and inhibition of *in vivo* tumor growth.^[94] By increasing protease-activated receptor 4 (PAR4) expression, curcumin (1) exhibited dose- and time-dependent effects on 4T1 cell survival and higher tumor shrinkage in the BALB/c tumor model.^[95] A recent study reported that curcumin (1) exhibited reduced tumor growth in 4T1 cells implanted BALB/c mice and exerted anti-proliferative effects in both MCF-7 and 4T1 cell lines, apparently in an iron-dependent manner.^[96] By promoting ferroptosis mediated by solute carrier family 1 member 5 (SLC1A5) in BC, curcumin displayed anti-proliferative effects both *in vitro* and *in vivo*.^[97,98] Furthermore,

several studies highlighted curcumin's capacity to, directly and indirectly, reduce programmed death-ligand 1 (PD-L1) levels in BC. The indirect suppression was achieved by inhibiting β -catenin and Axl kinase, which subsequently enhanced the immune system's ability to target cancer cells and restricted their metastatic spread.^[99]

Garlic (Allium sativum)

An aqueous extract of garlic affected MCF-7 human BC cells by downregulating the levels of E-cadherin and β -catenin, cytokeratin 8/18, and cyclin D1. It modified the phenotype of the cells, and arrested them in the gap 0 (G0)/gap 1 (G1) cell cycle, ultimately slowing their growth.^[100,101] Ethanolic extract of garlic also demonstrated cytotoxic effects against MCF-7 cells and the non-invasive MCF10DCIS cell line grown under moderate hypoxia.^[102,103] Moreover, the ethanolic extract exerted immunomodulatory, and preventative effects on inflammatory cytokines (interleukin [IL]-33 and tumor necrosis factor alpha [TNF- α]) in Wister albino rats with 7,12-dimethylbenz[a]anthracene (DMBA)-induced BC.^[104] In BALB/c mice with BC, garlic extract drastically reduced the expression of ATP-binding cassette super-family G member 2 (ABCG2) and secreted protein acidic and rich in cysteine (SPARC) (cancer biomarkers) and increased the amount of glutathione transferase (an antioxidant), thereby treating BC.^[105] Phytochemical screenings show that *A. sativum* possesses several bioactive compounds which are diallyl disulfide (2) (DADS), diallyl trisulfide (3) (DATS), allicin (4), and S-allyl mercaptocysteine (5) (SAMC). These bioactive compounds exert activity against BC cell lines (MCF-7, MDA-MB-231, TNBC, T47D) by various mechanisms, such as inhibiting cell proliferation, altering their phenotypes, accumulating the cells in G0/G1 and G2/M phases, triggering the mitochondrial apoptotic pathway, and generating intracellular ROS [Figure 4].^[106-109]

DADS (2) and DATS (3) increased the expression levels of pro-apoptotic BAX and p53 proteins and deregulated the Bcl-X_L protein which ultimately activated the caspase enzymes that ultimately led to cell apoptosis of MCF-7 human BC cell lines.^[110,111] DADS (2) and DATS (3) also triggered apoptosis in TNBC cells by targeting cluster of differentiation (CD) 151 and reducing PTX resistance of the cells.^[112] DADS (2) triggered caspase activation and controlled the production of Bcl-2 family proteins, and also downregulated and reversed MMP-9 and EMT in TNBC cells. DADS (2) halted the proliferation of cancer cells and impeded their ability to spread by blocking the β -catenin pathway. Therefore, TNBC cell invasion and migration were inhibited by DADS

(2).^[113] In MCF-7 and MDA-MB-231 BC cell lines, DADS demonstrated significant activation of caspase-3 and caspase-9 which caused significant cytotoxicity in both cell lines.^[114] Another organosulfur compound, DATS (3) exerted noticeable chemopreventive effects in MCF-10A BC cell lines by inhibiting cell proliferation, ROS formation, clonogenic formation, and decreasing 8-hydroxy-2-deoxyguanosine (8-OHdG) levels, as well as stopping protein expression of cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1), aryl hydrocarbon receptor nuclear translocator (ARNT)/HIF-1 β , and DNA polymerase β (POL β). DATS (3) was shown to mediate the suppression of breast cancer stem cells (bCSC) by lowering the protein level of Forkhead box Q1 (FoxQ1), which in turn reduces aldehyde dehydrogenase 1 activity.^[115,116] Additionally, DATS (3) activated AP-1 and phosphorylates c-Jun, triggering the JNK pathway, which causes MCF-7 cells to undergo apoptosis.^[117] Allicin (4) effectively blocked the extracellular signal-regulated kinase (ERK)_{1/2} and NF- κ B signaling pathways and enhanced interaction between ER- α and p65 which inhibited TNF- α -mediated induction of vascular cell adhesion molecule 1 (VCAM-1) in MDA-MB-231 and MCF-7 cell lines and finally suppressed the invasion and metastasis of the aforementioned BC cell lines.^[118] SAMC (5) activated Bax, decreased expression of Bcl-2 and Bcl-X_L, and subsequently activated caspase-9 and caspase-3 which triggered the mitochondrial apoptotic pathway of MCF-7 (ER-positive) and MDA-MB-231 (ER-negative) cells in a dose- and time-dependent manner.^[119]

Ginger (*Zingiber officinale*)

The ethanolic extract of ginger displays dose-dependent cytotoxic effects on BC cell lines, MCF-7 and MDA-MB-231^[120] whereby BC cell proliferation and colony formation were inhibited downregulation of NF- κ B, Bcl-X, myeloid cell leukemia 1 (Mcl-1), survivin, cyclin D1, cyclin-dependent kinase (CDK)-4, c-Myc, and hTERT.^[121] The study revealed that ethanolic ginger extract inhibited MCF-7 BC cell reproduction in a dose- and time-dependent manner, leading to apoptosis via increased p53 expression and decreased Bcl-2 expression.^[122] Another study reported that it also elevated p21 and p53 mRNA levels in MCF-7 BC cells.^[123] The methanolic extract of ginger also displayed significant cytotoxic effects against MCF-7 cells.^[124] Nedungadi *et al*^[125] evaluated the long-term growth inhibitory effect of the ethanolic extract of ginger on MDA-MB-231 cancer cells and observed a significant decrease in clonogenicity and increased sub-G1 phase cells. They also identified a caspase-independent death pathway in cancer cells.^[125] Several

bioactive compounds can be isolated from ginger such as 6-gingerol (6), 6-shogaol (7), 10-gingerol (8), zingerone (9), zerumbone (10), gingerenone A (11), and dihydrocapsaicin (12) that possess potent anti-BC activities [Figure 5].

Treatment with 6-gingerol (6) reduced the activities of MMP-2 and MMP-9 in MDA-MB-231 cells in a dose-dependent manner.^[126] One of the main bioactive components of ginger rhizomes is 6-shogaol (7), which is a dehydrated byproduct of 6-gingerol (6). It reportedly activates caspases-3 and caspase-9, causes G2/M cell cycle arrest and apoptosis, increases peroxisome proliferator-activated receptor c (PPARc) mRNA and protein levels, significantly reduces endogenous PPARc protein expression, and suppresses NF-κB transcription in the MCF-7 cell line.^[127] 10-Gingerol (8), significantly increased caspase-3, caspase-8, and caspase-9 expression and cell death in the MCF-7 cell line.^[128] Further, 10-gingerol (8), prevented TNBC from proliferating and induced apoptosis by activating the caspase-family protein,^[129] and inhibited proliferation, migration, invasion, and induced apoptosis in MDA-MB-231/ionizing radiation (IR) cells by targeting the PI3K/Akt signaling pathway.^[130] In a mouse model of BC, zingerone (9) enhanced antibody and T cell-mediated responses, lowered the percentage of splenic regulatory T (Treg) cells, downregulated T helper 2 (Th2) cells, raised interferon (IFN)-γ expression, decreased transforming growth factor beta (TGF-β) expression, and increased the percentage of splenic Th1 cells.^[131] Zerumbone (10), a bioactive sesquiterpene from ginger, reduced C-X-C chemokine receptor type 4 (CXCR4) expression in HER2-overexpressing BC cells in a dose- and time-dependent manner by reducing NF-κB activation. It inhibits C-X-C motif chemokine 12 (CXCL12)-induced BC cell invasion.^[132] Zerumbone suppressed osteoclast formation *in vitro* through receptor activator of nuclear factor kappa-B ligand (RANKL)-induced activation of NF-κB and MAPK pathways.^[133] Gingerenone A (11), reduced cellular adenosine tri-phosphate (ATP) content and cell viability in several BC cell lines, including SKBR3, MCF-7, and MDA-MB-231, and also demonstrated a delayed G2/M response in BC cells (MCF-7 and MDA-MB-231), and increased senescence-associated gene expression. The treatment increased ROS, MitoSOX, senescence, γH2AX, and 8-OHdG levels in BC cells.^[134] Dihydrocapsaicin (12), another active component of ginger, increased caspase-9 expression, caspase-3, and BAX, and inhibited the proliferation of MDA-MB-231 BC cells.^[135]

Clove (*Syzygium aromaticum*)

Clove buds exhibit significant anti-BC properties [Figure 6]. Several studies reported that clove bud extract demonstrated significant cytotoxic and anti-proliferative activities against MCF-7 BC cells.^[136–139] Kello *et al.*^[140] reported that MCF-7 cells underwent apoptosis when exposed to clove bud extract. ROS generation, DNA damage, and the subsequent activation of DNA repair mechanisms, such as H2AX, ataxia telangiectasia-mutated (ATM), and structural maintenance of chromosomes 1 (SMC1) protein phosphorylation and p53 activation, were all associated with apoptosis. Here, the apoptotic mitochondrial pathway was shown by the alteration of Bcl-2 family proteins and the leakage of pro-apoptotic proteins from the mitochondria. Furthermore, phosphorylation of Akt and MAPK signaling (Erk, JNK, and p38 MAPK) was observed.^[140] Apart from MCF-7 cells, clove bud extract also exhibited anti-proliferative activity against MDA-MB-231 (ER-negative) BC cell line.^[141] Another investigation revealed that the administration of a high dose of clove bud extract to female Sprague-Dawley female rats with breast tumors resulted in a decrease in the expression levels of Bcl-2, Ki-67, vascular endothelial growth factor A (VEGFA), CD24, and CD44, while increasing the levels of Bax, caspase-3, and aldehyde dehydrogenase 1 (ALDH1).^[142] The essential oil of cloves also exerted cytotoxic effects on the MCF-7 BC cell line.^[143]

Eugenol (13), a bioactive compound found in clove essential oil, exhibited a cytotoxic effect on BC cells (MDA-MB-231, MCF-7, and T47-D), as demonstrated by its targeting of the oncogenic pathway E2F transcription factor 1 (E2F1)/survivin. Additionally, eugenol inhibited BC-related oncogenes such as cyclin D1 as well as NF-κB, while increasing the expression of the CDK inhibitor, p21WAF1. Furthermore, eugenol (13) inhibited the growth of cancerous breast cells in a p53-independent manner.^[141,144]

Black pepper (Piper nigrum)

According to a study, methanol and dichloromethane extracts of black pepper demonstrated strong cytotoxic effects against MCF-7, MDA-MB-231, and MDA-MB-468 BC cell lines.^[145] *In vitro* studies revealed that the ethanolic extract of *P. nigrum* fruits notably reduced cell viability and glucose uptake while also triggering apoptosis in 4T1 cells. In the 4T1 breast tumor mouse model, treatment with this extract significantly decreased tumor size, as well as metastases. Moreover, it enhanced the frequency of multifunctional CD4⁺ and CD8⁺ T cells, thereby restoring immune function and counteracting the immunosuppressive properties of BC cells.^[146]

Piperine (14) (an alkaloid isolated from black pepper) inhibited the proliferation and colonization of MCF-7 and MDA-MB-231 BC cells. It suppressed the expression of the *Rac1* gene and its protein which can be attributed to this effect. BC cells exhibited cell decrease at the G0/G1 phase and cell arrest at the G2/M phase.^[147] Additionally, it suppressed the advancement of the cell cycle, triggered caspase-dependent apoptosis through the mitochondrial route, and prevented the expression of MMP-2 and MMP-9 mRNA, and the migration of TNBC cells.^[148] Moreover, two compounds, namely piperlonguminine (15) and (–)-kusunokinin (16), isolated from black pepper, also demonstrated cytotoxic activity against MCF-7 and MDA-MB-468 BC cells. Both compounds promoted apoptosis in cells and propelled them into the G2/M phase, and also reduced bcl-2 and topoisomerase II. Except for caspase-9, the activities of p21, bax, cytochrome c (cyt-C), caspase-8, -7, and -3 were also elevated by the increase in p53 levels.^[149]

Onion (Allium cepa)

Different onion extracts have demonstrated cytotoxic effects on MCF-7 BC cells,^[150] and the ethyl acetate (EtOAc) extract of onion effectively inhibited FAS and might thereby promote apoptosis in FAS-overexpressing MDA-MB-231 BC cells.^[151] Onion extract considerably reduced both the size and weight of breast tumors, induced by the injection of 4T1 cells in BALB/c mice, while concurrently reducing IFN- γ and IL-4 levels.^[152,153]

Quercetin (17), a bioflavonoid compound found in onion, has been reported to inhibit the growth of MCF-7 cells by at least two different mechanisms: either by blocking antisense p21CIP1/WAF1 expression, which induces apoptosis, or by preventing the progression of the cell cycle through a temporary accumulation in the M phase followed by arrest in the G2 phase.^[154] It also inhibited cell proliferation in a time- and dose-dependent manner by more efficiently down-regulating the expression of the mutant p53 protein present in MDA-MB468 cells.^[155] Jing *et al*^[156] demonstrated that quercetin facilitated T-cell activation by disrupting the programmed cell death protein 1 (PD-1)/PD-L1 interaction within MDA-MB-231 BC cells. Additionally, this compound impeded the growth of MDA-MB-231 cells when injected subcutaneously into BALB/c nu/nu mice through a mechanism reliant on T cells, as evidenced by elevated levels of CD8, granzyme B (GZMB), and IFN- γ proteins.^[156] 3-Epicaryoptin (18), a bioactive compound found in onion root apical meristem

cells, inhibited the proliferation of MCF-7 BC cells by depolymerizing cellular microtubule networks, which caused cell cycle arrest and apoptotic cell death.^[157]

Red pepper (*Capsicum annuum*)

The crude extract of red pepper exhibited dose-dependent cytotoxicity against MDA-MB-231 and MCF-7 BC cells.^[158] Moreover, aqueous pepper seed extract also showed a dose-dependent inhibitory effect on cell proliferation and invasion against these two cell lines.^[159]

Capsaicin (19), a potent component of red peppers in the genus capsicum, prevents the development of cancer by inducing human tumor cells, such as MCF-7 BC cells, to undergo apoptosis.^[160] According to a study, capsaicin (19) suppressed the growth of BC cells in MCF-7 and BT-20 cells by causing cell death and cell cycle arrest during the S phase. This apoptotic impact is triggered by activating caspase-7, which in turn cleaves PARP-1. It possibly might be induced through the mitochondrial pathway, initiated by capsaicin-induced mitochondrial malfunction. Furthermore, in caspase-3-deficient MCF-7 cells, capsaicin (19) caused apoptosis-inducing factor-mediated caspase-independent death.^[161] Moreover, another study reported that capsaicin also hindered the growth of both ER-positive (MCF-7, T47D, BT-474) and ER-negative (SKBR3, MDA-MB231) BC cell lines. This inhibition was linked to cell-cycle arrest at the G0/G1 phase, heightened levels of apoptosis, and reduced expression of proteins such as epidermal growth factor receptor (EGFR), HER2, activated ERK, and cyclin D1. Conversely, capsaicin (19) led to increased levels of the cell-cycle regulator p27^{KIP1}, caspase activity, and cleavage of PARP. Also, capsaicin (19) impeded BC cell migration *in vitro* and reduced the size of orthotopically growing MDA-MB-231 breast tumors by 50% in immunodeficient mice. *In vivo*, capsaicin (19) treatment significantly reduced the activation of ERK, as well as the expression of HER2 and cyclin D1, while enhancing caspase activity and the production of PARP cleavage products in tumors. Furthermore, capsaicin (19) exhibited potent inhibition of pre-neoplastic breast lesion development, reducing their occurrence by up to 80%.^[162] Pectic polysaccharides, derived from this fruit pepper fruit, inhibited cell viability and proliferation of MCF-7, MDA-MB-231, and MDA-MB-436 BC cells. It further induced necrosis and reduced vessel size in the mammary-origin Ehrlich tumor model. Notably, suppression of VEGF gene expression was observed within this tumor, a phenomenon consistent with the aforementioned BC cell lines.^[163]

Fenugreek (*Trigonella foenum-graecum*)

The ethanolic extract of fenugreek seed decreased mitochondrial membrane potential, cell viability, and induced apoptosis in the MCF-7 BC cell line.^[164] Chloroform extracts of fenugreek seeds decreased MCF-7 cell proliferation and activated ER-mediated transcription through estrogen responsive elements by partially triggering apoptosis by modifying the expression levels of caspase-3, -8, -9, p53, Fas, Fas-associated protein with death domain (FADD), Bax, and Bcl-2-antagonist/killer (Bak). Expression of the estrogen-sensitive gene *pS2* was stimulated in MCF-7 cells.^[165,166] The methanolic extract of fenugreek seeds also significantly reduced the cell viability of MCF-7 BC cells in a dose-dependent manner. In media with and without estrogen, it also increased the expression of the *pS2* gene. Moreover, it increased mitochondrial DNA damage and inhibited metastasis and proliferation. Lastly, due to a dose-dependent inhibition of migration and adhesion, it caused a p53-dependent mitotic catastrophe in BC cells, which resulted in apoptosis.^[167–170] Fenugreek seed extract dramatically reduced the frequency of breast hyperplasia caused by DMBA and reduced its occurrence.^[171] Al-Sallami, Al-Labban, and Ali^[172] demonstrated that rats administered with an ethanolic extract of fenugreek seeds displayed a greater rate of tumor inhibition, and the extract was associated with higher levels of aspartate transaminase and alanine transaminase in tumor aggregates.

Alkaloids extracted from fenugreek seed have demonstrated remarkable outcomes via multiple modes of action, including growth inhibitors via apoptosis, disruption of cell migration, inhibition of angiogenesis, and cell cycle arrest.^[173] A compound of fenugreek called diosgenin (20) mediated Fas receptor irrespective of FADD, caspase-8 or -3, and also interdependently with p53, thereby playing a crucial role in the initial apoptosis of BC cells.^[174]

Fennel (Foeniculum vulgare)

Methanolic extracts of fennel seeds exhibited potent free radical scavenging action, exhibiting significant cytotoxic effects.^[175] A study by Zaahkouk *et al*^[176] reported that the same extract demonstrated an anti-cancer effect on MCF-7 BC cells by inducing DNA damage, *p53* and *Bax* gene expression, and induced morphological alterations in the BC cells. Furthermore, the chloroform fraction of fennel seeds reduced the growth of MCF-7 and MDA-MB-231 cells in a time-dependent manner. It induced apoptosis in MCF-7 cells by promoting the formation of ROS, which triggered apoptosis via a mechanism dependent on mitochondrial caspase activation.^[177] Fennel seed extract significantly decreased tumor size in BALB/c mice which was induced by

subcutaneous injection of 4T1 BC cells. In tumor tissues, it resulted in an increase in the ratio of E-cadherin expression to that of Ki-67 and dysadherin. However, Ki-67 and HER2 expression levels were reduced in the ovary.^[178] Another study by Roudbari *et al*^[179] also reported that fennel seed extract significantly decreased tumor volume. However, this study also highlighted that *HER2* gene expression in tumor tissue and heat shock protein (HSP)70 and HSP90 protein expression in the liver were both markedly reduced by fennel extract.^[179] The essential oil from fennel seeds was also reported to exhibit cytotoxic properties against the MCF-7 and MDA-MB-231 BC cell lines.^[180,181]

Anethole (21), a major bioactive compound from fennel seeds, showed a dose-dependent suppression of cell survival and cell proliferation in MCF-7 BC cells. This compound heightened PARP cleavage, indicating enhanced apoptotic activity, while also boosting the expression of pro-survival proteins Bcl-2 and p21. Conversely, it decreased the expression of p53 protein. Additionally, it exhibited alternating modulation in the phosphorylation of Akt kinase and S6 pro-survival proteins with increasing concentrations.^[182] Moreover, Chen and deGraffenreid^[183] conducted a study that revealed that anethole (21) inhibited cell survival and triggered apoptotic events in MCF-7 and MDA-MB-231 cells in an ER-independent manner. Furthermore, nonspecific lipid transfer protein 1 (nsLTP1), a cationic protein extracted from fennel seeds, exerted dose-dependent antiproliferative effects on MCF-7 BC cells.^[184]

Rosemary (*Salvia rosmarinus*)

Several studies reported that the extract of the leaves of this plant exhibited anti-cancer effects against MDA-MB-231 (TNBC) and MCF-7 (ER- α positive) BC cells. It reduced cell viability and proliferation of these cells in a concentration- and time-dependent manner. Moreover, it induced apoptosis in MDA-MB-231 BC cells and blocked its motility.^[185-189] Rosemary essential oil also showed anti-proliferative activity against the MCF-7 BC cell line.^[190,191]

Carnosol (22), a bioactive compound isolated from rosemary, demonstrated an inhibitory effect on the ability of T47D (ER-positive) BC cells to proliferate by targeting the ER, particularly the ER- β pathway. Meanwhile, target cell ER subtypes, ER- α and ER- β , might be expressed and proportionately regulated by carnosol (22).^[192] Another study reported the effect of carnosol (22) on TNBC (MDA-MB-231). Carnosol induced p21 overexpression, which significantly reduced

cell viability and colony expansion by blocking the G2 phase and arresting the cell cycle. Additionally, it triggered the activation of caspase-8 and caspase-9, which induce cell death through both intrinsic and extrinsic apoptotic pathways. Carnosol (22) also reduced the anti-apoptotic Bcl-2 level which in turn increased the Bax/Bcl-2 ratio, causing apoptosis. Furthermore, depression of the mitochondrial potential and subsequent activation of apoptosis were also observed. Carnosol (22) caused Beclin-1-independent autophagy in these cells. In MDA-MB-231, a high concentration of this compound caused ROS generation which contributed to autophagy and apoptosis.^[193,194] Another bioactive molecule from rosemary, carnosic acid (23) has been reported to inhibit the G2/M phase and arrest the cell cycle in MDA-MB-231, thereby exhibiting anti-cancer activity.^[195] Further, Einbond *et al*^[196] demonstrated that in ER-negative human BC cells, high doses of carnosic acid (23) triggered the expression of certain genes implicated in apoptosis (DNA damage inducible transcript 3 (*DDIT3*), DNA damage inducible transcript (*GDF15*), pleckstrin homology-like domain, family A, member 1 (*PHLDA1*)) and antioxidant action (heme oxygenase 1 (*HMOX1*), aldo-keto reductase family 1, member C2 (*AKR1C2*), thioredoxin reductase 1 (*TNXRD1*)). The inhibitory gene Cyclin-dependent kinase inhibitor 2C (*CDKN2C*) and transcription factor, inhibitor of DNA binding 3 (*ID3*) were shown to exhibit reduced expression when exposed to this substance.^[196]

Coriander (Coriandrum sativum)

Several *in vitro* analyses using the MCF-7 cell line revealed that the crude extracts of the leaf, fruit, and seeds displayed significant anti-proliferative activity against BC cells.^[197,198] Apart from MCF-7 BC cells, leaf and fruit extracts also demonstrated a cytotoxic effect on the MDA-MB-231 BC cell line.^[199] Furthermore, several *C. sativum* extracts and essential oil, high in linalool, displayed anticarcinogenic activity against the MDA-MB-453 cell line.^[200]

Cumin (Cuminum cyminum)

Cumin seed powder, as well as the extract, demonstrated *in vivo* anti-cancer activity by safely and effectively delaying and inhibiting E2-mediated mammary carcinogenesis in 5- to 6-week-old female ACI rats. Both seed powder and extracts significantly decreased the volume and tumor multiplicity. The intervention with cumin powder in the diet exhibited a dose- and time-dependent ability to counteract pituitary growth induced by E2, while also decreasing circulating prolactin levels and reducing proliferating cell nuclear antigen (PCNA) levels in mammary tissues.

Additionally, it significantly reversed the effects of E2 on the expression of ER- α , CYP1A1, and cytochrome P450 1B1 (CYP1B1), as well as the expression levels of specific microRNAs (miRNAs) (miR-182, miR-375, miR-127, and miR-206). Gas chromatography-mass spectrometry (GC-MS) analysis showed that cumin seed ethanolic extract contained high amounts of cuminaldehyde (24).^[201]

A study by Ghosh *et al*^[202] reported that cuminaldehyde (24) associated targeted drug-nanoconjugates exhibited anticancer action both *in vivo* and *in vitro*. It resulted in halting of the cell cycle and triggered the intrinsic pathway of apoptosis in MCF-7 cells by causing mitochondrial damage. Furthermore, when administered via intravenous injection *in vivo*, it effectively reduced the growth of mammary pad tumors induced by 4T1 cells in female BALB/c mice, which was facilitated by increased accumulation of cuminaldehyde (24).^[202]

True cardamom (Elettaria cardamomum)

Several studies indicated that different crude extracts of true cardamom exerted *in vitro* cytotoxic effects against MCF-7 BC cells.^[203–206] Cardamomin (25), a bioactive compound isolated from this spice, is reported to possess *in vitro* and *in vivo* anticancer properties against TNBC. It induces apoptosis in BT-549 cells via activation of the mitochondrial pathway. Its *in vitro* mode of action involves suppressing the Wnt/ β -catenin signaling pathway, resulting in cell death and cell cycle arrest of BT-549 cells and reversing epithelial-mesenchymal transition in these cells. This process also involves alterations in Bcl-2, Bax, cyt-C, cleaved caspase-3, and PARP. Furthermore, it markedly reduced the tumor volume in BALB/c mice bearing murine BC (4T1) models when administered at a dosage of 5 mg/kg.^[207] Essential oils extracted from *E. cardamomum* also exhibited antimetastatic and antiproliferative properties against BC, effectively inhibiting tumor development and progression in the MDA-MB-468 cell line.^[208,209]

Caraway (Carum carvi)

Thymoquinone (26) (TQ), which is obtained from the volatile oil of black caraway seeds, impeded the proliferation of TNBC (MDA-MB-231 and MDA-MB-468) cell lines. This corresponds to apoptosis and G1 phase cell cycle arrest, which can be triggered by permeabilization of the mitochondrial membrane and the subsequent activation of caspase-dependent and -independent apoptotic pathways. TQ (26) did not impact the growth of normal mammary epithelial cells but

significantly suppressed the *in vitro* proliferation of the p53-deficient MDA-MB-231 and MDA-MB-468 TNBC cell lines. Furthermore, TQ increased the cytotoxic effects of docetaxel and cisplatin on TNBC cells.^[210] A GC-MS analysis showed that R-(–)-carvone (27) is the primary constituent of *C. carvi* seed essential oil.^[211] With a half-maximal inhibitory concentration (IC50) value of 14.22 µM, R-(–)-carvone (27) exhibited cytotoxic activity toward the MCF 7 cancer cell line.^[212] Moreover, nsLTP1 from the caraway seed extract was reported to inhibit the expansion of the human BC cell lines MDA-MB-231 and MCF-7 in a dose-dependent manner.^[213]

Nutmeg (*Myristica fragrans*)

According to a study, the methanolic extract of *M. fragrans* seeds, rich in malabaricone C (28), demonstrated a promising inhibitory effect against the MCF-7 BC cell line. Moreover, malabaricone C (28) alone induced apoptosis in MCF-7 cells via oxidative damage to the cells' DNA.^[214] Al-Jumaily Al-Shanon, and Al-Barzanchi^[215] found that natural lignan dimer from the nutmeg has the ability to scavenge free radicals, minimize the induction of ROS, and potentially have therapeutic effects on the MCF-7 BC cell line. From the EtOAc extract of nutmeg, two main diarylbutane-type lignans were identified as active ingredients: meso-dihydroguaiaretic acid (29) (MDGA) and macelignan (30). MDGA (29) and macelignan (30) both demonstrated a strong ability to trigger apoptosis, as proven by the cleavage of PARP and the phosphorylation of p53 at Ser 15. Furthermore, both substances markedly reduced the potential of MCF-7 cells to form colonies. On multiple BC cell lines, including MCF-7, MDA-MB-231, TAMR/MCF-7, and MCF-7/ADR, MDGA (29) and macelignan (30) exhibited equivalent inhibition patterns. The same study also reported the *in vivo* anticancer efficacy of MDGA (29) and macelignan (30). Using 6-week-old female BALB/c mice, they investigated the inhibitory effects of two lignans on 4T1 mammary cancer cells. They showed that administering MDGA (29) and macelignan (30) (20 mg/kg) intraperitoneally inhibited the growth of 4T1 mammary cancer cell tumors.^[216] Chumkaew and Srisawat^[217] isolated dehydrodiisoeugenol (31) from the EtOAc-hexane extract of *M. fragrans* seeds and found that it had strong cytotoxicity against MCF-7, with an IC50 value of 9.2 µM.

Parsley (*Petroselinum crispum*)

A recent study reported that *P. crispum* fresh leaf ethanolic extract displayed a concentration-dependent anti-proliferative effect on MDA-MB-231 cell lines, decreasing viability by 50% at 1.2 mg/mL concentration.^[218] A dichloromethane extract of *P. crispum* stems and leaves also

demonstrated antiproliferative and antioxidant properties against MCF-7 and MDA-MB-231 BC cell lines. Furthermore, it inhibited MCF-7 cells' migration in a denuded area induced by H₂O₂. Hence, it suppressed MCF-7 cell migration, suggesting that it may be beneficial to minimizing metastasis.^[219] Wu *et al*^[220] extracted an apiole derivative (AP-02) from *P. crispum* fruits. AP-02 induced cell death through inhibiting the proliferation of BC cell lines.

Chili pepper (Capsicum frutescens)

Dou *et al*^[221] showed that with no noticeable impact on normal breast epithelial cells, capsaicin-rich ethanolic whole pepper extracts significantly induced growth arrest and apoptosis in MDA-MB-231 and MCF-7 BC cell lines. A comparative study found that aqueous extracts of dried pepper (*C. frutescens*) fruits exhibited more anticancer properties against the MCF-7 BC cell line than sweet or red pepper (*C. annuum*).^[222] Moreover, ethanol and water extract of *C. frutescens* fruits drastically lowered MCF-7 cell survival. However, the ethanolic extract (2.88 µg/mL) outperformed water extract (2.68 µg/mL) in its ability to scavenge the MCF-7 cell line.^[223]

Ajwain (Trachyspermum ammi)

Ethanolic seed extract of *T. ammi*'s anti-cancer action on MCF-7 is mainly mediated by Bcl-2 mRNA and p53. By lowering p53, it might increase the MCF-7 cell's susceptibility to apoptosis. By reducing Bcl-2 expression, it induced apoptosis in MCF-7 cells.^[224]

Thymol (32) (a predominant constituent of this spice) had time and concentration-dependent cytotoxic effects on MCF-7 and MDA-MB-468 cell lines. It showed a higher effect on MCF-7 cells which showed its ER dependence characteristics. Also, thymol altered *p21* and *p53* gene expression as well as induced apoptosis in MCF-7 BC cells.^[225–227] nsLTP1 which is derived from *T. ammi* seeds demonstrated a substantial anti-cancer action on MCF-7, according to a pharmacological investigation. nsLTP1 efficiently reduces apoptosis in MCF-7 cancer cells through a dose-dependent mechanism.^[228]

Peppermint (Mentha piperita)

Different extracts of this plant's leaves reported concentration-dependent cytotoxic and apoptotic effects on MCF-7 cell lines.^[229] A recent study showed that at greater concentrations, *M. piperita* L. extract also showed antiproliferative action against MDA-MB-231 cell lines.^[230]

Rosmarinic acid (33), a bioactive molecule obtained from *M. piperita* leaves, has anticancer properties. Most notably, a dose of 1000 µL/mL reduced half of the cancer cells' viability and hindered the proliferation of MCF-7 cells.^[231] Safinejad *et al*^[232] reported that *M. piperita L.* essential oil also had dose-dependent cytotoxic and antiproliferative effects on MDA-MB-231, MCF-7, and T47D BC cell lines.

Basil (*Ocimum basilicum*)

According to a study, the methanolic extract of this plant had cytotoxic effects on MCF-7 cell lines.^[233] Another study reported that aqueous leaf extracts of this plant exhibited a dose-dependent decrease in cell viability against the MCF-7 BC cell line. It interrupted the energy metabolism of MCF-7, blocking the synthesis of lactate and consequently, glycolysis. It initiated apoptosis, which resulted in cell death. By stimulating the mTOR/Akt/70-kDa ribosomal protein S6 kinase (p70S6K) pathway, it also activated adenosine monophosphate-activated protein kinase (AMPK) by promoting higher phosphorylation of the enzyme at threonine 172.^[234]

Ursolic acid (34), a bioactive molecule from this plant, showed anti-proliferative activity against MCF-7 cells. Including F-actin aggregation and mitotic spindle deformation, ursolic acid (34) caused a reduction in the proportion of cells in the two mitotic cell division stages, anaphase or telophase.^[235]

Anise (*Pimpinella anisum*)

Kassi *et al*^[236] reported that the aqueous extract derived from anise exhibited anticarcinogenic properties against the MCF-7 BC cell line. Notably, it manifested an ER-mediated influence at lower concentrations and an ER-independent effect at higher concentrations.^[236]

True cinnamon (*Cinnamomum verum*)

Hydroethanolic extract of cinnamon has been reported to increase apoptosis in MCF-7 cells in a dose-dependent manner, causing a considerable decline in the mRNA expression of anti-apoptotic genes, which is the mechanism underlying the observed apoptosis.^[237]

Cinnamaldehyde (35), the primary ingredient in cinnamon, strongly suppressed the proliferation of BC cells, altered their morphology, prevented them from migrating or invading, and induced

cell death through several pathways, including the PI3K-Akt and peroxisome proliferator-activated receptor pathways.^[238]

Star anise (Illicium verum)

The methanolic extract of star anise, exhibits strong dose-dependent anticancer activity against MCF-7 and MDA-MB-231 cell lines and especially against TNBC, through cytotoxicity, proliferation decrease, and initiation of apoptosis mechanisms.^[239,240] Also, Najar *et al*^[241] reported that three BC cell lines (MCF-7, T47D, and MDA-MB-231) were significantly inhibited by the anethol (21)-rich essential oil of star anise, with corresponding IC₅₀ (ppm) values for MDA-MB-231, T47D, and MCF-7 being >300 ppm, 171.7 ppm, and 143.6 ppm, respectively.

Mustard (Brassica nigra)

Sinigrin (36) (a glucosinolate) is present in *B. nigra* seeds and is reported to inhibit phosphorylation of PI3K, AKT, and mTOR, which leads to the downregulation of proliferative and cell cycle regulatory proteins, including cyclin-D1, PCNA, CDK4, and CDK6. Additionally, it induced pro-apoptotic gene expression and increased nuclear fragmentation, which induced apoptosis in MCF-7 cells.^[242]

Oregano (Origanum vulgare)

Methanolic extracts of the above-ground parts of the *Origanum vulgare* plant were reported to exhibit strong, dose-dependent antiproliferative activity against the MDA-MB-231 cell line.^[243] Moreover, a TNBC cell line, Hamon Cancer Center 70 (HCC-70) exhibited susceptibility to the cytotoxic effects of *O. vulgare* leaf extracts and carvacrol (37), one of its primary constituents.^[244] A study by Kubatka *et al*^[245] reported significant *in vitro* and *in vivo* anti-BC activities of lyophilized oregano (ORE). In MCF-7 BC cells, ORE dramatically reduced cell survival in a dose- and time-dependent manner, causing the cells to undergo caspase-dependent apoptosis, but concurrent non-caspase-dependent apoptotic pathways were also observed shortly after mitochondrial protein cleavage. Here, the induction of apoptosis also occurred as a result of a notable deactivation of the anti-apoptotic activity of Bcl-2, and activation of the mitochondrial apoptotic pathway. In Sprague-Dawley female rats, ORE also markedly decreased the volume, incidence, and frequency of breast tumors by 44.5%, 44%, and 55.5%, respectively. Both a significant dose-dependent increase in caspase-3 expression and a decrease in VEGF-2 expression

were observed in tumor tissue.^[245] ORE essential oil also reduced cell viability and led to a decline in mitochondrial membrane potential in MCF-7 and MDA-MB-231 cells. Here, the activation of pro-caspases-9 and -3 and the fragmentation of PARP triggered by ORE essential oil led to a reduction in the levels of Bcl-2 and Bcl-XL, accompanied by an elevation in Bax and VDAC levels.^[246,247]

Clinical Trials Investigating the Use of Spices and Culinary Herbs for Managing Breast Cancer

Apart from *in vivo* and *in vitro* investigations, several clinical trials have evaluated the effectiveness of spices and culinary herbs against BC [Table 1].

In an open-label phase I dose escalation clinical trial involving 14 patients with metastatic or locoregionally recurrent advanced BC, the feasibility and tolerability of combining curcumin (1) (a major bioactive compound of turmeric) and docetaxel were assessed. The maximal tolerated dose of curcumin (1) was determined to be 8 g/day, with no significant adverse effects observed at higher doses. Most patients showed some degree of improvement in both clinical and biological responses, evidenced by reduced levels of carcinoembryonic antigen (CEA) tumor marker throughout the treatment and regression of non-measurable lesions. Disease progression was not observed in any of the patients. Additionally, after three cycles of treatment, the curcumin/docetaxel combination notably reduced VEGF levels.^[248] Also, a larger-scale comparative, randomized, double-blind, placebo-controlled clinical trial involving 150 participants was conducted to assess the effectiveness and safety of combining curcumin (1) with PTX in patients with advanced, metastatic BC. The intervention, administered intravenously at a dose of 300 mg of solution per week, resulted in improved physical performance and increased objective response rates among patients with metastatic BC. The contrast in overall response rates among the cohorts was notably more pronounced among patients who completed the treatment regimen. Moreover, there was a noteworthy variance in Response Evaluation Criteria In Solid Tumors (RECIST) scores, suggesting that curcumin treatment provided more substantial benefits than the placebo.^[249] Several case-control studies reported an inverse relation between BC and the consumption of onion and garlic. In a case-control study conducted in France ($n = 345$), a 70% reduction in risk was observed with the consumption of garlic and onion. In this study, a highly significant ($P < 10^{-6}$) and consistent decline was observed with the frequency of consumption.^[250]

Similarly, another case-control study in Puerto Rico ($n = 314$) found that consumption of sofrito (a diet based on garlic and onion) was inversely associated with the occurrence of BC. Consumption of onion and garlic at moderate and high levels demonstrated inverse relationships with BC risk, as indicated by odds ratios of 0.59 and 0.51, respectively, in contrast to low consumption ($P_{\text{trend}} = 0.02$).^[251] Additionally, in a study in Mexico, consuming one slice of onion per day compared to less than one slice per day was also linked to an approximately 70% decrease in risk. In this study, an adjusted odds ratio of 0.27, accompanied by a 95% confidence interval of 0.16–0.47, was observed, with a statistically significant trend ($P < 0.001$).^[252]

Limitations

This study summarizes the current understanding of the preventive and therapeutic roles of spices and culinary herbs against BC. However, the authors wish to mention some limitations of this study. First, some spices and culinary herbs have not been studied extensively, limiting our ability to provide precise mechanistic insights into their roles. Second, most studies have used “fresh and raw” plant parts rather than processed spices. This variation could change some of the reported effects. Third, the efficacy of these spices and culinary herbs requires further validation through clinical trials and epidemiological studies before they can be effectively utilized in clinical settings.

Conclusion and Future Perspectives

Given that BC constitutes the primary cause of female cancer-related fatalities globally, strategies such as chemoprevention offer tremendous potential for addressing this issue. Spices and culinary herbs have been utilized for both culinary and medicinal purposes for millennia. Research has substantiated their noteworthy anti-BC properties through experiments conducted on various BC cell lines and animal models with breast tumors. Extracts, essential oils, and isolated compounds from these spices and herbs have demonstrated the ability to diminish BC cell viability and impede proliferation, migration, angiogenesis, and metastasis. They induce apoptosis through diverse pathways, ultimately leading to cancer cell death. Furthermore, they exhibit significant inhibitory effects on pathways or proteins that are either overexpressed or dysregulated in breast tumor tissue. Consequently, these spices and herbs offer promising and safer alternatives for both the prevention and treatment of BC. Nevertheless, further research is required to fully explore the potential of these herbs and spices. Advanced analytical methods are needed to isolate pure compounds from

the plant extracts, to enable a more profound understanding of their precise mechanisms of action. Additionally, while these herbs and spices have demonstrated effectiveness and safety in *in vitro* and *in vivo* experiments, their efficacy and safety profiles have yet to be confirmed through appropriate clinical trials involving human subjects. This research comprehensively discusses the diverse anti-BC effects of spices and culinary herbs, including their mechanisms of action, pathways, synergistic interactions, and potential future applications. Consequently, further comprehensive investigation is required to confirm the precise roles of these spices and herbs. Such studies will facilitate the identification of clinical applications and aid in addressing the ongoing challenges posed by BC.

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Authors contribution

Md. Liakot Ali: conceptualization, supervision, manuscript revision, writing – original draft, data extraction, and data analysis; Fabiha Noushin: project administration, writing – original draft and data extraction; Qurratul Ain Sadia: writing – original draft; Afroz Fathema Metu: writing – original draft; Jannatul Naima Meem: writing – original draft; Md. Tanvir Chowdhury: writing – original draft; Md. Hossain Rasel: writing – original draft; Khurshida Jahan Suma: writing – original draft; Md. Abdul Alim: writing – original draft; Muhammad Abdul Jalil: writing – original draft; Md. Jahirul Islam Mamun: writing – original draft; Md. Mahmudul Hasan: writing – original draft; Neamul Hoque: writing – original draft; Eva Azme: writing – original draft. All the authors have read and agreed to publish the paper.

Ethics statement

None.

Data availability statement

The datasets used in this study can be obtained from the corresponding author upon reasonable request.

Conflict of 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.

Declaration of generative AI and AI-assisted technologies in the writing process

During the writing of this article, AI or AI-assisted technologies were used exclusively for correcting grammar and simplifying sentences. The authors have carefully reviewed and edited the material and accept full responsibility for its quality and accuracy.

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Figure Legends

Figure 1: Chemical structures of compounds (1–23) derived from spices and culinary herbs demonstrate efficacy against breast cancer.

Figure 2: Chemical structures of compounds (24–37) derived from spices and culinary herbs demonstrate efficacy against breast cancer.

Figure 3: A simple representation showing the mechanisms of anti-breast cancer effects of *Curcuma longa* and its major bioactive compound, curcumin. *C. longa* extract caused caspase-3-induced apoptosis by increasing *p53* gene expression and decreasing survivin protein expression. Both the extract and its active constituent curcumin inhibit telomerase activity and prevent cell growth in the S and G2/M phases of the cell cycle. Curcumin showed IGF-1 induced apoptosis by lowering IGF-1 in breast cancer cells. It also induced apoptosis through the p53-p21 pathway and enhanced BRCA1 protein expression which resulted in DNA damage and cell apoptosis. By decreasing fatty acid synthase, it triggered apoptosis. Again, it downregulated angiogenesis by lowering the VEGF, COX-2, and MMP-9 expressions. Through decreasing β-catenin and cyclin D1 protein expressions in the β-catenin pathway, curcumin showed G2/M arrest in breast cancer cells. BRCA1: Breast cancer gene 1; CDK: Cyclin-dependent kinase; COX-2: Cyclooxygenase-2; Cyt-C: Cytochrome c; DNA: Deoxyribonucleic acid; FAS: Fatty acid synthase; Fz: Frizzled; G1: Gap 1; G2: Gap 2; hTERT: Human telomerase reverse transcriptase; IGF-1: Insulin-like growth factor-1; M: Mitosis; MMP: Matrix metalloproteinase; VEGF: Vascular endothelial growth factor; S: Synthesis; Wnt: Wingless/int.

Figure 4: Potential molecular mechanism of the anti-breast cancer effects of bioactive compounds of *Allium sativum*. Diallyl disulfide and S-allyl mercaptocysteine both activated the caspases by increasing BAX and decreasing Bcl-XL proteins. Diallyl disulfide downregulated MMP-9 and blocked the β -catenin pathway, resulting in cell apoptosis. Diallyl trisulfide activated the JNK pathway by increasing the levels of FAS, cyclin D1, BAX, and P53 proteins. Finally, C-jun was phosphorylated and produced intracellular ROS which led the cell to undergo apoptosis. Allicin blocked the ERK_{1/2} and NF- κ B signaling pathways which inhibited the TNF- α -mediated induction of VCAM-1 which finally suppressed the invasion and metastasis of the breast cancer cell lines. S-allyl mercaptocysteine triggered the mitochondrial apoptotic pathway by caspase activation which potentially stimulated cell apoptosis. Bcl-XL: B cell lymphoma-extra large; BAX: Bcl-2-associated X protein; ERK: Extracellular signal-regulated kinase; FAS: Fatty acid synthase; G1: Gap 1; NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells; JNK: c-Jun N-terminal kinase; MMP-9: Matrix metalloproteinase; TNF: Tumor necrosis factor; VCAM-1: Vascular cell adhesion molecule 1.

Figure 5: Effects of ginger's major bioactive compounds on breast cancer. 6-Gingerol and 6-shogaol induced apoptosis through the downregulated hTERT and mTOR pathways. 6-gingerol and gingerenone A decreased cell invasion by raising ROS levels, zerumbone inhibited the formation of osteoclasts by RANKL-induced activation of NF- κ B and reduced cell invasion by blocking the CXCL12/CXCR4 pathway, dihydrocapsaicin and 10-gingerol enhanced caspase activity and disrupts phosphorylation-dependent signaling pathway such as PI3K/AKT/mTOR effectively inhibiting cellular proliferation and inducing apoptosis. ADRB2: Adrenoceptor beta 2; AKT: protein kinase B; BAX: Bcl-2-associated X protein; CASP: Caspase; CXCL12: C-X-C motif chemokine 12; CXCR4: C-X-C chemokine receptor type 4; hTERT: Human telomerase reverse transcriptase; MMP: Matrix metalloproteinase; mTOR: Mammalian target of rapamycin; NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: Phosphoinositide 3-kinase; RANKL: Receptor activator of nuclear factor kappa-B ligand; ROS: Reactive oxygen species.

Figure 6: Mechanism of action of clove bud in breast cancer. It induced apoptosis through increasing cell cycle arrest via increasing phosphorylation of ATM, HA2.X, Erk, p38MAPK, JNK, p53, SMC, BAX, and Caspase protein. It also inhibited angiogenesis and cancer stem cells via decreasing VEGFA and CD24/CD44 respectively. ALDH1: Aldehyde dehydrogenase 1; ATM:

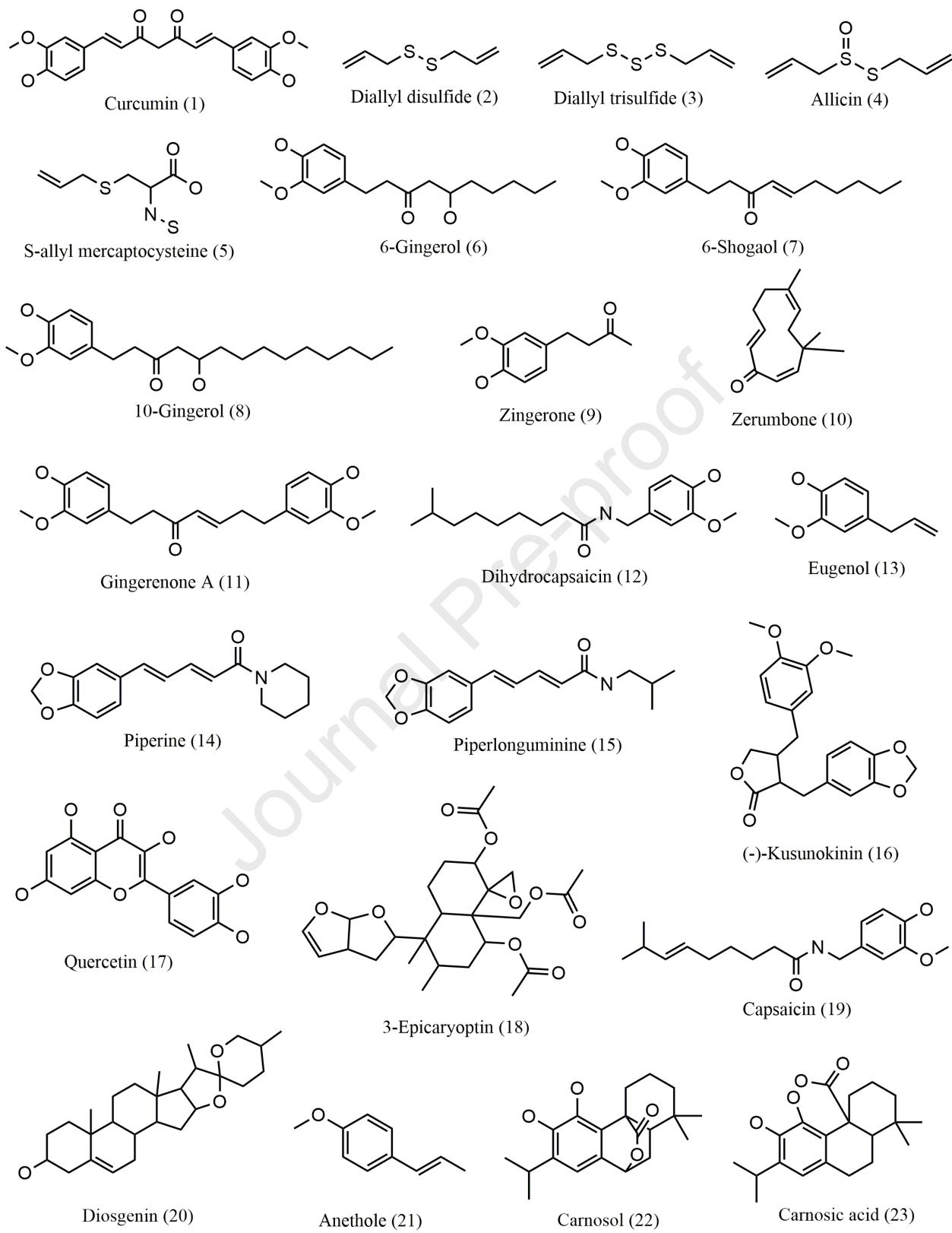
ataxia telangiectasia-mutated; BAX: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; CD: Cluster of differentiation; Erk: Extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinase; p38MAPK: p38-mitogen-activated protein kinase; ROS: Reactive oxygen species; SMC: Structural maintenance of chromosomes 1; VEGFA: Vascular endothelial growth factor A.

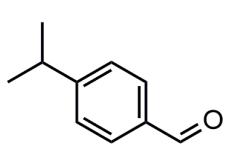
Table 1: Epidemiological and clinical studies regarding the effects of spice and culinary herb intake on breast cancer.

Intervention	Study design	Participants (<i>n</i>)	Outcomes	Reference
Curcumin (combined with docetaxel)	Open-label, phase I dose escalation trial	Patients with advanced or metastatic BC (<i>n</i> = 14)	Reductions in CEA tumor marker and VEGF levels. No disease progression was observed.	Bayet-Robert <i>et al</i> ^[248]
Curcumin (combined with paclitaxel)	Phase II, single-institution, randomized, placebo-controlled, double-blind, parallel group, two-arm trial	Patients with recurrent, locally advanced, or metastatic BC (<i>n</i> = 150)	Higher objective response rate and physical performance compared to placebo	Saghatelyan <i>et al</i> ^[249]
Onion and garlic	Case-control study	Patients with primary breast carcinoma (<i>n</i> = 345)	Significant reduction in BC risk	Challier, Perarnau, and Viell ^[250]
Onion and garlic-based diet, sofrito	Case-control study	Patients with primary breast carcinoma (<i>n</i> = 314)	Inverse association between consumption of sofrito and occurrence of BC	Desai <i>et al</i> ^[251]

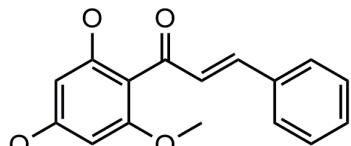
Onion	Case-control study	Patients with first-time diagnosed BC (<i>n</i> = 198)	Significant reduction in BC risk	Torres-Sánchez <i>et al</i> ^[252]
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BC; Breast cancer; CEA: Carcinoembryonic antigen; VEGF: Vascular endothelial growth factor.

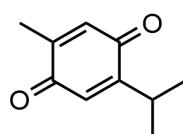




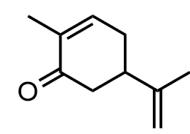
Cuminaldehyde (24)



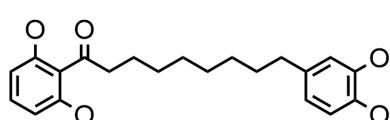
Cardamomin (25)



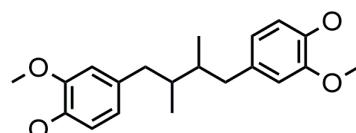
Thymoquinone (26)



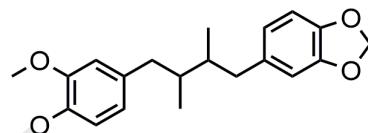
R-(−)-carvone (27)



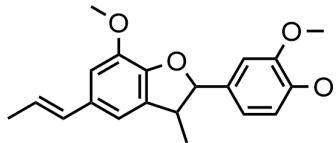
Malabaricone C (28)



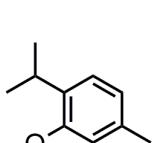
Meso-dihydroguaiaretic acid (29)



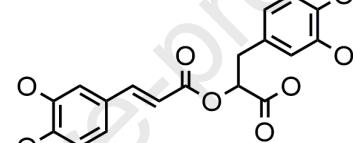
Macleignan (30)



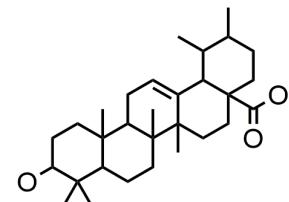
Dehydrodiisoeugenol (31)



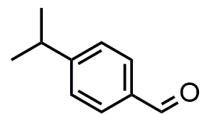
Thymol (32)



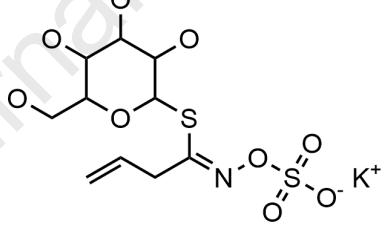
Rosmarinic acid (33)



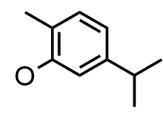
Ursolic acid (34)



Cinnamaldehyde (35)



Sinigrin (36)



Carvacrol (37)

