Review paper

Diallyl disulfide and diallyl trisulfide in garlic as novel therapeutic agents to overcome drug resistance in breast cancer

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ABSTRACT

Breast cancer is one of the leading causes of cancer-related deaths in women worldwide. It is a cancer that originates from the mammary ducts and involves mutations in multiple genes. Recently, the treatment of breast cancer has become increasingly challenging owing to the increase in tumor heterogeneity and aggressiveness, which gives rise to therapeutic resistance. Epidemiological, population-based, and hospital-based case-control studies have demonstrated an association between high intake of certain *Allium* vegetables and a reduced risk in the development of breast cancer. Diallyl disulfide (DADS) and diallyl trisulfide (DATS) are the main allyl sulfur compounds present in garlic, and are known to exhibit anticancer activity as they interfere with breast cancer cell proliferation, tumor metastasis, and angiogenesis. The present review highlights multidrug resistance mechanisms and their signaling pathways in breast cancer. This review discusses the potential anticancer activities of DADS and DATS, with emphasis on drug resistance in triple-negative breast cancer (TNBC). Understanding the anticancer activities of DADS and DATS provides insights into their potential in targeting drug resistance mechanisms of TNBC, especially in clinical studies.

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1. Introduction

Breast cancer (BC) is the most prevalent type of cancer globally, affecting approximately 2.1 million people every year and causing the most cancer-related deaths among women. The incidence of BC depends on several risk factors, including genetic predisposition, diet, age, family history, reproductive factors, lifestyle, and hormones. BC tumors are complex and exhibit a high-degree heterogeneity, with remarkably different alterations in the hormone receptor (HR) and the human epidermal growth factor receptor 2 (HER2) among tumors. The subtypes of BC include luminal cell-like BCs (luminal A and luminal B) which express receptors (estrogen receptors (ERs) and progesterone receptors), HER2$^+$ BC, and basal-like/triple-negative BC (TNBC). Luminal A BC (HR$^+$/HER2$^-$) tumors are usually slow growing and are less aggressive than luminal B BC (HR$^+$/HER2$^+$) tumors. HER2$^+$ SC is characterized by the increased levels of HER2$^+$/Erb-B2 and Ki67 proliferation marker [1]. TNBC (HR$^-$/HER2) is the most aggressive form of BC and has a poor prognosis due to the absence of HRs. TNBC patients with different molecular subtypes respond differently to treatment.

2. Drug-resistance mechanisms in TNBC

TNBC is curable, if localized at a primary site; however, the progression of primary tumors to distant organs is incurable and leads to death in patients. Chemotherapy is the most conventional approach to combating TNBC. Despite considerable developments, chemotherapy has become ineffective at combating advanced-stage BC due to multidrug resistance (MDR); therefore, treatment of TNBC patients is challenging for clinicians. In recent years, substantial efforts have been made to elucidate the molecular mechanisms of MDR in TNBC, especially to identify potential therapeutic targets [2]. These studies demonstrate that the mechanisms that

confer MDR are complex and involve the tumor microenvironment (TME), drug efflux, cancer stem cells, and bulk tumor cells in multiple signaling pathways (Fig. 1). Luo et al. [3] demonstrated that the aberration in the checkpoint kinase 2 (CHK2) controls the cell cycle and imparts chemoresistance to chemotherapeutic drugs in TNBC cells. This study concluded that the Y390 mutation in CHK2 confers cisplatin (CIS) resistance by inducing apoptosis and cell cycle arrest through control of the p53/CHK2 pathway. Shu et al. [4] demonstrated that bromodomain and extra-terminal motif bromodomodain inhibitors inhibit the oncogenic transcription programs by displacing the bromodomain and extra-terminal motif protein from chromatin, in order to compete with acetyl-lysine recognition modules in TNBC cells. Mani et al. [5] reported that enhanced DNA damage repair and checkpoint activation of the cell cycle are the major driving forces of drug resistance in TNBC. Prexasertib-treated TNBC cells had decreased levels of the DNA damage repair proteins, namely, BRCA1 and RAD51. Chen et al. [6] reported that the over-expression of cyclin E sensitizes TNBC cell lines and patient-derived xenograft models to Wee1 kinase inhibitors by inducing replication stress, indicating that drug resistance in TNBCs develops through decreased cyclin E expression.

Thu et al. [7] reported that the interruption of the anaphase-promoting complex results in drug resistance to the monopolar spindle 1 inhibitor, CFI-402257, by increasing tolerance to genomic instability and inactivation of the spindle assembly checkpoints. EDD E3 ubiquitin ligase, which regulates the S-phase and G2/M DNA damage checkpoints, promotes drug resistance to CIS and doxorubicin (DOX) in TNBC by activating the target of rapamycin complex 1 pathway and enhancing the expression of antiapoptotic proteins [8]. Ozawa et al. [9] demonstrated the development of drug resistance to docetaxel and DOX in non-tumorigenic breast cells by culturing these cells with exosomes from drug-resistant TNBC cells, and that the reported drug resistance was mediated by changes in the genes that promote cell proliferation, especially in the PI3K/AKT, mitogen-activated protein kinases (MAPK), and hypoxia inducible factor-1 α (HIF-1α) pathways. TNBC cells adapt to 5-fluorouracil, DOX, or docetaxel-induced apoptosis by enhancing cytoprotective autophagy through the overexpression of Bcl2-associated athanogene 3, an antiapoptotic co-chaperone [10].

In BCs, drug resistance is developed through the transformation of normal cancer cells into cancer stem cells (CSCs). For instance, MDA-MB-231 cells develop drug resistance to DOX via STAT3-dependent expressions of octamer-binding transcription factor4 (Oct4) and superoxide dismutase 2 (Sox2) [11]. Poly ADP ribose polymerase (PARP) inhibitors are used for treatment of heritable cancers. Liu et al. [12] reported that the BRCA1 mutant TNBC stem cells are resistant to PARP inhibitors. However, the silencing of RAD51 with siRNA sensitizes BRCA1 mutant TNBC stem cells to PARP inhibitors and reduces the tumor growth in xenograft models. They also reported that drug resistance to PARP inhibitors in TNBC stem cells is mediated by enhanced cell proliferation via RAD51. Chen et al. [13] demonstrated that components in conditioned media from mesenchymal stem cells, mainly IL-8, induce resistance to DOX in TNBC cells by enhancing stemness through the alteration of biological functions of BC-resistant proteins. Further, Yeh et al. [14] reported that CXCL1 present in the conditioned media from mesenchymal stem cells mediates resistance to DOX via miR-106a-dependent upregulation of ABCG2, an ATP-binding cassette transporter in TNBC. Stem cells are also associated with drug resistance in TNBC [15]. This mechanistic study revealed that caveolin-1 mediates drug resistance in stem cells via the upregulation of β-catenin/ABCG2. Recently, Ryoo et al. [16] reported the relationship between drug resistance and the expression of nuclear factor E2-related factor 2 (Nrf2), which is a key regulator of antioxidant genes and CD44 markers in TNBC stem cells. Nrf2 activation promotes drug resistance via CD44-dependent p62 signaling. TNBC stem cells develop resistance to drug-induced apoptosis through a positive feedback loop, via neurotrophin nerve growth factor-mediated overexpression of its receptors, namely, p75 neurotrophin receptor and TrkA [17]. Additionally, drug resistance is promoted by developmental pathways, such as the hedgehog pathway [18]. For example, BC cells develop resistance to tamoxifen by increased stem cell proliferation, and by the dissemination of paracrine signaling to the TME via PI3K/AKT-dependent overexpression of GLI1 [19]. A recent study showed that a subpopulation of TNBC stem cells increases chemoresistance and metastasis via Notch1 signaling [20]. Darvishi et al. [21] described NF-κB as a critical mediator of the development of TNBC resistance to tyrosine kinase inhibitors. Hypoxia, inflammation, and reactive oxygen species (ROS) in the TME are highlighted as the hidden factors that exacerbate the NF-κB-mediated drug resistance in TNBC.

Recent studies have suggested that miRNAs contribute to the drug resistance in TNBCs. For example, a study found that miR-301b promotes drug resistance in TNBC by targeting cylindromatosis, thereby inhibiting drug-induced apoptosis [22]. This study showed that miR-301b targets cylindromatosis by interacting with the 3′-UTR of cylindromatosis mRNA via NF-κB activation. However, miR-181a mediates DOX resistance by increasing metastasis via the activation of signal transducer and activator of transcription 3 (STAT3) in TNBC cells, and activation of STAT3 is reliant on NF-κB-mediated IL-6 induction [23]. Another study showed that miRNA-21, activated by matrix hyaluronan/CD44-induced c-Jun signaling, mediates drug resistance in TNBC cells [24]. The binding of hyaluronan to CD44 enhances the expression of BCL2, an anti-apoptotic protein, and the expression of inhibitors of the apoptosis family of proteins via the c-Jun signaling pathway [24]. miRNA-21 also mediates the resistance to trastuzumab by modulating epithelial-mesenchymal transition (EMT) through the IL-6/STAT3/NF-κB-dependent signaling loop, and activation of the PI3K pathway, in HER2 BC cells [25], in addition to expanding the cancer stem cell population [26].

Zhang et al. [27] demonstrated that autophagy confers resistance of TNBC to epirubicin through overexpression of p-glycoprotein and through interference with NF-κB-mediated pro-
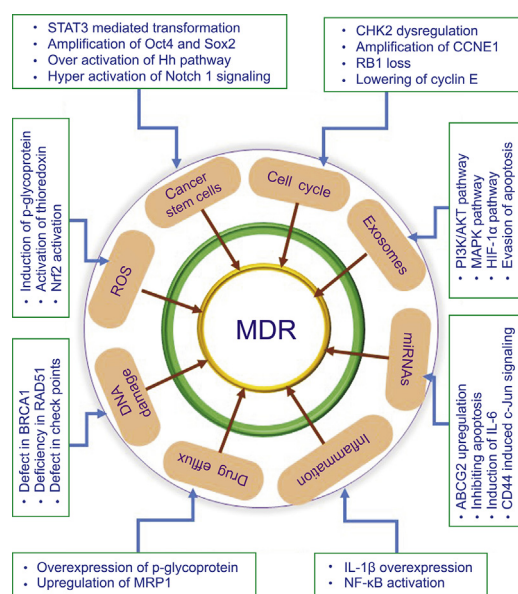

Fig. 1. Cellular and molecular mechanisms that are involved in driving drug resistance in breast cancer. ROS: reactive oxygen species; MDR: multidrug resistance; MAPK: mitogen-activated protein kinase; HIF: hypoxia inducible factor; IL: interleukin.

apoptosis. Yin et al. [28] found that FZD8, a Wnt receptor, and FZD8 targets, LEF1 and TCF, mediate resistance to CIS by inducing stem cell characteristics in TNBCs. Wang et al. [29] conducted a study on IL-6 dependent resistance in MDA-MB-231 cells and found that IL-6 promotes drug resistance by upregulating HIF-α via activation of STAT3 and by reducing the sensitivity of TNBC cells to drug-induced apoptosis, through the downregulation of BAX expression and the overexpression of BCL2 and drug transporters, such as p-glyco-protein and MRP1. In TNBC, PDGFRβ mediates drug resistance to inhibitors of JAK or MEK by promoting the infiltration of CD8$^+$ T cells [30]. In addition, inflammation is associated with TNBC drug resistance. IL-1β, one of the major inflammatory cytokines, mediates resistance to CIS by upregulating the expression of survival factors via ΔNP63α, an isoform of tumor protein 63, in BC cells [31]. Redox imbalance and reprogramming of cancer cell metabolism are also responsible for drug resistance in BC. BC cells develop resistance to tamoxifen by inducing ROS stress via thioredoxin (Trx) [32]. Wang et al. [33] demonstrated that the development of resistance to DOX, paclitaxel, or carboplatin in TNBC is associated with the overexpression of B7-H4, an immunoregulatory protein, through the PTEN/PI3K/AKT pathway.

3. Allyl sulfur compounds in garlic

Currently, phytochemicals are the most suitable lead candidates for anticancer drug development. Extensive research has been conducted on the development of novel therapeutic drugs from natural products [34]. Recent investigations have demonstrated that natural products work selectively and act specifically on tumor cells by targeting multiple pathways related to BC with minimal effect on normal cells [35]. Natural anticancer products that target drug resistance may be an effective treatment approach to mitigating TNBC. Examples of these natural anticancer products include taxanes derived from *Taxus brevifolia* [36], vinca alkaloids from *Catharanthus roseus* [37], and epipodophyllotoxins from *Podophyllum hexandrum* [38]. Dietary phytochemicals with anticancer properties against TNBC have therefore attracted the attention of researchers.

Allium sativum (garlic) was typically used in ancient Egypt, Greece, Rome, China, and India as a medicinal herb to treat wounds, digestive problems, and infections, in addition to being used as a seasoning for foods with religious significance. As an ancient Indian medicine, garlic was consumed as a tonic and rejuvenating agent to cure cough, loss of appetite, weakness, and hemorrhoids. Hippocrates used garlic to cure leprosy, whereas Aristophanes and Galena used it for the treatment of uterine tumors. The biological activity of garlic is attributed to the presence of water-soluble γ-glutamyl S-allyl cysteine and oil-soluble allyl sulfur compounds [39]. Water-soluble compounds include S-allyl cysteine and S-allyl mercapto-cysteine, whereas oil-soluble allyl sulfur compounds include diallyl sulfide, diallyl disulfide (DADS), and diallyl trisulfide (DATS) [40]. Allicin is one of the main bioactive compounds found in raw garlic cloves [41]. Allicin decomposes to diallyl sulfide, DADS, and DATS derivatives during cooking; however, in the presence of organic oils, allicin forms ajoene and vinyl dithiones [42]. The presence of different bioactive sulfur compounds in raw, preserved, or cooked garlic has made it an essentially recommended commodity from centuries.

3.1. Pharmacological importance of DADS and DATS

Recent evidence has garnered considerable interest in allyl sulfur compounds (such as DADS and DATS) owing to their potential health benefits. The chemical structures of DADS and DATS were drawn using the online version of PubChem sketcher version 2.4 to represent compounds (Fig. 2). DADS is known to have various pharmacological effects, such as antioxidant and anti-inflammatory effects. The anti-inflammatory effects of DADS include reduction of cytokine secretion and suppression of tumor necrosis factor-α (TNF-α) activity, while its antioxidant effects include enhancement of the activity of glutathione peroxidase and superoxide dismutase (SOD) [43]. DADS also has cardiovascular protective effects as it ameliorates cardiac dysfunction induced by streptozotocin, by activating Nrf2 signaling [44]. DADS inhibits thromboxane formation; therefore, it displays antiplatelet activity [45]. Additionally, DADS shows hepatoprotective activity in CCL$_4$-treated rats as it reduced CYP2E1 protein levels, prevents the depletion of cytosolic Nrf2, and reduces phase II detoxifying enzymes [46]. Furthermore, DADS protects human chondrocytes from IL-1β induced oxidative stress and apoptosis by reducing ROS levels, increases the nuclear translocation of Nrf2, and reduces the expression of BCL2 [47]. DADS has been reported to improve lipid metabolism by blocking the expression of PCSK9 and enhancing the uptake of low-density lipoprotein through the targeting of PI3K/AKT-SREBP2 signaling [48]. DADS has also been shown to have hypoglycemic activity as it regulates purine metabolism by reducing the activity of xanthine oxidase and adenosine deaminase in diabetic rats [49].

DATS is another important pharmacologically active compound found in garlic. It has been shown to have antithrombotic, anticoagulant, and antiplatelet activities [50]. DATS exhibits cytoprotective activity against valproate-induced hepatotoxicity by maintaining the integrity of hepatocytes and by reducing hepatic steatosis and inflammation-induced necrosis through blocking the production of TNF-α, IL-6, and IL-1β, as well as by reducing COX2 expression and inhibiting NF-κB activity [51]. DATS has also been reported to have protective effects against alcohol-induced oxidative stress, as it enhances the generation of H$_2$S through upregulation of cystathionine γ-lyase and cystathionine β-synthase expression, and reduces ROS. DATS also protects hepatocytes from ethanol-induced apoptosis by reducing the expression of BAX and enhancing the expression of BCL2 [52]. In rats with chemically-induced diabetes, DATS increases insulin secretion and improves oral glucose tolerance [53]. In CCL$_4$-treated rats, DATS showed hepatoprotective activity as it improves the integrity of liver cell histology, and reduces the levels of hepatic enzymes. DATS also attenuates collagen deposition and inhibits hepatic stellate cells by reducing the expression of TGF1β, PDGF-β, and EGF receptors [54]. In addition, DATS has cardioprotective activity as it increases the bioavailability of NO and releases H$_2$S [55]. These findings describe the pharmacological importance of DADS and DATS in ameliorating various stress-related diseases, including cancer.

3.2. Impact of DADS and DATS on BC

Epidemiological studies have shown that the intake of *Allium* vegetables is strongly associated with reduced BC risk. Population-based studies reveal that a high intake of garlic and onion may have preventive effects against BC [56]. Moreover, a hospital-based case-control study of 285 women confirmed to have an inverse association between consumption of *Allium* vegetables, particularly garlic
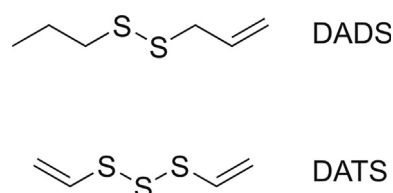

Fig. 2. Chemical structures of diallyl disulfide (DADS) and diallyl trisulfide (DATS).

and leek, and risk of BC [57]. Dietary guidelines for BC encourage increased intake of garlic and cruciferous vegetables, as a part of nutritional therapy, to improve the overall health of BC patients [58]. These vegetables contain highly reactive sulfur compounds that interact with cellular macromolecules, suggesting that these vegetables, especially garlic, are potent inhibitors of phospholipase A2 [59] and MAPKs [60], cytochrome P450 and glutathione-*s*-transferases [61] that may reduce cancer risk. DADS and DATS are major allyl sulfur compounds known to exhibit anticancer effects by interfering with cancer cell proliferation, tumor metastasis, and vascularization, which appears to be under redox control [62,63]. In addition, DADS and DATS interfere with cell signaling pathways that regulate cell apoptosis and cancer cell mitosis [64,65]. Furthermore, DADS antagonizes the effect of linoleic acid and synergizes the effect of eicosapentaenoic acid in BC [66]. These features suggest that allyl sulfur compounds should be considered as potential natural inhibitors.

3.3. Modulation of MDR by allyl sulfur compounds

The development of MDR is a considerable challenge in the treatment of TNBC. The cell cycle and apoptosis are regulated by various proteins (e.g., p53 and p21). The tumor suppressor gene, p53, is a master regulator of apoptosis. Many chemotherapeutics promote apoptosis in cancer cells by modulating pro-apoptotic and anti-apoptotic factors via the p53 pathway [67]. BAX is a pro-apoptotic protein that antagonizes BCL2, an anti-apoptotic protein, causing cytochrome leakage that subsequently activates APAF1. Activated APAF1 activates caspases, and the activated caspases induce cell-cycle arrest and subsequent cell death. Cells undergoing cell-cycle arrest can be protected from drug-induced apoptosis and ultimately develop drug resistance [68]. Migration and invasion are two distinctive characteristics of metastatic cancers. A recent study reported that metastasis-related genes promote drug resistance to chemotherapeutics by regulating various signaling pathways [69]. Preclinical studies have provided sufficient evidence indicating that angiogenesis is one of the hallmarks of cancer drug resistance [70]. Tumor cells protect themselves against oxidative damage by activating redox signaling and low oxygen conditions, thereby enhancing drug resistance. For example, the Trx system protects against oxidative damage, hypoxia, and oxidative stress. After rapid division, BC cells exceed Hayfleck's limit, and angiogenesis cannot supply required oxygen to the cells and develops hypoxia by increasing the expression of HIFs [71]. The changes in the epigenetic status of cancer are often linked to modifications in the function of miRNAs, the pattern of histone deacetylase activity, histone acetylation, hyperacetylation status, and histone deacetylation. This leads to gene silencing, which is progressively linked to cancer pathogenesis. Investigation of epigenetic mechanisms in drug-resistant cancers has revealed that drug resistance is induced by silencing or reactivating genes [72]. However, targeting the driving mechanisms of drug resistance sensitizes cancer cells to chemotherapeutics. The major proteins involved in the establishment of MDR are P-glycoprotein (ATP-binding cassette transporter) and multidrug resistant protein 2 (ATP-dependent transporter) [73]. Designing feasible therapeutic options against these drug transporters to kill more tumor cells is challenging. In line with this, the organosulfur compounds, DADS and DATS, may have different effects on drug transporter proteins. However, to date, there have been insufficient data on DADS and DATS in terms of the impact of these compounds on the mechanisms of MDR in BC. Therefore, the present review aims to highlight recent updates on the potential anticancer activities of DADS and DATS, with special attention to drug resistance in TNBC. The cellular

and molecular mechanisms modulated by DADS and DATS, to combat drug resistance in BC, are summarized in Table 1 [43, 74–127].

3.4. Effects of allyl sulfur compounds on the cell cycle and apoptosis-mediated drug resistance

Previous studies have reported that allyl sulfur compounds exert proapoptotic activity by activating p53 [74]. These compounds influence cellular mechanisms in BC cell lines by downregulating anti-apoptotic factors and upregulating proapoptotic signal proteins and caspases. DADS has antioxidant, antiangiogenic, and anticancer activities. In light of this, recent evidence on garlic suggests that DADS and DATS exert an anti-proliferative effect on MDR-colorectal carcinoma cells by changing the permeability of mitochondria [75]. DADS treatment reduces the viability and metastatic potential of TNBC cells in an in vitro model by down-regulating matrix metalloproteinase-9 (MMP-9) and promoting the reversal of EMT through inhibition of the β-catenin signaling pathway. DADS reduces tumor size by inducing apoptosis in the xenograft model, suggesting that DADS may be used as a potential therapeutic agent for treating or preventing BC [76]. Furthermore, DADS treatment remarkably reduces the proliferation, invasion, and migration of MDA-MB-231 BC cells in a xenograft tumor model and in an in vitro cell line model by downregulating uPA and MMP-9 expression and upregulating tristetraprolin expression [77]. A protein-nanoemulsion of DADS and α-linolenic acid substantially inhibits the proliferation of BC cells by inducing cell cycle arrest and apoptosis at the Go/G1 phase, via inhibition of the ERK1/2 pathway [78]. Palmitic acid containing solid-liquid nanoparticles with DADS causes apoptosis in BC cells by increasing the expressions of BAX, BAD, caspase-3, and caspase-9. However, negligible cytotoxicity to normal breast epithelial cells (MCF-12A) was reported in the pH-dependent release of DADS [79]. The receptor for advanced glycation end-products antibody-coated solid lipid NPs loads with DADS (DADS-SLN), specifically delivers DADS to TNBC cells, and induces cytotoxicity by downregulating BCL2 and survivin and upregulating caspase-9. This suggests that the receptor for advanced glycation end-products-mediated delivery improves the antitumor activity of DADS in TNBC patients [80]. A study showed that DATS treatment ameliorates endoplasmic reticulum (ER) stress-induced apoptosis and reduces tumor growth by progressive activation of ER stress proteins, such as CHOP/GADD153 and GRP78/Bip, and by upregulation of other proteins such as ATF4 and eIF2 [81]. The results of these studies suggest that DADS treatment sensitizes dysfunctional BC cells by targeting survival mechanisms.

3.5. Effects of allyl sulfur compounds on metastasis-dependent drug resistance

Targeting metastasis-related genes with natural compounds sensitizes BC cells to chemotherapeutics. Research has shown that oil-soluble allyl sulfur compounds of garlic effectively mediate the inhibition of these two crucial steps. DADS decreases forkhead box M1-dependent invasion by enhancing the expression of miR-134 [82]. An in vivo study using a zebrafish model showed the effectiveness of DATS in reducing metastasis by suppressing MMP2/9 via blocking NF-κB and extracellular-signal-regulated kinases (ERK)/MAPK signaling pathways [83]. Another study found that DATS treatment blocks the nuclear translocation of Trx-1 from the cytoplasm and diminishes production of the reduced form of Trx-1. In addition, DATS suppresses both spontaneous and experimental metastasis of TNBC cells by decreasing Trx-1, NF-κB, and MMP2/9 expressions in nude mice [84]. DATS has been shown to inhibit the

Table 1
Impact of diallyl disulfide (DADS) and diallyl trisulfide (DATS) on cellular and molecular mechanism mediating drug resistance in breast cancer (BC).

Garlic compound	Cellular mechanism affected	Signaling pathway affected by	Refs.
Allyl sulfur compounds	Exert proapoptotic activity	Activating p53	[74]
DADS and DATS	Exert an anti-proliferative effect on MDR-colorectal carcinoma cells	Changing the permeability of mitochondria	[75]
DADS	Reduce the viability and metastatic potential of TNBC cells	Downregulating MMP-9 and promoting the reversal of EMT through inhibition of the β-catenin signaling pathway	[76]
DADS	Reduce the proliferation, invasion, and migration of MCF-7 and MDA-MB-231 BC cells	Downregulating uPA and MMP-9 expression and upregulating TTP expression in vitro and in vivo	[77]
DADS	Inhibit the proliferation of BC cells	Inducing cell cycle arrest and apoptosis at the G0/G1 phase, via inhibition of the ERK1/2 pathway	[78]
DADS	Cause apoptosis in BC cells	Increasing the expressions of BAX, BAD, caspase-3, and caspase-9	[79]
DADS	Induce cytotoxicity in BC cells	Downregulating BCL2 and survivin and upregulating caspase-9	[80]
DATS	Ameliorate ER stress-induced apoptosis and reduce tumor growth of BC	Progressive activation of ER stress proteins, such as CHOP/GADD153 and GRP78/Bip, and upregulation of other proteins, such as ATF4 and eIF2	[81]
DADS	Decrease FOXM1-dependent invasion of BC cells	Enhancing the expression of miR-134	[82]
DATS	Reduce metastasis of BC cells	Suppressing MMP2/9 via blocking NF-κB and ERK/MAPK signaling pathways	[83]
DATS	Suppress both spontaneous and experimental metastasis of TNBC cells	Decreasing Trx-1, NF-κB, and MMP2/9 expressions in nude mice	[84]
DATS	Inhibit the proliferation, migration, and invasion of TNBC cells	Reversing the overexpression of lactate dehydrogenase A	[85]
DATS	Inhibit metastasis of TNBC cells	Blocking the activity and expressions of MMP2/9, via the NF-κB and ERK/MAPK pathways	[86]
DATS	Inhibit leptin-induced proliferation and metastasis of BC cells	Reducing the expression of BCL2, BCL-xL, cyclin D1, VEGF, and MMP-2 in BC cell lines and xenograft models targeting transcription factor STAT3	[87]
DATS	Inhibit angiogenesis in BC	Inactivating Wnt/β-catenin signaling and inhibiting VEGF expression	[88,89]
DADS	Inhibit BC growth by inducing apoptosis	Enhancing the expression of caspase-3 and blocking degradation of p53 via upregulating NAD(P)H:quinone oxidoreductase 1 and superoxide dismutase and reducing glutathione	[90]
DADS and DATS	Inhibit BC growth	Reducing angiogenesis	[91]
DATS	Inhibit metastasis of BC cells	Attenuating activated transforming growth factor-β1 signaling	[92]
DADS	Inhibit metastasis of BC cells	Downregulating TNF-α-induced CCL2 release primarily via the reduction of IKKε and phosphorylated-ERK expression, as well as impairment of MAPK/ERK and NF-κB signaling pathways in TNBC cells	[93]
DATS	Inhibit BC growth	Targeting Notch ligands (Jagged-1 and Jagged-2) and α-secretases (ADAM 10 and ADAM 17)	[94]
DATS	Suppress breast tumorigenesis	Suppressing the Wnt/β-catenin pathway	[95]
DATS	Increase cell-cell adhesion and decrease the attachment of the extracellular matrix component (type 1 collagen) and MMPs in BC cells	Upregulating E-cadherin	[96,97]
DADS	Inhibit histone deacetylase activity and induces apoptosis	Hyperacetylated histone-dependent alterations in the expression in proapoptotic genes and pathways and the expression of certain proteins in the antiapoptotic BCL2 family of proteins	[98]
DATS	Exert anticancer activity against BC	Epigenetic-mediated upregulation of metallothionein 2A, thereby diminishing NF-κB signaling	[99,100]
DADS	Reduce BC cell proliferation and invasion	Overexpressing miR-34a via the inhibition of the ERK signaling pathway, which regulates cell proliferation, cell survival, cell adhesion, and motility	[101]

(*continued on next page*)

Table 1 (*continued*)

Garlic compound	Cellular mechanism affected	Signaling pathway affected by	Refs.
DATS	Inhibit invasion and angiogenesis in BC	Targeting Notch-1 signaling, thereby inducing the expression of tumor suppressor miRNAs	[102,103]
DATS	Inhibit migration and angiogenesis in BC	Suppressing HIF-1α transcriptional activity and expression of VEGF-A, and EMT-related protein in MDA MB-231 cells	[104]
DADS and DATS	Sensitize drug-resistant BC cells	Bringing about the accumulation of ROS	[105]
DADS	Reduce the proliferation, metastasis, stemness of BCSCs, and glucose metabolism	Targeting the CD44/PKM2/AMPK signaling pathways in BCSCs	[106]
DATS	Reduce invasion of BCSCs	Decreasing the expression of FOXQ1, which negatively controls DACH1 expression by interacting with the DACH1 promoter region	[107]
DATS	Reduce tumorsphere formation of BCSCs	Reducing the expressions of CD44, ALDH1A1, Nanog, and Oct4	[108]
DATS	Inhibit the expression of EMT markers in BCSCs	Targeting Forkhead box Q1	[107,109,110]
DADS	Suppress inflammation	Lowering the expressions of proinflammatory cytokines	[111]
DADS	Mediate anti-inflammatory activity in BC	Blocking NF-κB pathway	[43,112]
DADS	Suppress inflammation in BC	Diminishing ROS production and targeting IκBα phosphorylation	[113]
DATS	Reduce inflammation	Activating the nuclear factor E2-related factor 2-anti-oxidant response elements pathway	[114]
DATS	Suppress inflammation in BC	Inhibiting the NF-κB/TLR 4 and CXCL12/CXCR4 pathways	[115]
	Autophagy promotes drug resistance in BC cells	Promoting cell survival	[116]
		Autophagosome formation	[117]
		Activation of autophagy-related gene signaling cascade	[118]
DADS	Modulate autophagy in BC	Controlling mTOR pathway	[119]
DADS and DATS	Increase the activation of autophagy in BC cells	Preventing mTOR phosphorylation activity and decreasing apoptotic cell death in macrophages, thus promoting immunomodulatory effects	[120]
DADS	Induce autophagy-mediated cell death in BC cells	Reducing p-mTOR kinase activity and inhibiting the PI3K/Akt/mTOR pathway	[121]
	Inflammatory microenvironment, with oxygen-deprived conditions was created	Infiltrating immune cells, cytokines, and numerous growth factors	[122,123]
DADS and DATS	Induce cellular immune response, lymphocyte activation, immunoglobulin production, and macrophage phagocytosis in BC model in rats	Producing cytokines, such as IL-2, IL-12, TNF-α, and IFN-γ	[124]
DADS and DATS	Induce the immunomodulatory activity of neutrophils	Increasing calcium influx	[125]
DADS and DATS	Enhance immunomodulatory and anti-inflammatory responses in rats	Reducing the levels of lymphocytes and monocytes	[126]
Aged garlic	Provoke immunomodulatory activity in the BALB/c mouse model	Substantially increasing T-cell response and decreasing tumor size	[127]
DADS	Regulate CD4+ and CD8+ T cells	Suppressing pro-inflammation cytokine production including TNF-α, IL-1β, and IL-6 via inhibiting the NF-κB pathway	[43]

MDR: multidrug resistance; MMP: matrix metalloproteinase; EMT: epithelial-mesenchymal transition; TNBC: triple-negative breast cancer; TTP: tristetraprolin; ERK: extracellular signal-regulated kinase; ER: endoplasmic reticulum; FOXM1: forkhead box M1; MAPK: mitogen-activated protein kinase; VEGF: vascular endothelial-derived growth factor; STAT: signal transducer and activator of transcription; ADAM: a disintegrin and metalloproteinase; HIF: hypoxia inducible factor; ROS: reactive oxygen species; PKM: pyruvate kinase M2; AMPK: AMP-activated protein kinase; BCSCs: BC stem cells; mTOR: mechanistic target of rapamycin; IL: interleukin.

proliferation, migration, and invasion of TNBC cells by reversing the overexpression of lactate dehydrogenase A [85]. DATS was also found to inhibit metastasis of TNBC cells by blocking the activity and expression of MMP2/9 via the NF-κB and ERK/MAPK pathways

[86]. An additional study showed that DATS inhibits leptin-induced proliferation and metastasis, as well as expressions of BCL2, BCL-xL, cyclin D1, vascular endothelial-derived growth factor (VEGF), and MMP-2 in BC cell lines and xenograft models by targeting

transcription factor STAT3 [87]. These studies suggest that DADS and DATS treatments eradicate metastasis-governed drug resistance in TNBC.

3.6. Impact of allyl sulfur compounds on angiogenesis-driven drug resistance

In the last decade, several antiangiogenic drugs, including drugs from phase I–III clinical trials, have been tested in preclinical studies. Recently, Almatroodi et al. [42] reviewed the potential impact of DADS and DATS on angiogenesis and related signaling pathways. Other studies have shown that DATS inhibits angiogenesis by inactivating Wnt/β-catenin signaling and inhibiting VEGF expression [88,89]. DADS also inhibits BC growth by inducing apoptosis via enhancing the expression of caspase-3 and blocking degradation of p53 via upregulating NAD(P)H:quinone oxidoreductase 1 and SOD and reducing glutathione [90]. Furthermore, the combination of garlic extract containing DADS and DATS with lemon extract was found to inhibit BC growth by reducing angiogenesis [91]. These studies suggest that DADS and DATS can be clinically beneficial for targeting tumor-induced angiogenesis in BC patients.

3.7. Effects of allyl sulfur compounds on EMT-mediated drug resistance

EMT has been recognized as a critical mechanism of drug resistance in BC. The potential activities of garlic extract and garlic-derived compounds on EMT and its signaling pathways have been explored in various cancer cell lines. Liu et al. [92] found that DATS inhibits metastasis of BC cells by attenuating activated transforming growth factor-β1 signaling. Bauer et al. [93] reported that DADS inhibits metastasis by downregulating TNF-α-induced CCL2 release primarily via the reduction of IKKε and phosphorylated-ERK expression, as well as by impairment of MAPK/ERK and NF-κB signaling pathways in TNBC cells. It is evident that the cytoskeleton, especially the tubulin component, is a direct target of DATS. In a study conducted by Kiesel and Stan [94], the effect of DATS on MDA-MB-231 cells was evaluated by targeting Notch ligands (Jagged-1 and Jagged-2) and α-secretases (a disintegrin and metalloproteinase (ADAM) 10 and ADAM 17). This study found that high responsiveness to garlic is exhibited during the initiation phase of breast tumorigenesis, rather than during the late stages. Notably, a study revealed that DATS can suppress the later stages of breast tumorigenesis by suppressing the Wnt/β-catenin pathway [95]. Accordingly, DATS is also shown to increase cell-cell adhesion and decrease the attachment of the extracellular matrix component (type 1 collagen) and MMPs by upregulating E-cadherin [96,97]. The findings of these studies suggest that DADS and DATS treatment may suppress drug resistance by preventing EMT in BC.

3.8. Effects of allyl sulfur compounds on epigenetic modulators of drug resistance

Allyl sulfur compounds in garlic function as epigenetic modulators and represent potential treatment options for BC. DADS inhibits histone deacetylase activity and induces apoptosis by histone-dependent alterations in the expressions of proapoptotic genes (under hyperacetylated state) and pathways and the expressions of certain proteins in the antiapoptotic BCL2 family of proteins [98]. DATS exerts anticancer activity by the epigenetic-mediated upregulation of metallothionein 2A, thereby diminishing NF-κB signaling [99,100]. Growing evidence indicates that miRNAs production is dysregulated in BCs. miR-34a is an important tumor suppressor in BCs. A study has reported that DADS reduces

BC cell proliferation and invasion by overexpressing miR-34a via the inhibition of the ERK signaling pathway, which regulates cell proliferation, cell survival, cell adhesion, and motility [101]. In addition, DATS inhibits invasion and angiogenesis by targeting Notch-1 signaling, thereby inducing the expression of tumor suppressor miRNAs [102,103]. The findings of the above studies suggest that DADS and DATS can potentially inhibit BC growth by targeting epigenetic modulators of drug resistance.

3.9. Effects of allyl sulfur compounds on redox-mediated drug resistance

HIF-1α is highly expressed in tumors and is known to be critical to inducing drug resistance. DATS has been reported to suppress HIF-1α transcriptional activity and expression of Trx-1 in MDA MB-231 cells [104]. In addition, DADS and DATS sensitize drug-resistant BC cells by bringing about the accumulation of ROS [105]. These studies show that disturbance of the redox system promotes drug resistance in highly aggressive metastatic BCs, which can be targeted by DADS and DATS.

3.10. Effects of allyl sulfur compounds on BC stem cell-mediated drug resistance

BC stem cells (BCSCs) are a group of specific cells with the distinct characteristics of self-renewal, differentiation, and tumorigenic ability, which facilitates the progression of BC. BCSCs have been highlighted as potential targets for BC therapy because they impart drug resistance. Experiments on BCSCs in a xenograft model demonstrated that DADS reduces the proliferation, metastasis, and stemness of these cells, and reduces glucose metabolism, by targeting the CD44/pyruvate kinase M2/AMP-activated protein kinase signaling pathways [106]. Exposure of TNBC stem cells to DATS considerably reduces invasion by decreasing the expression of FOXQ1, which negatively controls Dachshund homolog 1 (DACH1) expression by interacting with the DACH1 promoter region [107]. DATS also reduces tumorsphere formation and the expressions of CSC markers (CD44, ALDH1A1, Nanog, and Oct4) [108]. Recent studies reveal that DATS inhibits the expression of EMT markers in BCSC by targeting Forkhead box Q1 [107,109,110]. DATS administration sensitizes BCSCs to chemotherapeutics by suppressing the expression of FOXQ1, which is partly responsible for the gain of stem cell-like properties and elevated EMT during cancer metastasis [107]. The combined results of these studies suggest that DADS and DATS can be used to target BCSC-driven drug resistance.

3.11. Effects of allyl sulfur compounds on inflammation-mediated drug resistance

DADS and DATS have been well-established as suppressors of carcinogenesis, but DADS and DATS have also been reported to suppress inflammation. DADS suppresses inflammation by lowering the expressions of proinflammatory cytokines [111]. The anti-inflammatory activity of DADS is mediated by the blockade of the NF-κB pathway [43,112]. DADS suppresses inflammation by diminishing ROS production and targeting IκBα phosphorylation [113]. DATS reduces inflammation by activating the Nrf2-antioxidant response elements pathway [114]. DATS also suppresses inflammation by inhibiting the NF-κB/TLR 4 and CXCL12/CXCR4 pathways [115]. Due to these effects, DADS and DATS appear to be feasible anti-inflammatory agents for future treatment of inflammatory BCs.

3.12. Effects of allyl sulfur compounds on autophagy-mediated drug resistance

Autophagy is a self-degenerative and physiologically stressful process, involving the removal of aggregated proteins and damaged cell organelles to sustain a balance between cell survival and apoptotic cell death [116]. Autophagy occurs through autophagosome formation, where degraded components are engulfed and transported into lysosomes for recycling [117]. Research on autophagy has demonstrated that it increases tumour growth by promoting tumour cell survival through activation of autophagy-related gene signaling cascade; therefore, autophagy promotes drug resistance [118]. DADS modulates autophagy via the mechanistic target of rapamycin (mTOR) pathway [119]. Similarly, treatment with DADS and DATS has been shown to increase the activation of autophagy by indirectly preventing mTOR phosphorylation activity and decreasing apoptotic cell death in macrophages, thus promoting immunomodulatory effects [120]. A study showed that DADS induces autophagy-mediated cell death reducing p-mTOR kinase activity and by inhibiting the PI3K/Akt/mTOR pathway [121].

3.13. Effects of allyl sulfur compounds on antitumor immunity-mediated drug resistance

Cancer immunotherapy combats MDR cancers by targeting various mechanisms that are involved in drug resistance. Immune infiltration of tumors creates a highly inflammatory microenvironment, with oxygen-deprived conditions supported by infiltrating immune cells, cytokines, and numerous growth factors [122,123]. Therefore, the modulation of immune responses may be a promising strategy to combat cancer. DADS and DATS were found to exhibit beneficial immune modulatory activities via the production of cytokines, such as IL-2, IL-12, TNF-α, and IFN-γ, suggesting that DADS and DATS induce cellular immune response, lymphocyte activation, immunoglobulin production, and macrophage phagocytosis [124]. DADS and DATS also induce the immunomodulatory activity of neutrophils by increasing calcium influx [125]. DADS and DATS were shown to enhance immunomodulatory and anti-inflammatory responses in rats by reducing the levels of lymphocytes and monocytes [126]. A study reported that the protein fraction of aged garlic provokes immunomodulatory activity in the BALB/c mouse model by substantially increasing T-cell response and decreasing tumor size [127]. DADS treatment was also found to regulate CD4$^+$ and CD8$^+$ T cells by suppressing the production of pro-inflammation cytokines including TNF-α, IL-1β, and IL-6 via inhibiting the NF-κB pathway [43]. These studies indicate that DADS and DATS appear to modulate immune responses in drug-resistant cancers.

4. Conclusion and future directions

Drug resistance is a challenge in combating BC and is driven by regulators of the cell cycle, apoptosis, metastasis, and angiogenesis in TME. Drug resistance is also induced by EMT, epigenetic modulators, redox regulation, cancer stem cells, inflammation, and autophagy. Presently, garlic continues to be of interest because of its chemistry and unique biological action. Epidemiological studies suggest the ability of garlic to reduce BC risk, while several experimental studies have indicated the potential impact of sulfur-containing garlic compounds in modifying the behavior of BC cells at each stage of BC carcinogenesis. Interaction studies on BC have revealed that DADS and DATS bind to BC targets. Further analysis is required to study the development of these compounds into suitable therapeutics against BC. Additionally, the consumption of garlic compounds DADS and DATS for BC prevention is also dependent on several dietary and environmental variables such as gut microbiota. Finally, DADS and DATS in garlic as therapeutic agents are beneficial for management of drug resistance in BC patients.

CRediT author statement

RamaRao Malla: Conceptualization, Supervision; **Rakshmitha Marni**: Writing - Original draft preparation; **Anindita Chakraborty**: Writing - Reviewing and Editing; **Mohammad Amjad Kamal**: Writing - Reviewing and Editing.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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