REVIEW ARTICLE

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Curcumin, Diallyl Sulphide, Quercetin and Gallic Acid Uses as Anticancer and Therapeutic Agents for Breast Cancer: Current Strategies and Future Perspectives

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ABSTRACT

Globally, Breast cancer is a complex and common disease. 12.5 % of all new annual cancer cases worldwide. In 2020 there were 2.3 million women with breast cancer diagnosed and 685,000 died globally. For long time, breast cancer treatments options include surgery, chemotherapy, hormone therapy and radiotherapy. However adverse effects from treatment options are frequently reported and multidrug resistance, fever, weakness, allergy and the absence of treatment for metastasis are the main issues with breast cancer treatment. Due to their safety, dietary bioactive molecules have become effective tools for the treatment and prevention of cancer cell lines and animal models in recent years. It has been demonstrated that the compounds curcumin, diallyl sulfide, quercetin and Gallic acid which are used as Indian spice and widely consumed fruits, suppress the growth of breast cancer cells and trigger apoptosis. The effects of curcumin, diallyl sulfide, quercetin and Gallic acid in the combat against breast cancer are covered in this review. These agents have been shown to have effects both in vitro and in vivo.

Keywords: Breast cancer, curcumin, diallyl disulfide, gallic acid, Quercetin.

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I. Introduction

In 2022 there will be an estimated 1.9 million new cancer cases diagnosed and 609, 360 cancer deaths in United States. This result should not be tract with previous result because estimates for 2022 do not reflect the impact of the COVID 19

pandemic they are on incidence and mortality data reported through 2018 and 2019 [1]. There are presently several treatment options for the breast cancer Surgery, chemotherapy, hormone therapy and radiotherapy. Unfortunately, these current treatments do not always effectively combat the disease and they have had only a minimally impact on the cancer's notable morbidity [2]. In addition to treatments like radiotherapy, hormone therapy and chemotherapy frequently have negative effects and tumor recurrence of breast cancer is multidrug resistance. Therefore, the discovery of effective medications is required to decrease the occurrence of breast cancer. Successful treatment of breast cancer remains a challenge. Due to their lack of minimal side effects, low cost and low toxicity when compared to manufactured medications, dietary phytochemicals have recently gained popularity as beneficial agents for the prevention and treatment of cancer [3]. Past few decades a number of phytochemicals have been discovered in plants and human diets. Research has revealed that these phytochemicals are crucial in the prevention of several malignancies, including breast cancer. The effectiveness of several dietary phytochemicals in breast cancer prevention and treatment was examined in several clinical trials [1], [4]. Due to their numerous biological actions and various molecular targets, dietary phytochemicals such as curcumin, diallyl sulfide, quercetin and gallic acid have drawn interest. Spices like turmeric and ginger contain phenolic acid curcumin (Table I). Curcumin, a phenolic molecule has been weel researched in relation to breast cancer. Diallyl sulfide is an organo sulfur chemical that is present in various well-known fruits (Table I). Breast cancer has been extensively examined using quercetin and various common fruits contain gallic acid (Table I). Breast cancer has also been the subject of substantial research on gallic acid. The anti-breast cancer properties of curcumin, diallyl sulphide, quercetin and gallic acid have been documented and their effectiveness has been shown with cancer cell lines (Table II-V) and animal models (Table VI). The use of these substances for prevention and therapy of breast cancer has not previously been widely covered, despite the fact that several outstanding studies provide information on the anticancer potential of these compounds against various malignancies [5]. Therefore, the potential use of these chemicals in the treatment and prevention of breast cancer is critically examined in this review.

II. Bioavailability and Metabolism of Curcumin, Diallyl Sulphide, Quercetin and Gallic Acid

Due to curcumin numerous biological properties such as antioxidant, anti-inflammatory, antiarthritic and antibacterial activites as well as its potential therapeutic applications for conditions like cancer and neurodegenerative diseases, has long been used as a traditional medicine and spice. Numerous investigations have demonstrated that after a short time, the in vivo metabolites of high doses of curcumin are very low in serum and tissues. Additionally, curcumin has a flexible backbone, is hydrophobic by nature and has access to a variety of hydrogen bond (H bond) donors and acceptors, making it an ideal structure for enzyme inhibitors [6]. The safe dose of curcumin was investigated in a phase I clinical trial and it was found that 10 g/day in humans showed adequate bioavailability. Due to limited absorption, fast metabolism and rapid systemic clearance curcumin appears to have low plasma and tissue levels. Several studies have been conducted to increase bioavailability. First, glucuronidation interfering adjuvants like piperine, followed by liposomes, phospholipid complexes and in fourth place, the utilization of structural analogues [7]. Oral administration of curcumin, a bioactive compound with high potential for health promotion, is generally limited by low water solubility and rapid degradation in the gastrointestinal tract, which encourages curcumin to be transported to the systemic circulation via the lymphatic system and portal vein [8]. Curcumin tolerated at high doses, without adverse effects. Curcumin is highly active biological material with the potential to treat different diseases in modern medicine [9]. Curcumin use as therapeutic agent relies on its bioavailability but rather its medicinal benefits may also arise from its positive influence on gastrointestinal health and function. Curcumin has been presented to inhibit IL6 induced STAT3 phosphorylation and consequent STAT3 nuclear translocation in multiple types of myeloma cell line [10]. Diallyl disulphide is thought effective against atherosclerosis. It preserved the interaction of eNOS with caveolin -1 in the membrane. DADS suppressed eNOS protein degradation by MG132 [11]. Diallyl disulphide has anticarcinogenic effects in animal model. Oral administration of 200 mg/kg to rats absorbed and transformed into allyl mercaptan, allyl methyl sulphide, and allyl methyl sulphoxide and allyl methyl sulphone which are detected the mention period [12]. Diallyl disulphide is a potent polysulphide present in garlic and contains three sulfur atoms in its molecular structure [13]. Numerous anticarcinogenic characteristics of diallyl disulfide include the prevention of tumor cell growth. In colonocytes purified from non-tumorous rats, the effects of diallyl disulfide on histone H4 and H3 acetylation levels were examined. Adminstered via gaveage, perfusion or intracaecal ingestion. In vivo, this has anticarcinogenic effects [14]. A dietary antioxidant flavonoid with anticarcinogenic effects is quercetin. After consuming fried onions, apples and pure quercetin rutinoside the plasma content of quercetin in patients with an intact colon gradually declined with elimination half-lives of around 25 h. Dietary quercetin may boost blood plasma's antioxidant capability [15]. Consumption of foods or beverages containing plant derivatives, quercetin is absorbed in the small intestine and either metabolized by the body or susceptible to catabolism by the gut bacteria, with the products them being absorbed by the colon [16]. Free radical damage is caused by the secondary metabolites called flavonoids that plants produce during metabolism. These compounds have a large number of double bonds and hydroxyl groups, which can donate electrons through resonance to stabilize the free radicals [17]. Onion quercetin glycosides were absorbed more quickly than the aglycone form. The metabolism and absorption of rutin and quercetin in rats were found to be influenced by a diet rich in quercetin [18]. Rats were given radioactive quercetin, which was found in body tissue in the digestive system. This reflection was found in faces, urine and cage washing for 72 hours after intake [19]. Moxidectin is a common antiparasitic medication used on livestock, sheep and pet animals. The

effects of ivermectin, quercetin and ketoconazole on the moxidectin metabolism in culture over a period of 72 hours demonstrated that certain compounds can increase the bioavailability in lambs [20]. Fruits, vegetables and herbal remedies like grapes all contain gallic acid [21]. Encapsulated polyherbal nanoparticles anticancer activity and pharmacokinetic characteristics increase their oral bioavailability and anticolon cancer efficacy [22]. Rats were given gallic acid and epicatechin and it was discovered that these substances were phenolic components due to their existence in the circulatory system [23]. Although the antioxidant and hepatoprotective properties of gallic acid are widely recognized, their efficiency is limited by the substances quick metabolism and excretion. Phospholipid complex higher absorption and greater bioavailability in rat serum have strengthened its therapeutic efficacy [24]. Diltiazem has an extremely low oral bioavailability because of the fast first pass metabolism it undergoes in the liver and intestine. Gallic acid treated group's duodenum, jejunum and ileum significantly increased diltiazem intestinal transit and apparent permeability [25]. Two substances, phosphatidylcholine and polyamidoamine dendrimer, were used to conjugate gallic acid. The release of both components has been greatly delayed by gallic acid conjugations for up to 12 hours. Gallic acid may become more bioavailable and have a greater hepatoprotective impact by conjugation [26].

III. Curcumin, Diallyl Sulphide, Quercetin, Gallic Acid and Breast Cancer

A. *Curcumin*

Sources: Curcumin [(1E, 6E)-1, 7-bis (4-hydroxy, 3-methoxyphenyl)-1, 6-heptadiene-3, 5-Dione) is present in turmeric, ginger, curry powder, curry dishes, red lentil coconut soup, butter chicken [27].

1) *Biological Effects*

In vitro studies: Curcumin inhibits MMP-2 and MMP-9 while increasing TIMP1 and TIMP4 gene expression on breast cancer cells, which helps to control cell metastasis. The effect of curcumin is explored on metastatic MMPs and anti-metastatic TIMPs genes on MDA breast cancer cells at 10, 20 and 40M concentration [28]. At all doses, curcumin caused the apoptosis of MCF 7 and MCF 10A cells. Among the 214 apoptosis related genes in the array, curcumin therapy changed the expression of 104 genes. On MCF 7 cells gene expression was altered 14 times more than on MCF 10A cells. At both 25 g/mL and 50 g/mL dosages in MCF 7 cells, about 22 genes were upregulated and 17 genes were downregulated. Upregulated genes include HIAP1, CRAF1, TRAF6, CASP1, CASP2, CASP3, CASP4, HPRT, GADD45, MCL-1, NIP1, BCL2L2, TRAP3, GSTP1, DAXX, PIG11, UBC, PIG3, PCNA, CDC10, JNK1 and RBP2. And Downregulated genes were TRAIL, TNFR, AP13, IGFBP3, SARP3, PKB, IGFBP, CASP7, CASP9, TNFSF6, TRICK2A, CAS, TRAIL-R2, RATS1, hTRIP, TNFb and TNFRSF5 [29]. Myristic acid chitosan nanogels were administered to MDA-MB 231 cells, curcumin and nanocurcumin inhibited cell proliferation in a concentration-dependent manner over predetermined periods of time [30]. MCF 7 has more telomerase activity than human mammary epithelial cells. With rising curcumin doses, this became inhibitory at 100 M concentration, telomerase activity in MCF 7 cell culture decrease. As hTERT expression is downregulated in MCF 7 cells. Telomerase activity is inhibited [31]. Anti-proliferative, pro-apoptotic and cell cycle arrest at G2/M phase inducing actions. Curcumin downregulated the important epigenetic regulator EZH2 by targeting numerous signals involved in growth maintenance, including NF-kB, Src and Akt/mTOR pathways [32]. In triple negative breast cancer, curcumin causes DNA damage that is accompanied by phosphorylation, increased expression and cytoplasmic retention of BRCA1 protein and limited nonspecific activity, all of which may improve survival for triple negative breast cancer patients [33]. Using p53 null MDA-H041 cells, low and high levels of p53 expressing TR9-7 cells and p53 downstream effector Bax, we were able to induce apoptosis in MCF 7 cells by increasing p53 levels and DNA binding activity. Tetracyclin tightly regulates p53 expression and Bax is the p53 proteins downstream effector [34]. Effect on MMPs and NFkB cell cycle regulating proteins in the cell lines BT 483 and MDA-MB-231 and expression of CDK4 and cyclin D1 respectively decreased [35]. A BALB/c mouse in vivo study using MDA-MB-231 cells found that when curcumin was given, the expression of the BCL-2 and Bax proteins changed, resulting in a higher Bax/Bcl2 ratio [36]. Inducing cytotoxicity in MDA-MB-231 and PA1 metastatic and stem cell characteristics by activating the intrinsic route of apoptosis. Migration is induced byMMP1 inhibition [37]. Activation of the CYP1A1 xenobiotic response elements DNA binding ability of the AhR as determined by the electrophoretic mobility shift experiment (EMSA). In isolated MCF 7 cytosol, curcumin was able to out bind 2, 3, 7 and 8-tetrachlorodibenzo-p-dioxin, the prototypical AhR ligand, showing that it directly engages the receptor [38]. The MCF 7 cell exhibits apoptosis inducing behavior, Akt phosphorylation and enhanced phosphorylation of glycon synthase kinase 3, a signaling enzyme known to promote cell proliferation, combining PI3K inhibitor with curcumin enhances the anti-apoptotic impact and the inhibitor is able to reduce the Akt phosphorylation and glycogen synthetase kinase 3 activation caused by curcumin [39]. Combination or alone treatment of PGV-0 and PGV-1 with doxorubicin on MCF 7 /Dox cells features over expression of HER2 IC50 value 80 μM, 21 μM and 82 μM. And this combination increase cell sensitivity and increased sub G-1 cell population and high affinity of HER2 at ATP binding site [40]. Curcumin is a polyphenol effective because of low solubility, bioavailability and quick degradation and metabolism and the efficiency of pure curcumin and curcumin loaded PLOGA-PEG in MCF 7 breast cancer cell [41]. HIF1 α accumulated in normoxia and curcumin proved to lower HIF 1 α and HIF 2 α level and HIF transcriptional activity reduced where curcumin negatively impact on clonogenic cell survival f Hep3B hepatoma and MCF 7 breast carcinoma cells. [42] BPA's proliferative effects on MCF 7 cells are inhibited. Curcumin modulates the miR19/PTEN/AKT/p53 axis to inhibit protective effects against BPA associated breast cancer promotion. BPA induced upregulation of oncogenic miR-19a and miR-19b and dysregulated expression of miR-19 related downstream proteins, including PTEN, p-AKT, p-MDM2, p53 and proliferating cell nuclear antigen were

reversed [43]. In MCF 7 cells treated with curcumin, upregulation of miR15a and miR-16 and downregulation of Bcl-2 were observed. Bcl-2 expression was recovered after miR-15a and miR-16 selective were silenced [44]. Overexpression of Bcl 2 also blocked curcumin induced autophagy in MCF 7 cells through its inhibitory interactions with Beclin 1 [45]. A549 and MCF 7 cell lines curcumin at 2, 20 M concentration had a highly substantial inhibitory effect on the expression of both PRMT5 and MEP50. PKC-p37-ERK-cFos and AKT-mTOR pathways were found to be active in lowering Sp1 and NF YA expression [46]. Downregulation of cyclin B1 and Cdc2 induces cell cycle arrest at G2/M phase and prevents colony formation in MCF 7 cell line. Following curcumin treatment in MCF 7 cells that had Bcl 2 overexpression, NF kB elevated the SSAR [47]. Expression of uPA and NF kB DNA binding activity reduce proliferation in a dose dependent manner and curcumin inhibits adhesion and invasion by down regulating the expression of the uPA protein via NF kB activation [48]. ROS production, DNA production, DAPI nuclear staining and DNA damage In TPH1 cells, cur SPD NPs decrease IL6 levels while raising TNF levels. MMPs including MMP8 cause the synthesis of TNFα and act as tumor suppressors in some malignancies [49]. MiR21 expression, which curcumin downregulated to induce apoptosis and aid to boost caspase 3/9 activities by upregulating PTEN/AKT signaling pathway was what influenced the expression of pAKT and pTEN protein [50]. Ginger contains curcumin and its extract treats breast cancer by regulating the proteins Bax and Bcl 2 in dose dependent manner. Prosurvival genes like NFkB, Bcl-X, Mcl-1 as well as cell cycle regulating proteins like cyclin D1 and CDK 4 were downregulated [51]. Induction of apoptosis in MCF 7 with an IC 50 10.12 g through the loss of mitochondrial membrane potential [52]. Ginger Extract expresses antioxidant activity due to curcumin and induces apoptosis with IC50 34.8 μg/ml on MCF 7 cell and IC50 value 35.53 μg/ml on MDA-MB-231 cell line [53].

2) Additive or Synergistic Effect of Curcumin with Other Phytochemicals and Therapeutic Agents

Curcumin and docosahexanoic acid were applied synergistically on SK-BR-3, MDA-MB-231, MDA-MB-361, MCF 7, MCF 10AT cell. Those genes involved with cell cycle arrest, apoptosis, inhibition of metastasis and cell cycle progression were downregulated. PPARγ and phosphor-p53 proteins were increased by combination or alone [54]. Breast cancer and normal cells were treated with citral in combination or alone. Inducing cell cycle arrest at the G0/G1 phase and inducing apoptosis in breast cancer cells, they both produce ROS and activate the p53 and poly (ADp-ribose) polymerase-1 mediated apoptotic pathways [55]. The combination of berberine a well-known natural chemical with strong anticancer properties, suppressed the proliferation of MCF 7 and MDA-MB-231 breast cancer cells more effectively than each compound used alone. Inhibition of JNK decreased LC3-II and Beclin1 restored phosphorylated Bcl-2 and reduced the induction of cytotoxicity. This combination elevated phosphorylation of JNK and Beclin1 and decreased phosphorylated Bcl-2. Additionally, the idea that JNK/Bcl-2/Beclin1 pathway was crucial in the induction of ACD in combination therapy [56]. Xanthorrhizol was combination used on MDA-MB-231 cells and induction of cell death and apoptosis was seen. Apoptotic cell death and further confirmed by DNA fragmentation assay [57]. Four anticancer chemotherapeutic agents doxorubicin and curcumin applied on breast cancer cell and the tyrosin kinase inhibitors like erlotinib, sunitinib, sorafenib are acting different cell pathways there synergistic effect was examine both in vitro and in vivo [58]. Quinacrine synergistically used on cancer stem cell and breast cancer cell, and they synergistically inhibited the proliferation, migration and invasion and increased DNA damage and inhibited DNA repair pathways SP cells. This combination therapy inhibited the ABCG2 activity by the reduction of ATP hydrolysis in cells. In vitro DNA binding reconstitution system suggests that quinacrine specifically binds to DNA and caused DNA damage inside the cell [59]. MCF 7 cell is synergistically treated with bisphenol, causing the cells to enter S phase. MiR-19a and miR-19b expression was upregulated, while the expression of miR-19-related downstream proteins such pTEN, p-AKT, p-MDM2, p53 and proliferating cell nuclear antigen was dysregulated. To present its preventive benefits against the promotion of breast cancer linked to bisphenols, curcumin regulates miR-19/ PTEN/ AKT/p53 [60].

3) Effect of Curcumin after Encapsulation

It has also been reported that this dietary agent induced apoptosis, and reduced AKT/mTOR activation and express antioxidant activity [61].

4) In vivo Studies

Curcumin and PGV-0 prevented HER2 from localizing to the membrane. The expression of MMP-2 and MMP-9 proteins was suppressed by curcumin and PGV-1, which also exhibit inhibitory actions against cell migration. In Mice, curcumin inhibits the growth of tumors from a xenograft model of metastatic breast cancer [62]. In allograft model MDA-MB-231 and MCF 7 express higher potency and tumor volume lowered as well as inhibited migration by downregulating the MMP1, 2 and vimetin while increasing immunity with minimal side effects [63]. After dosing procedure 27 mice were divided into 40 and 80 mg/kg groups of DNC on tumor bearing mice. Under the dosing procedure DNC was safe at 80 mg/kg and lower doses. Animal treated with DNC had smaller tumor volume than control group. Suppression of NF kB expression by DNC led to down-regulation of VEGF, COX-2 and MMP9 expressions in breast tumor, the lung, the brain, the spleen, and the liver tissues [64]. Application another xenograft model of MDA-MB-231 cell of subcutaneous injection in nude BALB/c mice and curcumin administered to the mice. The tumor size and weight were monitored. The expression of Bcl-2 protein decreased and the expression of Bax protein increased in vitro and tumor size and volume decrease in vivo study [65]. In vivo and in vitro model of MCF 7, MDA-MB-231, MCF-10A, BT-474 and SK-BR-3hr cells and the in vivo effect of curcumin on HER2 overexpressed breast cancer investigated with the HER 2 overexpressed BT-474 xenograft model. The combination of taxol and curcumin had an antitumor effect comparable with taxol and Herceptin [66]. In Xenograft model curcumin 100 μmol/L and mitomycin 2 μmol/L for 4 weeks applied. The combination effects more G1 arrest than mitocin alone treatment. The cell cycle arrest associated with cyclin D1, cyclin E, cyclin A CDK2 and CDK4 with

induction of cell cycle inhibitor p21 and p27 both model. The all-protein mention was regulated through p38 MAPK pathway [67]. MDA.MB231 by in vitro and in vivo experiments. We showed that curcumin is able to deregulate the expression of cyclin D1, PECAM-1, and p65, which are regulated by NF-κB [68]. Human breast cancer cell line induce athymic mice and treated with 300 mg/kg/day of curcumin administered intraperitoneally. Tumor size decrease and VEGF-c detect in vivo expression of VEGFR2/3 [69]. Modulation of miR181b in metastatic breast cancer cells in vivo model that miR181b down-modulates CXCL1 and -2 throug a direct binding to their 3-UTRs [70].

B. *Diallyl Sulphide*

Sources: Diallyl Sulphide (4, 5-dithia-1, 7-octadien) is oragnosulpher compound abundant in garlic, onion, Masterd, Japanese horseradish shalock [71].

1) *Biological Effects*

In vitro studies: Cleavage of caspase 3 and caspase 3 substrate poly (ADP-ribose) polymerase were observed. Diallyl sulfide 200 μmol applied and ERK and mitogen activated protein kinase inhibit and JNK, SAPK and p38 protein activated after 6 h. The mechanism involve with inhibition of ERK and SAPK/JNK and p38 pathways [72]. Diallyl sulfide decrease viability and increased apoptosis and suppression of metastatic potential in TNBC cells. Dysregulation of Bcl-2 protein and Downregulation of MMP-9 protein [73]. Diallyl disulfide and Diallyl trisulfide presents in galic and effective on triple negative breast cancer with expression of cell proliferation, tumor metastasis and angiogenesis. [74] Modulation of Bax, Bcl2 and Bcl-w level in dose dependant manner. Upregulation of Bcl 2 familly protein and Histone deacetylation inhibitors and Diallyl disulfide helps lower the removal of an acetyl group from an acetylated substrate and induces Histone4 hyper acetylation [75]. The expression of TTP, uPA, MMP-9 protein found in xenograft mouse model with Diallyl disulfide treatment. Down-regulation of uPA and MMP9 protein expression and significantly TTP expression upregulated [76]. Cell cycle arrest at subG0/G1 cell population and induce phosphorylation of the anti-apoptotic Bcl 2 and PARP protein. Diallyl Disulfide treatment activate JNK and induce phosphorylation and expression of c-JUN which exhibit increased DNA binding activity of AP-1, blocked by NAC and JNK inhibitor. Oral administration of 5 μmol/kg to female Balb/c mice inhibited tumor xenograft model of MCF 7 [77]. Treatment on MDA-MB-231 helps up-regulate the expression of miR-34a which enhanced antitumor effect both in vivo and in vitro model and miR-34a inhibiting SRC expression and trigger the suppression of the SRC/Ras/ERK pathway [78]. Triggering of CD44, PKM2, AMPK signaling pathways and 125 breast cancer patients this protein pathways expression positively correlated [79]. Treatment on MDA-MB-231 and HS578t breast cancer cell suppressed the migration and invasion and changed morphology as well as mRNA/enzymes activity of MMP2/9 via attenuating the NF kB pathways. Diallyl trisulfide inhibits ERK/MAPK rather than p38 and JNK pathway and MMP2/9 activity and the metastasis of triple negative breast cancer cells [80]. Diallyl disulfide loaded solid lipid nanoparticle with RAGE antibody to achieve site specific delivery of triple negative breast cancer cells. Downregulating anti-apoptotic proteins and upregulating pro-apoptotic proteins observed and improve antitumor activity and reducing off target effects [81]. Diallyl disulfide and Diallyl trisulfide non cytotoxicity against MCF-12A cells and high cytotoxicity against MDA-MB-231 ad MDA-MB-468 cells and induces apoptosis by activation caspase 3 and 9 and intracellular ROS release by cysteine pre-treatment. Diallyl disulfide also inhibited the surface expression of CD151 in triple negative breast cancer cells [82]. Treatment on MCF 7 and T47 result downregulation of ER α protein and mRNA suppression and inhibition of ERE2e1b luciferase repoter activity also diallyl trisulfide decrease Pin1 protein level and overexpression of Pin1 partially attenuated ERα downregulation [83]. Diallyl disulfide treated on liquid tumor in xenograft model and decrease tumor size by induce apoptosis by promoting caspase 3 expression and preventing degradation of anti-tumor proteins p53 upregulating antioxidant enzymes NQO1, SOD and reducing agents GSH [84]. Diallyl sulfide, Diallyl disulfide and Diallyl trisulfide were applied to MDA-MB-231 cells and the mRNA expression of HIF-1 target genes ANGPTL4, LOXL4 and LOX were downregulated. L1CAM, VEGF-A and EMT related proteins (slug, snail and MMP2) were also inhibited dose dependently, particularly by diallyl trisulfide [85]. Diallyl trisulfide cultured with MCF 7 and MCF 12a cells that induce apoptosis and decrease population at G2/M phase. The expression of FAS and cyclin D1 enhanced and down regulated the expression levels of Akt and Bcl 2. Furthermore, DATS induce apoptosis on MCF 7 cell with induction of proapoptotic Bax protein and p53 protein expression was upregulated and translocation to nucleus [86]. Diallyl trisulfide treatment of MDA-MB-231 and MCF 7 cell which inhibit the expression of ADAM10 and ADAM17 protein. It inhibits Notch ligands Jagged-1,2 involved in NOTCH signaling pathway [87]. Inhibition of invasion and migration of MCF 7 cells in dose dependent manner and down regulated protein expression of vimentin and MMP9 and upregulated E cadherin expression. [88] Preventing the creation of DNA adducts, reducing the amount of reactive oxygen species produced, controlling cell cycle arrest and triggering apoptosis. It counteracts the breast cancer enhancing effects of linoleic acid and enhances the breast cancer suppressing effects of eicosapentaenoic acid [89]. Suppress TNF-induced release of CCL2 and release of IL6, IL8, plasminogen activator1, TIMP1/2 and IL8 from triple negative breast cancer [90]. After a 24-hour treatment period on the MCF 10A cell line, diallyl sulfide with DES 10M in combination with 1, 10 and 100 M increased cell viability by 31%, 34% and 36% respectively [91]. FoxQ1 overexpression and protein level reduction in MCF 7 and SUMI159 cells elevated ALDH1 activity and the CD49F/CD24 fraction. Small hairpin RNA-based stable FoxQ1 knockdown enhanced bCSC suppression. Compared to normal mammary tissues, triple negative breast cancer has increased expression of the FoxQ1 protein [92].

2) *Additive or synergistic effect of Diallyl Sulphide with other phytochemicals and therapeutic agents*

Catechins and diallyl disulfide are synergistically treated in MCF cells. Halting the advancement of the cell cycle at the G0/G1 phase causing apoptosis with a rise Bax/Bcl-2 ratio and activating caspases 3 and 9 through an excess of reactive

oxygen species [93]. Tamoxifen inhibited ER dependent transcription, estradiol-induced phosphorylation and nuclear localization of mitogen activated protein kinase when used in combination or alone to treat MCF 7, ZR75 and T47D in vitro [94]. At low antiestrogen dosages, tamoxifen and diallyl rich extract jointly suppress the development of MCF 7 and MDA-MB-231 cells and induce apoptosis by modification of mitochondrial membrane potential, activation of caspase 8/9 and participation of intrinsic and extrinsic signaling pathways [95]. Allium tissue with selenium in combination with a diallyl disulfide rich extract caused the induction of apoptosis, but alone there was no evidence of cell viability. Both activated p53 and up-regulated GSK3/triggered the JNK pathway in the early stages of apoptosis [96]. Thirodxin was administered to tumor cells and this resulted in decreased Trx-1 production, NF kB expression and MMP2/9 expression. Combination siRNA mediated the expression of downstream genes related to metastasis [97]. Combining and applying allium tissue resulted in lower levels of AKT, GSK-3 proteins and higher amounts of phosphorylated c-JUN. Increased levels of phosphorylated p53, Bax and Bad signal apoptosis via the mitochondrial route. A caspase independent mechanism for apoptosis was implied by the absence of caspase 6/7 activation [98]. MCF 7, PaCa, PC3 treated with doxorubicin both in combination and alone by using chowtalaley method, the synergistic activity at various concentrations and times was estimated [99]. On MCF 7, ZR 75 and MDA-MB-231 cell lines, tamoxifen and diallyl disulfide rich extract of turmeric, ginger and garlic were administered together. Three cell line expressed an induction of apoptosis and the production of the caspase 9 protein [100]. On MDA-MB-231, HeLa, HepG2, and MCF 7 cell lines, tamoxifen is applied in combination with and alone in a dose- and time-dependent manner. Cell cycle arrest at the S and G2/M phase, downregulation of the proteins Cdk1, Bcl2 and Caspase 3/8/9 in the MCF 7 cell and MDA-MB-231 cell cycle arrest at the S phase with downregulation of the proteins Cdk1, Bcl2 and p53 as well as Sub G0 cell cycle arrest in HeLa cells with the downregulation of Cdk1. In HepG2 cells cell cycle arrest in the G0/G1, S and G2/M phases increased the caspase dependent protein p53 [101].

3) In vivo studies

Diallyl disulfide of 1.8 to 18.1 μM treated on MDA-MB-231 xenograft mice model and induction of tumor cell growth and apoptosis seen at sub G1 phase. The apoptosis cascade comprise up-regulation of Bax protein and down-regulation of Bcl-XL protein and activation of caspase 3 protein compared with control treated mice [102]. Application on animal models and in female ACI rats 4/6 weeks and the production of ROS and effectively inhibit DES bioactivation for chemopreventive intervention [103]. Treatment in vivo model induces Female ACI rats and RNA isolated from breast tissue and mRNA levels of CYP1A1, CYP1B1 and SOD increase but GST decrease [104]. Benzopyrine in combination treated with in vivo study in nude mice in time and dose dependent manner. Cell proliferation, cell cycle arrest, reactive oxygen species and DNA damage happen in breast cancer cell line [105].

C. Quercetin

Sources: Quercetin [2-(3, 4-Dihydroxyphenyl)-5, 7-dihydroxy-4H-1-benzopyran-4-one] is a polyphenolic flavonoid present in Grapes, Onion, cherry, Citrus fruit, berries, broccoli. Blueberry, peppers, Letus, cane berry, black tea, Red wine, Asperagus, Cabbage [106].

1) Biological effects

In vitro studies: 100M quercetin applied to 4T1 cells, cell viability and toxicity were observed. In vivo treatment quercetin inhibits the development of tumors and prolongs survival in BALB/c mice. The effects of quercetin on both tumor and normal cells were eliminated by HIF1 siRNA [107]. Foxo3a's protein level, transcriptional activity and nuclear translocation were stimulated by an increase in FasL, mRNA expression, p51, p21 and GADD45 signaling activities. Cell cycle arrest and apoptosis ere significantly reduced when Foxo3a was knocked down. JNK is a potential upstream signaling in the regulation of Foxo3a activity. Treatment with a JNK inhibitor eliminated quercetin stimulated Foxo3a activity [108]. Decrease the expression of VEGF, MMP2/9 cell migration markers. By reducing levels of PKM2, GLUT1 and LDHA and decreasing the generation of lectic acid and glucose absorption, quercetin effectively prevented cellular glycolysis [109]. Tamoxifen induced antiproliferation in MCF 7 cells was reduced by quercetin at low concentrations. High doses synergistically improved cell apoptosis through the ER route, it causes cell metastasis, cell cycle arrest and death [110]. in a dose dependent manner, quercetin and rutin reduce Pgp pump efflux activity. Pgp expression is decreased in MCF 7 ADR resistant cells when quercetin at 10 mM is added [111]. when administered to MCF 7, quercetin, myristin and epicatechin suppressed the synthesis of protein, DNA and RNA. Quercetin alone inhibit cytochrome p450 while myricetin and quercetin together lower GSH. While epicatechin only boosted NADPH cytochrome c reductase activity, three synergistic effects increased DT-diaphorase, NADPH cytochrome c reductase, and glutathione reductase [112]. Applying 1-100M quercetin to MCF 7 cells for 24, 48 and 72 hours causes cell cycle arrest, apoptosis and a decrease in cell viability, growth rate and colony formation [113]. Treatment on MCF 7 cells induce cell cycle arrest at G2/M phase and MMP2 protein, cyclin B1, Cdc2 kinase activity found in M phase and their level decrease. Increased cdk-inhibitor p21CIP1/WAF1 protein level and induction increased its association with Cdc2-cyclin B1 complex. Upregulation of p53 was not observed [114]. Topotecan 100 ng/ml on MCF 7 cells and 160 ng/ml in MDA-MB-231 cells and quercetin in combination and lone helps increase ROS and nitrite levels [115]. Induction of apoptosis and inhibition of proliferation on MCF 7 cells in time and dose defendant manner, mRNA and protein expression levels of surviving were reduced and induce apoptosis G0/G1 phase [116]. Induction of apoptosis on CT-23, LNCaP, MOLT-4 and Raji cell lines and tumor bearing mice of MCF 7 and CT 26 tumor size decrease at the dose and time dependent manner [117]. Quercetin and Fe_3O_4 conjugated applied on MCF 7 cell lines and cell morphology seen which helps to reduce cell number [118]. 50 and 200 μM treatment of Quercetin on MCF 7 Bcl 2 expression downregulated and Bax expression upregulated [119].

2) Additive or synergistic effect of Quercetin with other phytochemicals and therapeutic agents

Application of quercetin and kaemferol to breast cancer cells resulted in a synergistic impact that reduced nuclear proliferation antigen Ki67 expression and decreased levels of total protein in the treated cells [120]. Quercetin and curcumin modulate BRCA1 level, inhibits triple negative breast cancer cell survival and migration and induces histine acetylation of the BRCA1 promoter. Furthermore, reduction of BRCA1 promotes cell migration and survival in estrogen receptor positive cells while reducing the effectiveness of combination therapy [121]. Therapy with vitamin C in combination or alone induces apoptosis in breast cancer cells MCF 7, MDA-MB-231 and MDS-MB-468 at an early stage as opposed to treatment alone. The same therapy combined with cell cycle arrest in G0/G1 and S phase results in a notable increase in S and G2/M phase in A549 cells [122]. Treatment of MCF cells with 5 FU in combination or alone results in cell viability, apoptosis, gene expression of Bax, Bcl-2, p53 and caspase activity as well as overexpression of Bax, p53, and caspase-9 activity and downregulation of Bcl-2 gene expression [123]. Fisetin culture on the breast cancer cell lines MCF 7, MDA-MB-231, BT549, T47D and 4T1 alone induce colony formation and limit. Fisetin culture on the breast cancer cell lines MCF 7, MDA-MB-231, BT549, T47D, and 4T1 alone induce colony formation and limit cancer progression [124]. Combination therapy with quercetin and doxorubicin at 21 and 103 M concentrations on breast cancer cells was reported to have synergistic effects [125]. Rutin 20 M increases the cytotoxicity of cyclophosphamide and methotrexate on MDA-MB-231 cells. Application of quercetin and cell cycle arrest at G2/M and G0/G1 phases with rutin at 20, 50 M increases apoptosis in triple negative breast cancer [126]. In both combination and alone treatments 50 M quercetin and 32 nM doxycycline cause cell migration and suppress the production of MMP2 and MMP9 [127].

3) In vivo studies

Quercetin 20 µg/mL and siamois 1, 2 with 100, 200 µg/mL in combination and alone application induce apoptosis in vitro and in vivo on triple negative breast cancer [128]. Breast cancer cells exposed to quercetin exhibit cytotoxicity both in vivo and in vitro as well as cell cycle advancement and S phase cell cycle arrest. When quercetin was administered to mice with breast tumors, the mices lifespan increased by more than five times and the size and weight of the tumors shrank [129]. After 21 days of treatment with tamoxifen 5.6 mg/kg, tacrolimus 3 mg/kg and quercetin mg/kg on tumor bearing mice, there was a decrease in tumor development, a restriction on oncocyte proliferation and a promotion of tumor necrosis. In tumor tissue, the calcineurin/NFAT pathway lowers levels of VEGF, VEGFR2 and NFATc3 and downregulates the production of tumor necrosis. Calcineurine/NFAT pathway lowers levels of VEGF, VEGFR2 and NFATc3 and downregulates the production of VEGF, VEGFR2 and NFATc3 [130]. Control without quercetin, low dose with 0.02/ diet quercetin, moderate dose with 0.2% quercetin and High dose 2% diet quercetin injects on tumor bearing mice in time and dose dependent manner. The size and weight of tumor will decrease. About 31 genes were down-regulated and 9 genes were up-regulated by quercetin treatment [131]. Applying cisplatin to tumor bearing mice both alone and in combination lowers serum blood urea and creatinine levels, increases renal glutamyltranspeptidase and alkaline phosphatase activity, decreases renal thiobarbituric acid reactive substance and synergistically increases cellular toxicity in breast cancer cells while lowering renal toxicity and breast cancer growth inhibition [132].

D. Gallic acid

Sources: Gallic acid (3, 4, 5-trihydeoxybenzoic acid) is trihydroxybenzoic acid found in Strawberry, Banana, Grape, Apple, Walnut, Cashew, Avocado, Guava, Mango, Mulberry, Blackcurrant, Green Tea, Pomegranate. [133]

1) Biological effects

In vitro studies: By activating the extrinsic or Fas/FasL pathway, gallic acid causes apoptosis and suppresses proliferation in MCF 7 cells. Cross-linking between two pathways amplified the apoptotic signals that Gallic acid caused [134]. Mango and vimang extracts are both used to treat triple negative breast cancer. They inhibit NFkB activation by IKKα/β kinase, impaired IkB degradation, NFkB translocation, NFkB/DNA binding and NF kB target genes involved in inflammation, metastasis, anti-apoptosis and angiogenesis such as IL6, IL8, COX2, CXCR4, XIAP, Bcl2, VEGF [135]. A dose dependent slowing down of cell proliferation on MCF 7 cells. Cell cycle arrest at the G2/M phase and induction of apoptosis had a minimal impact on the number of sub G1 cells. Cyclin A, XDK2, cycline B1, cdc2/CDK1, p27 and p21 protein upregulation. Skp2, a particular E3 ligase for polyubiquitinating the p27 protein is downregulated [136]. Both alone and incombination gallic acid and curcumin slowed the development of MDA-MB-231 cells. Combination boosted the number of sub G1 cells in triple negative breast cancer cells. Bcl2 protein is downregulated whereas Bax, cleaved caspase 3 and PARP levels are upregulated [137]. 40, 80 M octyl gallate and gallic acid inhibit cell development and trigger apoptosis. Cell cycle regulators such as cyclin D1, D3, CDk4, p18, INK4, p21, waf 1 and p27 KIP are upregulated [138]. MMP9 protein and mRNA levels were upregulated and MCF 7 cells underwent cell proliferation and apoptotic induction. Phosphorylation of EGFR and Src is increased along with phosphorylation of Akt/ NFkB, p 65 and ERK/ cJUN pathway [139]. Treatment of melanoma and breast cancer cells with low laser level irradiation boost the generation of ROS and induce apoptosis. [140] Decrease in a dose-dependent way in MDA-MB-231 and HS578T extend the G0/G1 and sub G1 phase. Induce apoptosis by downregulating cyclin D1/CDK4 and cyclin E/CDK2 and upregulating p21 and p27 [141]. MCF 7 cell lines analogs 12 and 19 displayed antitumor activity. While on MDA-MB-231 cell lines Analogues 12, 19 and 22 showed. Compound 10 inhibits tubulin polymerization to manifest estrogen antagonistic action in vivo [142]. Upregulation of MMP9 and inhibited EGF cause Akt/p65 and ERK/cJUN phosphorylation, while down-regulation of MMP9 mRNA and protein expression is regulated in EGF-treated cells [143]. A549, MCF 7, HT 29 and 3T3 in vivo and in vitro culture in dose dependent manner tumor cell volume decrease and induction of apoptosis found in this treatment [144].

MCF 7 cell culture with gallic acid, GA/PLGA-IONPs and optimized FA-GA/PLGA-PEGylated-LIONPs were administered. Cell proliferation, apoptotic induction and cell cycle arrest were discovered [145].

2) Additive or synergistic effect of SF with other phytochemicals and therapeutic agents

Three mango extract contain polyphenol and 56 µg/mL combination culture with MCF 7 cells and triple negative breast cancer. Cell cycle growth and induction of apoptosis was seen [146]. Gallic acid and tamoxifen in combination and alone culture with breast cancer cell and downregulation of BCL2 and upregulation of SIRT1 expression rather than alone treatment [147]. Apple extract contain gallic acid and the combination and alone treatment of MCF 7 cell induce cell proliferation in dose dependent manner [148]. 159, 18 µg/ml caffeic acid and gallic acid culture on MCF 7 cells and combination and alone treatment occur activation of intrinsic apoptotic signaling pathway by upregulating p53, Mcl-1, p21 gene and protein expression [149].

3) In vivo studies

Gallic acid identified as an Ahr ligand with agonistic properties which induce binding of Ahr/Arnt to the SRE-box, enhanced of Ahr downstream genes including cytochrome p450 1A1 (CYP1A1), SRY related HMG box4 (SOX4) targeting miR212/132 cluster and miR-335 in both MDA-MB-231 and T47D cells. Apoptosis, inhibition of proliferation, migration, invasion by down-regulation of Bcl2, COX2 and SOX4 and up-regulation of p53 protein [150]. Tumor bearing mice was feed gallic acid containing grape seed extract that reduce tumor size and weight decrease as well as combination and alone treatment of genistein expressed the potent chemopreventive activity [151]. Increase cell cycle arrest in G1 phase and lowering tumor size and weight were seen MCF 7 and MDA-MB-231 tumor cell bearing mice when treatment incombination and alone with doxorubicin [152]. Peanut shell extract culture with MCF 7 cells tumor volume reduces in vivo. Cell cycle arrest, inducing apoptosis by upregulating Bcl-XL, Bax and p53 protein and their gene as well as down-regulate cell regulators cyclin A, Cyclin B and CDK2 [153]. Triple negative breast cancer bearing mice ingested walnut extract and tumor growth was inhibited after ten days. Eicosatetraenoic and docosahexaenoic acids, which help reduce tumor cell growth were discovered in the treated mice livers but walnut consumption had no effect on apoptosis [154]. Tamoxifen, 17-estradiol, MCF-7, MDA-MB-231, HEC-1A, SiHA, HeLa, SKOV3, and MCF 10A cells were treated in vivo and in vitro model where ER positive breast cancer cells growth and proliferation inhibited. [155].

TABLE I: CHEMICAL STRUCTURE AND FOOD SOURCES OF CURCUMIN, DIALLYL SULPHIDE, QUERCETIN, GALLIC ACID

Dietary compound	Chemical structure	Representative source	All dietary sources
Curcumin			Turmeric, Ginger, Curry Powder, and Curry dishes, red lentil coconut soup, Butter chicken.
Diallyl sulfide			Onion, Garlic, Garlic oil, Black Mustard, Japanese horseradish, shallot, leak.
Quercetin			Grapes, Onion, cherry, Citrus fruit, berries, broccoli. Blueberry, peppers, Letus, cane berry, black tea, red wine, Asperagus, Cabbage.
Gallic acid			Strawberry, Banana, Grape, Apple, Walnut, Cashew, Avocado, Guava, Mango, Mulberry, Blackcurrant, Green Tea, Pomegranate.

TABLE II: EFFECT OF CURCUMIN ON BREAST CANCER CELLS

Cell line	Model	Dose/duration	Effect	Mechanism	Reference
MDA-MB-231	In vitro	IC50 10, 20, 40 µM	Plays cell metastasis.	↓MMP2, MMP9 ↑TIMP1, TIMP4	[28]
MCF-7, MCF-10A	In vitro	25 and 50 µg/mL;24h	Treatment for cancer and cell apoptosis by multiple signaling pathways	↓TGFβ, RATS1 ↑BCL2, CASP1	[29]
MDA-MB-231	In vitro	37.75µg/mL; 12, 24 and 48 h.	Anti-cancer properties.		[30]
MCF-7, MCF-10A	In vitro	100 µM; 24 h	Inhibiting growth of breast cancer by inhibiting telomerase activity	↓hTER	[32]
MCF-7 /LCC2, MCF-7/LCC9	In vitro	2.50 µmol/L, 3 days	Antiproliferative, pro-apoptotic, induced cell cycle arrest at G2/M phase.	↓Cyclin D, C-Myc ↑P21	[33]
MCF-7	In vitro	5,10 and 20µM; 72 h	Phosphorylation, increase expression and cytoplasomic retention in BRCA1 protein.	↓HER2 ↑ER α	[34]
MCF-7	In vitro	10-7 to 10-9 M; 24 h	Induced apoptosis in breast cancer cell.	↓BcLxL,↑Bax, P53	[35]
MDA-MB-231, BT-483	In vitro	20 and 40 µM; 72 h	Antitumor activity by breast cancer cell proliferation and invasion by downregulating NFκB protein	↓ NFκB, CDK4, MMP1	[36]

TABLE II: EFFECT OF CURCUMIN ON BREAST CANCER CELLS (CONT)

Cell line	Model	Dose/duration	Effect	Mechanism	Reference
MDA-MB-231, MCF-7	In vitro, In vivo	10 and 50 μM; 72 h	Induction of apoptosis	↓BcL 2 ↑Bax	[37]
MDA-MB-231, PA1, MCF7	In vitro	30 and 40 nM; 72 h	Inhibition of MMP1 in breast cancer	↓Caspase 3, 9, MMP1	[38]
MCF7	In Vitro	10 and 20 μM; 72 h	Use as natural ligand and substrate AHR pathway	↓BCL2	[39]
MCF7	In Vitro	40 μM; 48 h	Induced apoptosis by blocking PKI3/AKt pathway	↓PKI3, AKT	[40]
MCF7	In Vitro	80, 21, 82 μM; 72 h	inhibition of HER2 activity and NF-kB activation	↓NFκB, ↑HER2	[41]
MCF7	In Vitro	10 μM; 72 h	Potential drug for breast cancer		[42]
MCF7, HPE3B	In Vitro	10 and 20 μM; 48, 72 h	Effects of curcumin on cell growth and survival factor expression.	↓HIF 1α, HIF 2α,	[43]
MCF7	In Vitro	40 μM; 72 h	Breast cancer promoting effect and trigger G1/S phase.	↑miR-19a and miR-19b ↓PTEN, AKT, MDM2, p53	[44]
MCF7	In Vitro	20 μM; 72 h	Anticancer drug on breast cancer cell and help to reduce Bcl2 via mir RNA expression	↓BCL2	[45]
MCF 7	In Vitro	100 μM; 48, 72 h	Induced apoptosis and use as anti-cancer drug	↓BCL2,PIK3, AKT	[46]
MCF 7, A549	In Vitro	2 - 20 μM; 72 h	Affects the PRMT5-MEP50 methyltransferase expression.	↓Sp1, NF γB	[47]
MCF 7	In Vitro	10 μM; 72 h	Cell cycle arrest at G2/M phase	↓BCL2 , NFkB	[48]
MCF 7	In Vitro	20 μM; 72 h	Induced apoptosis and cell cycle growth decreased	↓U PA, NF kB	[49]
MCF 7, HeLa Cell	In Vitro	5 - 20 μM; 72 h	Development of co-delivery of multifunctional nanoparticles with anti-cancer properties introduction	↓TNFα ↑MMPS, MMP8	[50]
MCF 7	In Vitro	2, 5 μM; 72 h	Anti-cancer properties on breast cancer by blocking miR-21/PTEN/Akt signaling pathway	↓PTEN, PAkt ↑Caspse 3/9	[51]
MCF-7, MDA-MB-231	In Vitro	0.2 mg/mL; 72 h	Antiproliferative activity and inhibit breast cancer cell growth	↓BCL2, NF-κB, Bcl-X, Mcl-1 ↑Bax	[52]
MCF 7	In Vitro	0, 20, 60 and 100 μg/ml; 72h	Uses of medicinal purpose and evaluate inhibition of growth and induction of apoptosis	↑ P53	[53]
MCF-7, MDA-MB-231	In Vitro	32.53, 30.20 μg/ml; 72h	Use as spice and find out antioxidant and anticancer activity		[54]
SK BR 3, MDA-MB-231, MDA-MB-361, MCF7 and MCF10AT	In Vitro	30 μM; 72 h	Antiproliferation synergy accompanies many signaling pathway	↓PPARγ ↑ P53	[55]
MCF-7, MDA-MB-231, MCF 10A	In Vitro	10-80 μM and 20-160 μM, 72h	Use of therapeutic intervention of breast cancer	↑P53, ADPrisbose	[56]
MCF-7, MDA-MB-231	In Vitro	5, 10, 20 μM; 72 h	potential application of curcumin and berberine in combination for the chemoprevention and treatment of breast cancer	↑Bcl2, Beclin1, pJNK ↓LC3 II	[57]
MDA-MB-231	In Vitro	15 μg/ml	Induced cell death by combination therapy	↑P53	[58]
MCF-7	In Vitro, In vivo		minimizing the toxicity and use combination therapy		[59]
MCF-10A-Tr	In Vitro	2.7, 4.9 μM; 72h	causing the DNA damage and inhibiting the DNA repair pathways through modulating the ABCG2 activity	↓ABCG2	[60]
MCF-7	In Vitro		Clinically use chemopreventive and therapeutic purpose of breast cancer	↓PTEN, p-AKT, p-MDM2, p53	[61]

TABLE III: EFFECT OF DIALLYL SULPHIDE ON BREAST CANCER CELLS

Cell line	Model	Dose/duration	Effect	Mechanism	Reference
MCF-7	In vitro	200 μmol/L; 6 h	Inhibit cell proliferation and induced apoptosis, ERK and the activation of the SAPK/JNK and p38 pathways	↓ ERK ↑ p38, Jnk, SAPK	[72]
TNBC and MDA-MB-231	In vitro, In vivo	20 μM	Antitumor effect and use of therapeutic purpose	↓ MMP9 , β catenine	[73]
MCF-7, MDA-MB-231	In vitro		Multidrug resistance mechanisms and their signaling pathways in breast cancer	↓ Wnt, NF kB, β catenine, ↑ E Cadherin	[74]
MCF-7	In vitro	20 μM, 72 h	Increase sub G0 population and induce apoptosis	↓ Bcl-2, Bcl xl, Bcl w, Bax ↑ caspase 3	[75]
MCF-7, MDA-MB-231	In vitro, In vivo	200 μM; 48 h	Antitumor, antiangiogenic, anticancer activity and stop cell progression	↓ uPA, ↓ MMP9	[76]

TABLE III: EFFECT OF DIALLYL SULPHIDE ON BREAST CANCER CELLS *(CONT)*

Cell line	Model	Dose/duration	Effect	Mechanism	Reference
MCF-7	In vitro	5 µM; 24 h	Induce apoptosis and activate jnk, APk1 protein and increase G0/G1 sup population	↓ JNK, ↓ NAC	[77]
MDA-MB-231	In vitro, In vivo	200 µM; 12, 24, 48 h	Antitumor effects of DADS	↓ RAS, ↓ ERK, ↓ SRC	[78]
MCF-7, MCF-7SC and MDA-MB-231, MDA-MB-231SC	In vitro	70 µM; 24 h	Suppresses cell stemness, proliferation, and metastasis and glucose metabolism	↓ CD44, PKM2, AMPK	[79]
HS578T and MDA-MB-231	In vitro	10, 20 µM; 48 and 72 h	Suppressed cell migration and invasion	↑ MMP2/9, ↓ ERK ↓ MAPK	[80]
MCF-7 and MDA-MB-231	In vitro	12.5 µM; 72h	Improving antitumor activity and reducing off target effects	↓ BCL 2,surviving ↑ caspase 9	[81]
MCF-12S and MDA-MB 231 PR and MDA-MB 468 PR	In vitro	5-50 µM, 24, 48h	Increase activity of drug resistance breast cancer	↑ caspase3/9, ↓ Wnt, β-catenine	[82]
MCF-7, T47D, MDA-MB-231	In vitro, In vivo	40 µM;12, 24 h	Inhibited growth and ER-α as a novel target of DATS in mammary cancer cells	↓ ERα	[83]
MCF-7	In vitro	20 µM; 24, 48 h	Induced apoptosis and G0/G1 and G2/M phases' cell cycle arrest	↑ caspase 3, P23 ↓ GSH	[84]
MDA-MB-231	In vitro	12.5, µM; 24, 48 h	Increase cell activity in drug resistance breast cancer	↓ HI 1F α	[85]
MCF-7, MDA-MB-231, ADAM 10, ADAM 17	In vitro	25 µmol/L; 48 and 72 h	Induce apoptosis and cell cycle arrest at G2/M phase	↑ p38, ↑ Bax ↓ AKT, Bcl 2	[86]
MDA-MB-231, MDA-MB-468, MCF-7 and T47D	In vitro	IC50 30, 40 µM	Inhibited growth, and induced apoptosis, functional bioactive compound	↑ HRAS, ↓ Jagged-1 and Jagged-2	[87]
MCF-7	In vitro	200 µmol/L; 24 h	Inhibit invasion and metastasis	↓ Vimetin, MMP9 ↑ E cadherin, TGF-β 1, P38	[88]
MCF-7	In vitro		Cell growth suppress and use as antagonize	↑ p53	[89]
MDA-MB-231	In vitro	100 µM	Inhibit cell growth by increase cell growth factor protein and use anticancer and chemo preventive agent	↓ TNFα	[90]
MCF-10A	In vitro, In vivo	1, 10, 100 µM; 24h	Altering cell viability by induce DNA Damage		[91]
MCF-7, SUM 159	In vitro In vivo	2.5, 5 µM; 72h	Inhibit cell growth and use anticancer drug	↑ FOXQ1, DACH1	[92]
MCF-7	In vitro	IC50; 172.2 µg/mL	Antitumor effect against breast cancer	↑ P53, caspase 3/9	[93]
MCF-7, ZR75, T47D	In vitro In vivo	0.5-10 µg/mL	Express anti-proliferative acitivity and inhibit cancer cell growth	↓ ERα	[94]
MCF-7, MCF 10A, MDA-MB-231	In vitro In vivo	8.5 and 15.0 µg/ml; 48h	Reduce side effect and effect in vivo studies	↑ caspase 8/9	[95]
MDA-MB-231	In vitro	10 µM; 48h	Induction of apoptosis	↑ GSK-3α/β, P53 ↓ JNK	[96]
MDA-MB-231 and HS 578T	In vitro, In vivo	20 µM; 72h	Effective antioxidant and metastasis	↓ MMP2/9, NFkB, TrX1	[97]
MCF-7	In vitro	62 µM and 91 µM	Anticancer effect of CySSPe	↓ AKT, GSK3, cJUN ↑ P53, Bax, Bad	[98]
MCF-7, PaCa, PC3	In vitro	0.29-290 µg/mL;72h	Synergistic effect on breast, prostate and pancreatic cancer	↑ P53	[99]
MCF-7, ZR-75, MDA-MB 231	In vitro	20 µM	Use as spice and anticancer effect finding	↑ P53, caspase 9	[100]
MCF7 and MDA-MB-231, HeLa and HepG2	In vitro	100 µg/m; 24, 48, 72h	Cell cycle arrest at G2/M phase and induce apoptosis	↓ P53, cdk1 ↑ caspase 3/8/9,Bcl 2	[101]

TABLE IV: IN VITRO EFFECT OF QUERCETIN ON BREAST CANCER CELLS

Cell line	MODEL	Dose/duration	Effect	Mechanism	Reference
4T1, HIF 1 alfa	In vitro	100 µM; 72 h	Induced cell cycle growth in breast cancer cell but opposite effect on normal cell.		[107]
MDA-MB-231, MDA-MB-157	In vitro	230 to 415 µM; 24 h	Induced apoptosis via targeting de novo fatty acid synthesis pathway.	↓ β-catenine, Bcl 2, FAS ↑ Caspase-3	[108]
MCF-7	In vitro	80 µM; 48 h	Induced autophagy	↓ MMP2, MMP9, AKT, mTOR	[109]

TABLE IV: In vitro Effect of quercetin on breast cancer cells *(CONT)*

Cell line	MODEL	Dose/duration	Effect	Mechanism	Reference
MCF-7	In vitro	30 µM; 72 h	Cell proliferation, migration, inhibition, invasion, apoptosis and cell cycle arrest	↑ P53	[110]
MCF-7	In vitro	10 µM; 48 and 72 h	Inhibition of breast cancer cell growth	↓ PGP	[111]
MCF-7	In vitro	100, 200 µM; 72 h	Antitumor efficacy	↑ cytochrome C	[112]
MCF-7	In vitro	100 µM; 24, 48 and 72 h	Inhibit Cell cycle growth, arrest G1/S phase and induced apoptosis.	↑ P53	[113]
MCF-7	In vitro	150 µM; 6, 48 h	Inhibition of tumor growth, cell cycle arrest at G2/M phase	↑ P53	[114]
MCF-7, ZR-75, MDA-MB 231	In vitro	100 and 160 ng/ml; 48, 72 h	Cytotoxicity and antitumor effect		[115]
MCF-7	In vitro	40 mg/ml; 72 h	Induced apoptosis at G0/G1 cell cycle arrest	↓ survivin	[116]
MCF-7, PC3, LNCap, CT 26, MOLT 4T	In vitro, In vivo	120 µM; 24h	Anticancer properties on 9 cell lines		[117]
MCF-7	In vitro	40 µM; 48 h	Anti-cancer agent and inhibit breast cancer growth.	↑ P53	[118]
MCF-7	In vitro, In vivo	50 - 200 µM; 72 h	Inhibit breast cancer growth and induce apoptosis	↑ Bax ↓ Bcl 2	[119]
HUTU80, CACO2, PMC42	In vitro	5 - 10 µM; 72 h	Anticancer activity and decide that this synergistic effect could be taken in orally.		[120]
MDA-MB 231	In vitro		Synergistically induce apoptosis	↓ BRCA1	[121]
MDA-MB 231, MDA-MB 468, A459	In vitro	2.28 – 7.7 and 10.5–66.6	Antitumor effect		[122]
MCF-7	In vitro		Cell proliferation, induction of apoptosis and suggestive for in vivo study	↑ Bax, P53 ↓ Bcl2	[123]
MCF7, MDA-MB-231, BT549, T47D, 4T1	In vitro		Cell proliferation, migration, colony formation and apoptotic pathway	↑ P53	[124]
MCF-7	In vitro	21 µM and 103 µM	Reduce cancer resistance		[125]
MCF7, MDA-MB-231	In vitro	20, 50 µM; 24, 48 and 72 h	Reverse multidrug sense and restore chemo sensitivity	↓ PGP	[126]
MDA-MB-231	In vitro	50 µM and 32 nM	Inhibit viability and migration	↑ MMP2/9	[127]

TABLE V: In vitro Effect of Gallic acid on Breast Cancer Cells

Cell line	Model	Dose/duration	Effect	Mechanism	Reference
MCF-7	In vitro		Induced apoptosis by cross link between two pathways.	↑ Fas/FasL	[134]
MDA-MB-231	In vitro		multifocal inhibition of NFκB activity in the cancer-inflammation network	↓ IL-6, IL-8, COX2, CXCR4, XIAP, bcl2, VEGF	[135]
MCF-7	In vitro	30 lmol/l; 48 h	Induced apoptosis, and leadinag G2/M cell cycle arrest.	↑ P27 ↓ P21	[136]
MDA-MB-231	In vitro	50, 150 µM; 24 and 48 h	Chemo preventive agent in triple negative breast cancer	↑ Bax, caspase 3, PARP ↓ Bcl 2	[137]
MCF-7, MDA-MB-231	In vitro	40 and 80 µM; 72 h	Induced apoptosis and use as anticancer agent.	↓ Cyclin D1, D3, CDK-4, CDK-6, p18 INK4, p21Waf-1 and p27 KIP	[138]
MCF-7	In vitro	10, 50 µM; 72 h	Induced apoptosis	↑ MMP9, AKT, MEK1 ↓ P65, C JUN,	[139]
MCF-10A and MDA-MB-231, A3575	In vitro	100, 200 µg, 48 and 72 h	Gallic acid and low level laser reduce cancer cell.		[140]
MDA-MB-231, HS578T	In vitro		Cell cycle arrest at G1 phase and induced apoptosis via p38 mitogen-activated protein kinase/p21/p27 axis	↓ cyclin D1/CDK4 and cyclin E/CDK2 ↑ P21, P27	[141]
MDA-MB-231, MCF 7	In vitro, In vivo	>300 mg/kg; 1 month and 5 µM; 72 h	Use as anti-breast cancer cell		[142]
MDA-MB-231	In vitro		Inhibit tumor growth and improve anti-tumor activity	↑ ↓ MMP9	[143]
MCF 7, HT 29, A549	In vitro, In vivo	50, 100 µM; 24, 48, 72 h	Anticancer activity		[144]
MCF 7	In vitro	75, 100 µM; 72h	Inhibition of tumor growth and induce apoptosis		[145]
MDA-MB-231, MCF 7	In vitro	56 µg/mL; 72 h	Induced apoptosis		[146]
MCF 7	In vitro	200 µM; 48 h	Suppress breast cancer growth and induced apoptosis	↑ SIRT1 ↓ BCL2	[147]
MCF 7	In vitro	100 µM; 72 h	Cell proliferation and synergistic effect increase	↑ P53	[148]
MCF 7	In vitro	159, 18, 16 µg/mL; 48, 72 h	Induce apoptosis and reduce cytotoxicity.	↑ P53, MCL 1 ↓ P21	[149]

TABLE VI: EFFECT OF CURCUMIN, DIALLY SULPHIDE, QUERCETIN AND GALLIC ACID ON BREAST TUMORS IN ANIMALS

Phytochemical	Effect	Dose/duration	Route	Reference
CURCUMIN	Inhibit cell growth of metastatic breast cancer	25 mg/kg; 2 and 12 days	Diet	[62]
CURCUMIN	antiproliferative, cytotoxic, and migrastatic properties have been explored.	30 mg/kg, 4 weeks	Intravenous	[63]
CURCUMIN	chemoprotective effect and suppression of NF-κB and its regulated gene products	40 and 80 mg/kg, 24 h	Intravenous	[64]
CURCUMIN	Antitumor effect and induction of apoptosis.	50, 200 ug/kg; 4 weeks	Intravenous	[65]
CURCUMIN	Reduced mammary tumor volume and multiplicity in estrogen treated ACI rats	200 μL; 14, 21 days	Intravenous	[66]
CURCUMIN	Inhibit cell proliferation and cell cycle inhibition	100 mg/kg/daily; 28 days	Intraperitoneal	[67]
CURCUMIN	adjuvant agent to chemotherapy in treatment of triple negative breast cancer	100 mg/kg, 30 days	Diet	[68]
CURCUMIN	Reducing tumor growth and cell proliferation, as well as in the inhibition of angiogenesis.	300 mg/kg/day for 4 weeks	Intraperitoneal	[69]
CURCUMIN	Bridge to bring metastasis modulation into the clinic, placing it in a primary and tertiary preventive, as well as a therapeutic, setting.	50 um/day; 13 days	Diet	[70]
Diallyl Sulphide	anticancer agent for both hormone-dependent and -independent breast cancers, and may harmonize with polyunsaturated fatty acids known as modulators of breast cancer cell growth	2 mg/kg/day; 7 weeks	Intravenous	[102]
Diallyl Sulphide	Inhibit tumor growth and use anticancer agents.	20 mg/kg/day; 4-6 weeks	Diet	[103]
Diallyl Sulphide	Induced tumor growth by altering DNA damage.	50 mg/kg; 4 days	Intravenous	[104]
Diallyl Sulphide	Cell proliferation, cell cycle arrest at G2/M phase and induce apoptosis	6, 60 μM; 24h	Intravenous	[105]
Quercetin	Induce apoptosis	20, 100, 200 μm/mL	Diet	[128]
Quercetin	Cell cycle arrest in S phase and increase life span of tumor bearing mice.	20, 40 and 55 μM; 48 h	Intravenous	[129]
Quercetin	Inhibit angiogenesis and suppress tumor growth	tamoxifen 5.6 mg/kg tacrolimus 3 mg/kg, Qu 34 mg/kg;21 days	Intravenous	[130]
Quercetin	Tumor volume and number decrease and about 31 gene upregulate and 9 gene downregulate	136 mg/day; 16 days	Diet	[131]
Quercetin	Enhance antitumor effect and decrease renal toxicity.	CP +Q = 7, 30 mg/kg	Intravenous	[132]
Gallic Acid	Important therapeutic implication through activation of Ahr signaling.		Intravenous	[150]
Gallic Acid	Use as chemopreventive in animal model	80 mg/kg, 50, 120days	Diet	[151]
Gallic Acid	Anticancer agent for independent estrogen receptor status cancer cell	GSE 100 μg/ml, Dox 25–75 nM	Intravenous	[152]
Gallic Acid	Inhibit tumor cell growth and use as anticancer agent in vivo study.	426 mg/g	Diet	[153]
Gallic Acid	Cell proliferation decrease but no apoptosis found in vivo study.	2.9 g per day	Diet	[154]
Gallic Acid	Protective effect for estrogent related breast cancer and beneficial for other hormone dependent tumor.	50 and 100 mg/kg	Diet	[155]

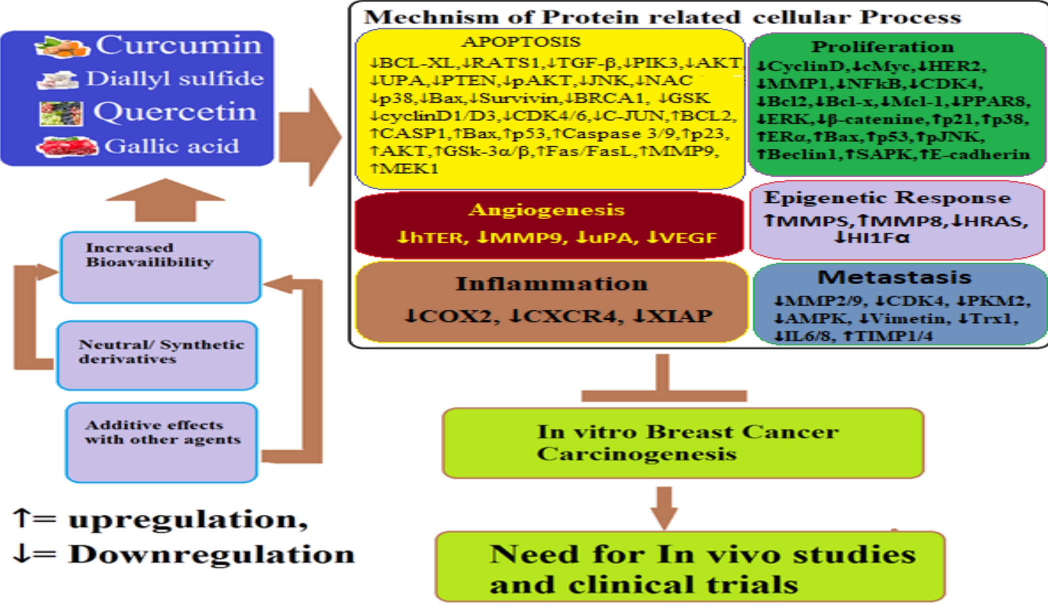

Fig. 1. Schematic representation of the role of curcumin, diallyl sulfide, quercetin, gallic acid in breast cancer with future directions.

IV. Future Directions and Conclusions

To ensure safety, study on dietary phytochemicals has become more important in the drug discovery field. Spices and a number of dietary phytochemicals have been recognized as having anti-breast cancer properties. Evidence points to curcumin, diallyl sulfide, quercetin and gallic acid as prospective candidates to be used in the development of an all-encompassing, effective strategy for the treatment and prevention of breast cancer. These dietary components have been shown to decrease tumor cell growth both in vivo and in vitro by inducing apoptosis, arresting the cell cycle and other anti-breast cancer activities. The majority of investigations have been carried out using in vitro models, according to the literature. In vivo investigations with suitable animal models of breast cancer must be carried out to confirm their efficiency. These phytochemicals might make the chemotherapy medications more effective and sensitive. In majority of the investigations, specific chemicals have been examined. More research is required to determine the agent's potential as a sensitizer and potentiator of chemotherapeutic medicines. Attention should be paid to improving bioavailability in preclinical research on curcumin, dially sulfide, quercetin and gallic acid as anticancer agents for the prevention of breast cancer (Fig. 1). Adding synthetic analogs of them might be a way to increase bioavailability. The improvement of bioavailability may also be facilitated by combinatorial therapy. Epidemiological investigations, clinical trials, the evaluation of safety profiles and the identification of novel target proteins and the pathways in which they function are also required. The in vitro and in vivo research that was looked at in this review points to curcumin, diallyl sulfide, quercetin and gallic acid as promising treatments for breast cancer.

Abbreviations

AKT, protein kinase B; Apaf-1, apoptotic protease activating factor 1; AIF, apoptosis inducing factor; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2 associated X; Bad, Bcl-2 associated agonist of cell death; CDK4, cyclin-dependent kinase 4; CDC2, cell division cycle2; COX-2, cyclooxygenase-2; CYP19/1A1/1A2, cytochrome P45019/1A1/1A2; DNMT1/3a, DNA (cytosine-5)-methyltransferase 1/3a; DMBA, 9,10-dimethyl-1,2-benzanthracene; ER-α, estrogen receptor- α; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FoxM1, fork head box M1; GSTA1, glutathione S-transferase A1; HDAC, histone deacetylases; HER2, human epidermal growth factor receptor 2; hTERT, human telomerase reverse transcriptase; JNK, jun N-terminal kinase; LC3, microtubule-associated protein light chain 3; mTOR, mammalian target of rapamycin; MMP-2, matrix metalloproteinase-2; MAPK, mitogen-activated protein kinases; NQO1, NAD(P)H quinone dehydrogenase 1; PTEN, phosphatase and tensin homolog; RARbeta2, retinoic acid receptor beta2; STAT3, signal transducer and activator of transcription 3; TrxR1, thioredoxin reductase 1; VEGFR-2, vascular endothelial growth factor-2. DADS, Diallyl disulfide; DATS, Diallyl trisulfide; TNBC, Triple Negative Breast Cancer.

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Conflict of Interest

Authors declare that they do not have any conflict of interest.

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