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Hydrogen sulfide donors and inhibitors in cancer research: A state-of-the-art review

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Abstract

Hydrogen sulfide (H_2S), a gaseous biomolecule, is considered a key player in the regulation of various essential cellular events. Normal physiology is determined by the level of endogenous H_2S. Any alterations (upregulation and downregulation) to the level of endogenous H_2S may lead to illness, including the onset of tumorigenesis. Over the past two decades, extensive research on the role of H_2S in cancer development has affirmed the potential pharmacological means to suppress cancer progression by either inhibiting H_2S synthesis in cells or exposing exogenously supplied H_2S donors to treat different cancers. Some H_2S donors and inhibitors release H_2S or affect its synthesis. As a result, they have progressed through the development process into widespread clinical use and become increasingly important. The present study draws a detailed discussion on the types of H_2S donors and inhibitors and their role in cancer research. We believe that this state-of-the-art review will empower the synthesis of H_2S-based chemopreventive drugs and promote the need for further in-depth exploration of the associations between H_2S and cancer treatments in clinical settings.

Keywords: Cancer; Diagnosis; H_2S donors; H_2S inhibitors; Hydrogen sulfide; Treatment

1. Introduction

Hydrogen sulfide (H_2S) is a colorless, flammable gas with water-soluble properties and a rotten-egg odor. H_2S has historically been considered toxic and occupationally/

environmentally harmful[1]. In mammals, H_2S can be endogenously generated through the catalysis of L-cysteine and homocysteine by cystathionine γ-lyase (CSE) and cystathionine β-synthase (CBS), which are the two members of pyridoxal-5bers of pyri(PLP)-dependent enzymes that are predominantly found in the cytosol form[2]. Besides, 3-mercaptopyruvate sulfurtransferase (3-MPST), which is a non-PLP-dependent enzyme, acts in unison with cysteine aminotransferase (CAT) and in the presence of α-ketoglutarate to produce H_2S from L-cysteine. Both enzymes are colocalized in the cytosol and mitochondria[3]. Moreover, it has been indicated that D-amino acid oxidase can catalyze D-cysteine to form Achiral ketoacid and 3-mercaptopyruvate, which is further processed by 3-MPST into H_2S in both the brain and kidneys (Figure 1)[4]. The produced H_2S is then instantly released or converted into acid-labile sulfur or bound sulfane sulfur and stored in mammalian cells[5]. The catabolism of H_2S can occur through mitochondrial oxidation to sulfate and thiosulfate, excretion from the kidney or lung, sulfhemoglobin-mediated scavenging, and thiol methyltransferase and rhodanese-mediated methylation to generate methanethiol and dimethylsulfide[6].

Due to its unique chemistry, molecular reactivity mechanisms, ability to modify proteins, and active participation in many redox reactions with metal, H_2S has emerged as an essential signaling molecule in cancer biology. A huge volume of research has indicated the key roles of H_2S in a wide range of physiological activities related to cell cycle and tumorigenesis. H_2S is involved in angiogenesis, tumor growth, cellular and mitochondrial biogenesis, migration and invasion, tumor blood flow, metastases, epithelial-mesenchymal transition (EMT), DNA repair, protein sulfhydration, and chemotherapy resistance[7-10].

Since the last decades of research trend in translating H_2S to therapeutic forms, extensive efforts have been made by exploring natural H_2S-based molecules and designing synthetic ones (donors and inhibitors) to exploit the role of H_2S in cancer development. H_2S donors and inhibitors have gained importance and are being extensively explored to determine their clinical application in research, especially cancer. The research community is constantly struggling to design H_2S-based pharmacological drugs using these molecules and expecting significant breakthroughs in H_2S research in cancer. Considering the clinical importance of these naturally existing and those pharmacologically synthesized H_2S-based chemicals and research trends, it is worth summarizing the relevant literature that focuses on their use in translational research. The present study provides a detailed discussion of the types of H_2S donors and inhibitors and their role in cancer research. We anticipate that this state-of-the-art review will empower the synthesis of H_2S-based chemopreventive drugs and promote the need for further in-depth exploration of the associations between H_2S and cancer treatments in clinical settings.

2. Targeting exogenous H_2S for cancer treatment

2.1. Natural world

2.1.1. Allicin

Diallyl thiosulfinate, also known as allicin, is a biologically active compound found in garlic. Having antitumor and antimicrobial properties, this compound induces antitumor activities by regulating cellular processes, such as apoptosis, inflammation, oxidative stress, autophagy, and angiogenesis[11]. The mechanisms targeted in mediating its effects include post-translational modifications of the protein cell cycle, mitochondria apoptotic pathways, redox-sensitive signaling cascades, catalytic actions of telomerase enzyme, and activities of intercellular glutathione (GSH) and nucleic acid modifications[12]. The effects of allicin vary with different cancers and cell types[13]. It has been shown that the treatment of colon cancer cells (HCT-116) with allicin can effectively inhibit cell proliferation by promoting pro-apoptotic events characterized by the upregulation of Bax and cytochrome (Cyt)-c expressions, the downregulation of Bcl-2 and Bcl-xL, and subsequently, the activation of nuclear factor erythroid-2-related factor 2 (Nrf2) and deactivation of signal transducer and activator of transcription 3 (STAT-3) pathways[14]. The administration of allicin induces autophagic cell death in liver and thyroid cancer through the stimulation of p53 and the inactivation of protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, respectively[15].

In ovarian cancer, glioblastoma, gastric cancer, cervical cancer, and cholangiocarcinoma, the anti-carcinogenic effects of allicin have been found to be associated with the activation of c-Jun N-terminal kinase (JNK) mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and p38 MAPK/Nrf2 pathways as well as the inhibition of STAT-3 cascades[16]. Furthermore, the loss of mitochondria potential, the activation of caspases, and the overexpression of p21, NOX4, and Bak have been reported in a breast cancer cellular model following the treatment with allicin[17]. A recent study has also revealed that allicin can effectively suppress the migration and invasion of gastric cancer cells by elevating miR-383-5p and inhibiting the receptor protein-tyrosine kinase ERBB4[18]. In addition, allicin effectively reverses the oncogenic properties of ornithine decarboxylase in neuroblastoma[19].

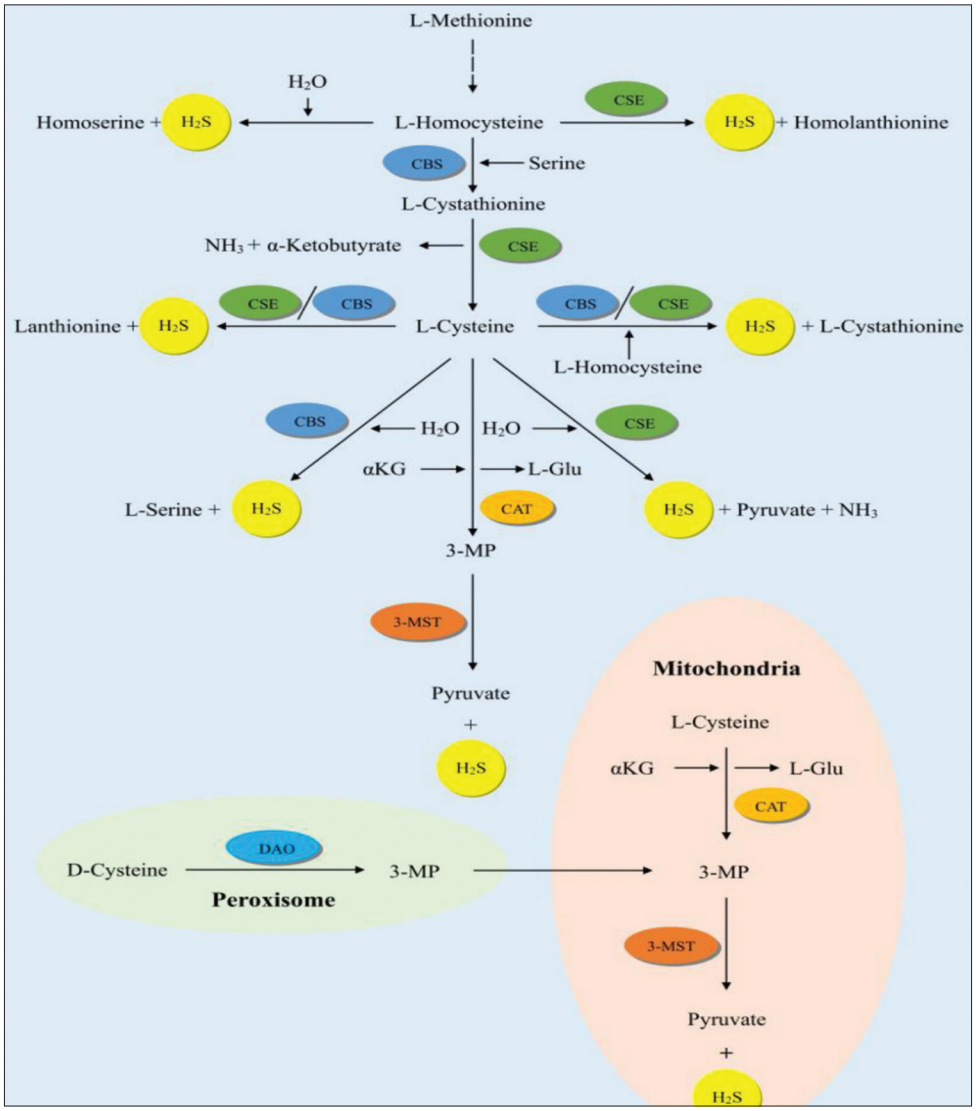

Figure 1. A schematic illustration of the biosynthesis of endogenous H_2S in mammals. H_2S: Hydrogen sulfide, H_2O: Water, CBS: Cystathionine β-synthase, CSE: Cystathionine γ-lyase, NH_3: ammonia, L-Glu: L-glutamate, αKG: α-ketoglutarate, 3-MST: 3-mercaptopyruvate sulfurtransferase, CAT: Cysteine aminotransferase, 3-MP: 3-mercaptopyruvate, DAO: D-amino acid oxidase.

Besides that, numerous studies have revealed the potential of allicin in enhancing the sensitivity effects of other anticancer therapeutics when used synergistically. For example, a combination of artesunate and allicin induces osteosarcoma cell death through caspase-dependent apoptotic pathways[20]. Similarly, the side effects of the anticancer drug cisplatin, especially in damaging stria vascularis, could be successfully reduced by synergizing the drug with allicin as shown in a mice model[21]. It has also been indicated that the sensitivity of temozolomide, a chemotherapy drug, can be significantly enhanced by allicin in glioblastoma through the upregulation of miR-486-3p[22]. The compound has also been reported to improve the sensitivity of 5-fluorouracil in different types of cancer, including hepatocellular, lung, and colorectal cancer (CRC)[23,24]. In addition, the cardiotoxicity of the anticancer drug doxorubicin in rats can be reduced by allicin through the attenuation of apoptotic, oxidative stress, and inflammatory responses[25].

In multiple myeloma, the use of allicin with dexamethasone increases the sensitivity of side population cells to the latter by upregulating the expression of miR-127-3p and inhibiting phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway[26]. Allicin can also increase the sensitivity of cisplatin-resistant lung cancer cells by suppressing hypoxia-inducing factors 1α and 2α in hypoxic cells. Apart from chemotherapy, allicin can enhance the

radiosensitivity of cancer cells by suppressing the nuclear factor-kappa B (NF-κB) signaling pathway in CRC[27] and through the promotion of intracellular DNA damage that is related to the downregulation of interleukin (IL)-6 and interferon-β as well as the increase in p53 expressions in glioblastoma[28]. Despite the promising anticancer effects of allicin, a recent study has shown that allicin can trigger hemolysis, eryptosis, and oxidative stress in erythrocytes through calcium overload and the activation of MAPK and casein kinase-1α[29]. The combined treatment of allicin with eryptosis inhibitors could be helpful in reducing the effect.

In recent years, nanoparticles have been established as effective and efficient carriers for delivering numerous drugs. In the case of allicin, its cytotoxicity in HepG2 cells has been demonstrated to be enhanced with the encapsulation of gelatin nanoparticles coated with glycyrrhetinic acid[30]. Moreover, the loading of allicin with cyclodextrin-based nanoparticles also enhances its delivery and the resulting corresponding pro-apoptotic effect on cancer cells[31]. Overall, allicin has shown promising anticancer activity. In addition, it is cost-efficient and can be used in combination with other drugs to increase sensitivity and alleviate side effects.

2.1.2. Ajoene

The anticancer properties of ajoene have been widely recognized and attentively investigated. Ajoene (4,5,9-trithiadodeca-1,6,11-triene-9-oxide) is a sulfur-containing organic compound formed after the rearrangement of allicin. Ajoene occurs in two forms: Z- and E-isomers. By characterization, the former is more bioactive, while the latter is relatively more stable. Recently, the compound has been shown to be synthesized in the laboratory through a new technique involving four key steps: (1) propargylation; (2) radical addition of thioacetate; (3) deprotection; and (4) disulfide formation/allylation. Ajoene has antimicrobial, antithrombosis, anti-inflammatory, and anticancer properties[32]. In cancer, the compound targets several activities, such as migration, apoptosis, oxidative stress, and protein folding[33]. A previous study has suggested that ajoene can induce anticancer effects in leukemia cells (HL-60) by triggering G2/M arrest, attenuating proteasome-mediated trypsin- and chymotrypsin-like activities as well as inhibiting ERK-1/2 signaling cascade[34]. Moreover, the ajoene has been shown to promote apoptosis in leukemic cells but not in peripheral mononuclear blood cells of healthy individuals by elevating the oxidative status and activating the NF-κB pathway[25]. Similarly, in lung adenocarcinoma, the treatment with 25 μM of ajoene significantly reduced the cell viability of cancerous cells A549, NCI-H1373, and NCI-H1395, but not non-carcinogenic bronchus cells BEAS-2B, partially through reactive oxygen species (ROS)-induced apoptosis and the activation of JNK/p38 cascade[25].

In a human study of basal cell carcinoma, the patients were topically treated with ajoene. The study showed that ajoene can effectively suppress tumor growth through the activation of mitochondria-dependent apoptosis and the subsequent reduction of antiapoptotic Bcl-2 expression[35]. Besides, apoptotic regulators such as p53, p63, and p73 have also been demonstrated to be activated by the compound in cellular models[36]. Furthermore, Z-ajoene could selectively inhibit cancer stem cells from glioblastoma multiform by attenuating phosphorylated (p)-SMAD4, p-AKT, and FOXO3A expressions[37]. In MDA-MB-231 and HeLa cancer cells, ajoene has shown to reduce migration and invasion activities through s-thiolation of cysteine-328 of the vimentin, thereby disrupting it and subsequently inhibiting metastatic activities[38].

An analog of ajoene, bis[(para-methoxy) benzyl], has more substantial anticancer effects. It acts by activating unfolded protein response mechanisms through CHOP/growth arrest- and DNA damage-inducible protein 153 (GADD153) in esophageal carcinoma[39]. In the treatment of colon cancer cells, Z-ajoene effectively inhibits tumor growth by decreasing the expression of β-catenin and increasing CK-1α-mediated β-catenin phosphorylation and prevents skeletal muscle atrophy induced by colon cancer by suppressing muscle-specific E3 ligases and NF-κB[40]. Therefore, ajoene can specifically and selectively target cancer cells as well as promote apoptosis and antimetastatic activities.

2.1.3. Diallyl sulfide (DAS)

DAS is a significant component of garlic with protective properties against various physiological disorders. The regulation of cellular markers associated with apoptosis, redox status, necrosis, angiogenesis, and cytotoxicity (cytochrome P450 2E1), as well as the interaction with membrane lipids are among the mechanisms targeted by the compound[41]. In cancer, DAS has been previously shown to delay the onset of cancer in chemically induced skin tumors in mice[42]. The corresponding effects of DAS are associated with the inhibition of key cellular pathways, such as p53, p21/Ras, PI3K/AKT, and p38 MAPK cascades, with JNK1 and ERK1/2 remaining unaffected[43]. *In vitro* evidence has revealed that DAS can effectively protect normal human breast cells MCF-10A from a carcinogenic chemical compound, diethylstilbestrol, which can cause DNA damage and lipid peroxidation[44].

In prostate cancer, DAS has been shown to improve oxidative status by suppressing a testosterone-mediated decrease in antioxidants[45]. It has also been reported that

DAS can potentially induce antiproliferative properties in thyroid carcinoma by activating the mitochondria apoptotic pathway as displayed by the elevation of Bax, caspase-3, -9, and cytochrome c (cyt c) expressions, as well as the suppression of Bcl-2 expression[46]. DAS can also prevent the progression of colon cancer by containing the gene expression and activities of arylamine N-acetyltransferase and downregulating ERK1/2 pathway[47]. In a leukemia model, DAS restored the elevated levels of P-glycoprotein (P-gp), a multidrug protein[48]. The treatment of cervical cancer cells with DAS has been reported to promote cell cycle arrest and apoptosis by increasing ROS, calcium ions (Ca^{2+}), and the number of cells accumulated in the gap 0 (G0)/G1 phase[49]. The treatment increases the expressions of p21, p27, p53, Bad, Bid, Bax, apoptosis-inducing factor (AIF), caspases, and cyt c but decreases the expressions of Bcl-xl, Bcl-2, cyclin-dependent kinase 2 (CDK2), CDK6, checkpoint kinase (CHK)2, and human papillomavirus (HPV) oncogenes E6 and E7[50].

Furthermore, treating neuroblastoma cells SH-SY5Y with DAS has been shown to suppress pro-proliferative activities and trigger apoptosis by increasing caspases activation and Ca^{2+} levels while suppressing NF-κB pathway[51]. In a mice lung cancer model, DAS significantly reduced tumor growth and increased antioxidant levels and apoptotic activities by suppressing the expression of fatty acid synthase[52]. In a recent study, the combination of paclitaxel and DAS has been demonstrated to improve skill texture and downregulate antiapoptotic protein Bcl-2 in a mice skin cancer model[53].

Alternatively, in esophageal carcinoma, a previous study has revealed that DAS is only effective when administered after its exposure to carcinogen, which suggests that the compound is more effective as a treatment rather than for prevention purposes[54,55]. Overall, DAS has considerable potential as a therapeutic option for cancer. However, further studies are required to shed light on the possible ways of improving its efficiency and reducing the side effects.

2.1.4. Diallyl disulfide (DADS)

DADS is an organosulfur compound from garlic with strong anticancer properties. It is formed from allicin. DADS has demonstrated its effects in different types of cancers through the regulation of apoptosis, oxidative stress, and cell cycle, along with several cellular pathways associated with cancer survival and progression[56]. For example, in colon cancer cells HT-29 and Caco-2, treatment with DADS has shown to induce anticancer effects by activating histone 3, inhibiting histone deacetylase (HDAC), and increasing p21 expression[57]. In HCT-116, DADS has been shown to trigger G2/M arrest by activating cyclin B1 and promoting apoptosis through ROS-mediated activation of p53 pathway, thereby promoting cell death[58]. In another colon cancer cell line SW480, treatment with DADS has shown to inhibit migration and invasion by downregulating glycogen synthase kinase (GSK)3β/NF-κB and LIM kinase-1 (LIMK-1)/dextrin/cofilin cascades, resulting in the suppression of vimentin, Ki-67, and CD-34 expressions and the elevation of E-cadherin[59]. Other signaling markers targeted with DADS treatment in colon cancer cells include the elevation of Ca^{2+} levels, phosphorylation of ERK, activation of STAT-1, and inhibition of Rac1/PAK1/LIMK1/cofilin pathways[60].

In leukemia, DADS induces cell death through the inhibition of Rac1/ROCK1/LIMK1/cofilin and ERK pathways as well as the activation of p38MAPK, Rac2/JNK, and caspase-dependent apoptotic pathways[61]. Its anticancer effects in leukemia cells are evident through the downregulation of vascular endothelial growth factor (VEGF) and calreticulin. It inactivates epidermal growth factor receptor (EGFR) and mTOR pathways that mediate the induction of G2/M and G0/G1 arrest through the downregulation of PARK-7, cofilin 1, and Rho GDP dissociation inhibitor 2[62].

In a mice prostate cancer model, testosterone and N-methyl N-nitroso urea-induced cancer and its associated features such as dysplasia, hyperplasia, and prostatic intraepithelial neoplasia were significantly reduced with DADS treatment[63]. In addition, it has also been reported that DADS treatment can promote apoptosis through G2/M arrest due to decreased CDK1 expression and the activation and inhibition of JNK and PI3K/AKT pathways, respectively. Furthermore, DADS also initiates histone hyperacetylation, increasing DNA damage, raising the expression of pro-apoptotic cell markers, and decreasing migration and invasion-associated proteins[64]. In hepatocellular carcinoma (HCC), DADS has been reported to reduce cell proliferation and migration by promoting apoptosis by regulating associated markers and G2/M arrest. Moreover, it also been reported to induce antiapoptotic activities and reduce toxicity by inhibiting CYP2E1[65]. Albeit, the pro-apoptotic effects of DADS can be increased in HCC by cotreating with other compounds, such as p38 or p42/44 MAPK inhibitors[66].

DADS enhances programmed cell death in breast cancer by promoting G0 arrest, altering Bcl-2 family proteins, inhibiting HDAC through histone-4 hyperacetylation, suppressing ERK, and activating SAPK/JNK and p38MAPK pathways[67]. The inhibition of ERK by DADS in breast cancer is initiated through the upregulation of miR-34a expression, leading to the inhibition of upstream cascades,

SRC and Ras[68]. Similarly, other studies have shown that DADS treatment can reduce breast cancer progression and metastases by elevating the expressions of tristetraprolin[68]. Furthermore, the investigation of normal breast cancer cells MCF-10A has indicated that DADS pre-treatment can protect against benzo(a)pyrene-induced cancer and the compound can help to avert environmentally induced cancer initiation[69]. It has also been demonstrated that DADS treatment can effectively inhibit pro-cancer activities in triple-negative breast cancer (TNBC) cells by suppressing antiapoptotic proteins and β-catenin activation[70]. In addition, nanoemulsions of DADS with α-linolenic acid can trigger G0/G1 arrest and regulate the ERK pathway in MCF-7 cells[71]. Moreover, the modification of DADS loaded in solid-lipid nanoparticles with receptor for advanced glycation end products antibody improves the efficiency of DADS by facilitating target-specific delivery and reducing off-target effects in TNBC[72].

DADS exerts its anticancer effects in lung cancer by regulating the expression of apoptotic proteins, increasing ROS levels, and Ca^{2+} elevation, inducing G2/M arrest, and activating p53, p42/44MAPK, and JNK pathways[73]. Cisplatin-resistant lung cancer cells A549/DPP can be sensitized to DADS by cotreating with small interfering (si)RNA *BCL-2*[74]. In a recent study, DADS has been shown to prevent cancer growth and EMT in A549 cells by suppressing E-cadherin and cytokeratin-18 as well as elevating N-cadherin and vimentin through inactivating Wingless and Int-1 (Wnt)/β-catenin pathway[75].

Moreover, the treatment of esophageal carcinoma models with DADS has been reported to cause cell death through the suppression of NAT and CYP2E1 expressions, the activation of mitochondria-apoptosis and p53/p21 pathways, and the inhibition of Raf/mitogen-activated protein kinase kinase (MEK)/ERK pathway[76].

In a recent study, DADS has also been shown to prevent the metastasis of type 2 esophageal-gastric junction adenocarcinoma cells by decreasing the expression of matrix metalloproteinases (MMPs) and increasing the expression of MMP tissue inhibitors partly through the inactivation of NF-κB and PI3K/AKT pathways[55]. Furthermore, DADS inhibits the cell cycle. DADS promotes ROS production, causes DNA damage, upregulates miR-34a, miR-22, and miR-200b expressions, as well as inhibits PI3K/AKT and Wnt/β-catenin cascades[77]. However, a possible resistance to DADS by gastric cancer cells has been found to be associated with the increase in GSH peroxidase or GSH levels, resulting in the alteration of ROS status. This suggests that the compound may not be fully efficient in treating this type of cancer[78]. Studies on skin cancer have demonstrated that DADS can prevent the progression of cancer by regulating cell cycle, apoptosis, and oxidative stress events by promoting the activation of p53- and p21-mediated Nrf2[42]. In brain tumors, treatment with DADS can effectively reduce p38 MAPK, NF-κB, and H-RAS expressions, increase peroxisome proliferator-activated receptor-gamma coactivator-1α and Ca^{2+} levels, trigger G2/M arrest, and activate JNK/c-Jun pathways and mitochondria-dependent apoptosis, which ultimately result in tumor suppression[79].

Furthermore, in the treatment of cervical cancer with DADS, the compound inhibits cell proliferation by targeting TAp73/ΔNp73 status and activating p53/p21 signaling pathways[80]. DADS induces its anticancer effects in bladder cancer by inhibiting N-acetyl transferase (NAT) activities as well as promoting ROS production and G2/M arrest[81]. Besides, the inhibitory effects of DADS have been reported in other types of cancers, including the suppression of EMT through MAPK/ERK inactivation in oral cancer, G2/M arrest in pancreatic cancer, G1/S arrest associated with MAPK phosphorylation in nasopharyngeal carcinoma, the upregulation of miR-34 and p21 expressions and inactivation of PI3K/AKT/mTOR in osteosarcoma[82], as well as C-MYC, specificity protein 1 (SP1), and MAD1-mediated attenuation of human telomerase reverse transcriptase (hTERT) in lymphoma. Overall, the role of DADS in cancer has been extensively studied, and numerous pathways have been implicated in the process. However, the research on the side effects of the drug and its elimination mechanisms is still lacking, thereby requiring further investigations.

2.1.5. Diallyl trisulfide (DATS)

Similar to DAS and DADS, DATS is an organic compound produced by garlic. It has immense therapeutic significance in different types of cancers. Dose combination also affects various cellular processes, including cell cycle, apoptosis, proliferation, EMT, and oxidative stress. Numerous *in vitro* and *in vivo* studies of different types of cancers have been conducted to investigate the drug's potential for therapeutic purposes. In prostate cancer models, DATS treatment has been shown to promote a decrease in the expression of X-linked inhibitor of apoptosis protein (XIAP), an increase in pro-apoptotic protein Bak, JNK1-mediated activation of ITCH ubiquitin ligase signaling axis, JNK1/2 and ERK1/2 activation; AKT, NF-κB, and p-STAT-3 inhibition; as well as G2/M arrest due to CHK1 activation and increase in p53 and p-Cdc25C expressions[82,83].

In breast cancer, DATS treatment suppresses the expressions of Bcl-2, Bcl-xL, MMP-2, estrogen receptor (ER)-α, lactate dehydrogenase-A (LDHA), Forkhead box Q1 (FOXQ1), hypoxia-inducible factor (HIF)-α, and

thioredoxin, increases ROS generation and Bak expression, stimulates activator protein (AP)-1 and apoptosis signal-regulating kinase (ASK)1-JNK-Bim signaling axis, and deactivates transforming growth factor (TGF)-β1, Wnt/β-catenin, NF-κB, ERK/MAPK, AKT, and Notch pathways[84]. In mice models, the combination of DATS and doxorubicin has been reported to induce multi-signaling targeted apoptosis, inhibit Notch and NF-κB pathways, and activate the p53 apoptotic axis[85]. Similarly, treatment with DATS in bladder cancer markedly suppresses EMT. DATS also elevates apoptotic activities in a caspase-dependent manner through the inhibition of PI3K/AKT and the activation of JNK pathway[86].

Recent studies have reported an increase in apoptosis and a decrease in EMT in bladder carcinoma cells following DATS treatment. G2/M arrest, NF-κ2 inactivation, ATM-mediated CHK2/Cdc25C/Cdc2 stimulation, and ERK1/2, JNK, and p38 phosphorylation were observed[87]. In gastric cancer, DATS treatment exerts pro-apoptotic properties by inducing mitotic arrest through ROS-dependent activation of AMP-activated protein kinase (AMPK) pathway, regulating apoptotic markers[88], and reducing ROS, sulfiredoxin, and malondialdehyde (MDA) levels. DATS also sensitizes gastric cancer cells to docetaxel and cisplatin by elevating the levels of metallothionein 2A, which leads to NF-κB pathway inhibition, and inhibiting Nrf2/AKT as well as activating p38MAPK/JNK signaling cascades, respectively[89].

Besides that, in the treatment of osteosarcoma with DATS, the compound also suppresses tumor growth by targeting G0/G1 through decreasing cyclin D1 and upregulating p21 and p27 by ROS-mediated PI3K/AKT inhibition[90]. DATS also suppresses P-gp and glucose-regulated protein 78, switches microRNA levels, downregulates NF-κB and Notch 1 pathways, as well as upregulates the expression of Ca^{2+}-binding protein calreticulin[91]. A recent study has also reported the downregulation of vimentin and Bcl-2 as well as the upregulation of Bax, Bak, and E-cadherin due to PI3K/AKT/GSK3β inhibition following the treatment of osteosarcoma cells with DATS[92].

Otherwise, in the treatment of lung cancer with DATS, the compound promotes DNA damage and apoptosis through the elevation of caspase-3, -8, -9, Bax, and Bak; the attenuation of Bcl-xl and Bcl-2 proteins; as well as the induction of JNK, p53, and p38 pathways[93]. DATS can also potentiate its protective effect in lung cancer by suppressing Wnt/β-catenin[94]. Furthermore, its modification with extracellular microparticle carriers enhances anti-inflammatory and ROS activities by suppressing S100 calcium-binding protein A8/A9, serum amyloid A, fibronectin, IL-6, and toll-like receptor-4. In thyroid carcinoma, it has been found that the induction of apoptosis is associated with the activation of ERK, JNK, and MAPK pathways, G2/M arrest through ATM and H2AX phosphorylation, and a positive feedback loop due to a rise in H_2S and CSE levels, resulting in NF-κB hyperactivation[95]. It has been shown that treating colon cancer cells with DATS can significantly promote cell death and reduce migration activities by inhibiting focal adhesion kinase (FAK), Src, and Ras, facilitating G1/S arrest by oxidating β-tubulin, ROS production, and mitochondria-mediated apoptosis[96].

The elevation of Ca^{2+} levels, the generation of ROS, the downregulation of antiapoptotic proteins, integrins, and FAK, and the activation of caspases and p53 pathway have been observed in skin cancer cells following DATS treatment[97]. Likewise, DATS improves the anticancer effects of cisplatin in ovarian cancer cells (SKOV-3)[98]. In leukemia, DATS treatment suppresses cancer progression by triggering G0/G1 arrest and caspase activation, the disruption of mitochondria potential due to high ROS levels[99], and the dimerization of heat shock protein (HSP)-27. In brain cancer, DATS reduces migration and proliferation activities by suppressing Wnt/β-catenin, mTOR, EGFR, C-MYC, active Bcl-2, and HDAC activity, and increasing histone acetylation and p21/p53 levels[100].

In pancreatic cancer, lymphoma, and nasopharyngeal carcinoma, DATS induces apoptosis through p53 elevation, TRAF-6 degradation and NF-κa inactivation, as well as caspase-8 and MAPK pathway activation, respectively[101]. Collectively, the above data confirms the potential of DATS in cancer treatment by targeting numerous vital signaling pathways associated with proliferation and migration activities. However, the research on the possible side effects and mode of action of this drug is still lacking regardless of the possibility. Figure 2 explains the signaling pathways involved in the apoptosis induction effect of DATS exposure.

2.1.6. Sulforaphane (SFN)

SFN is a sulfur-rich isothiocyanate (ITC) member commonly found in cruciferous vegetables, such as broccoli and cabbages. The compound is known to have anticancer properties. In a study, SFN has been reported to have a potent inhibitory effect in bladder cancer cells, which is associated with the suppression of growth promoters such as survivin, EGFR, and human epidermal growth factor receptor 2 (HER2)[102]. Treating bladder cancer cells with SFN also upregulates insulin-like growth factor (IGF)-binding protein-3, caspase-3, cyt c, and cell cycle inhibitor p27, resulting in G0/G1 arrest, as well as induces ROS-dependent mitotic arrest, Nrf-2 activation, HDAC inhibition[103], NF-κB

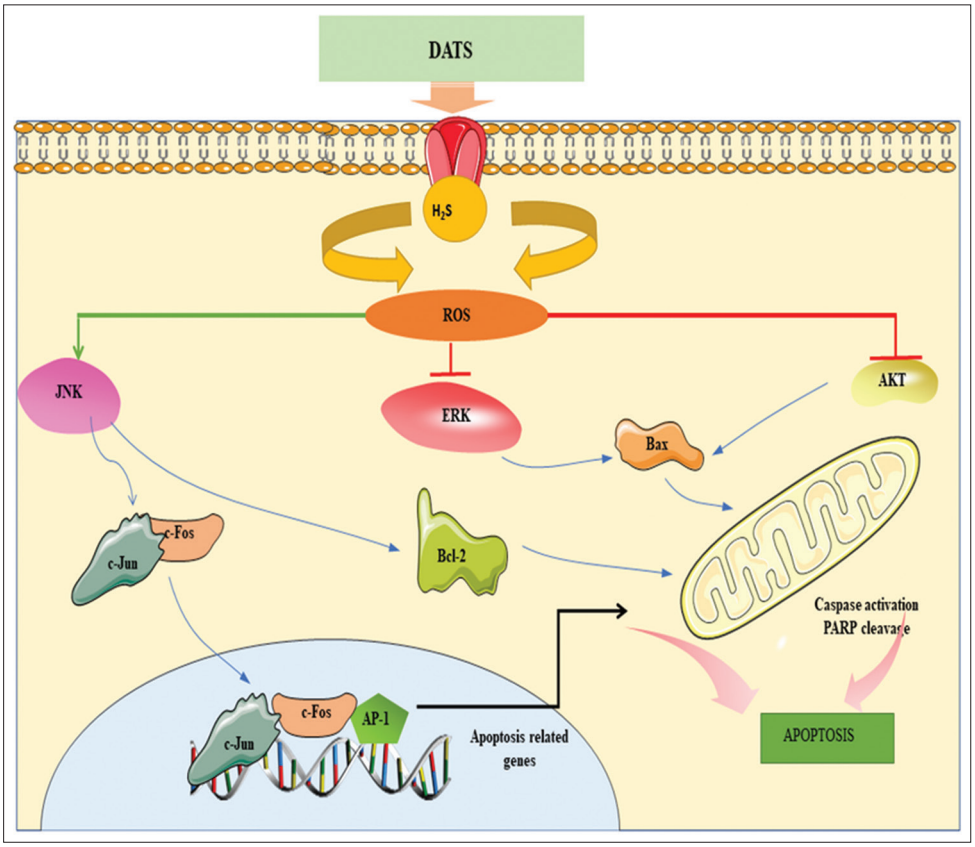

Figure 2. A schematic diagram of the signaling pathways involved in the apoptosis-induction effect of DATS exposure. DATS: Diallyl trisulfide, ROS: Reactive oxygen species, JNK: c-Jun N-terminal kinase, AP-1: Activator protein-1, ERK: Extracellular signal-regulated kinases, Bcl-2: B-cell lymphoma-2, Bax: Bcl-2-associated X protein, AKT/PKB: Protein kinase B, PARP: Poly-ADP-ribose polymerase.

deactivation, and cyclooxygenase (COX)-2 suppression through the elevation of p38 expression and activities. In addition, by downregulating COX-2 and upregulating miR-200c, SFN suppresses several EMT markers, including MMP-2, -9, Snail, and zinc-finger E-box-binding homeobox 1[104]. In recent studies, SFN has been shown to prevent the progression of bladder cancer by regulating the composition of gut bacteria and protecting the gut barrier, increasing the expression of FAT atypical cadherin[105], as well as downregulating HIF-1α expression and activities, thereby reducing glycolysis. The chemoresistance against everolimus, an mTOR inhibitor, and the upregulation of integrins α6, αV, and β1 in bladder cancer can be prevented by cotreatment with SFN[106]. In colon cancer, SFN promotes apoptotic activities by arresting cells at G1 and inhibiting ERK1/2 and AKT kinases, activating caspase-3 and chromatin condensation, upregulating p27 through S-phase kinase-associated protein inhibition, phosphorylating stress-activated protein kinase and suppressing C-MYC, overexpressing p21 and inducing G2/M arrest, activating MAPK pathways, suppressing HIF-1α and VEGF expressions, as well as increasing ROS generation[107]. Moreover, further studies have indicated that SFN treatment can also suppress the proliferation and metastasis of colon cancer by promoting Nrf2 expression through demethylation of its promoter, upregulating NmrA-like redox sensor 2, pseudogene and pseudogene activating ROS/p38 axis, and downregulating COX-2/microsomal prostaglandin E synthase-1 cascades as well as HDAC, hTERT, and miR-21 expressions. SFN also induces the downregulation of pro-inflammatory markers in colon cancer cells[108,109].

In breast cancer, SFN has been reported to prevent cell progression through the upregulation of early growth response 1 and thioredoxin reductase 1 expression and redox status, a reduction in the phosphorylation of AKT and S6K1 kinases, and a suppression in the expression of SERTA domain containing 1, cyclin D2, and HDAC 3, resulting in G1/S arrest[110]. In addition, the treatment of TNBC stem cells with SFN promotes cell death by inhibiting the expressions of Nanog, aldehyde dehydrogenase 1A1, Wnt3, Notch 4, and Crypto/Alk4 protein complex formation[111]. Moreover, in the treatment of gastric cancer with SFN, the compound inhibits the progression of cancer by mediating the induction

of G2/M arrest through the activation of mitochondria apoptotic pathway, p21 upregulation, and histone H3 phosphorylation, accompanied by the activation of ROS-AMPK pathway[112]. In addition, SFN causes cell death by inducing cell cycle arrest at the S phase through p21/53 upregulation and reducing the expressions of suppressor of variegation, enhancer of zeste, trithorax (SET) and myeloid-Nervy-DEAF1 domain-containing 3, myosin regulatory light chain 9, as well as cysteine-rich angiogenic inducer[113]. SFN also promotes the maturation of miR-29a-3p, reduces COL3A1 and COL5A1, inhibits the Wnt/β-catenin pathway phosphorylation of MAPK, deactivates EGFR and p-ERK1/2, and inhibits the Sonic hedgehog pathway[114].

In prostate cancer, SFN treatment facilitates apoptosis by increasing mitochondria ROS, apoptotic protease-activating factor-1, and Bax expression, and reduces the expression of phosphoglucomutase 3, the activation of caspases, the upregulation of Nrf2, the demethylation of cyclin D2, the suppression of androgen receptors, and the inhibition of STAT-3, HDAC6 deacetylase, ERK1/2, hTERT, and C-MYC[115,116]. In a recent study, treatment with N-acetyl-L-cysteine has been reported to inhibit fatty acid metabolism by acetyl-CoA carboxylase and fatty acid synthase suppression, which, in turn, inhibits prostate cancer inhibition[117]. SFN also induces the acetylation of histone H3 and H4, which leads to cell cycle arrest[118]. SFN has also been demonstrated to exert an inhibitory effect on ovarian cancer cell proliferation by attenuating retinoblastoma protein phosphorylation and E2F-1 expression[119]. Besides, SFN also triggers G1/G2/M arrest and inhibits the PI3K/AKT pathway[120]. In recent studies, SFN has been shown to increase the sensitivity of ovarian cancer cells to cisplatin by inhibiting NF-κB, HER2, and C-MYC as well as upregulating p53, p27, Bax, and miR-30a-3p, thus facilitating DNA damage[121]. In neuroblastoma, SFN promotes anticancer activities through caspase-dependent apoptosis, which is mediated by MEK/ERK activation[122]. Furthermore, in HCC, SFN reduces the expressions of Bcl-2, HIF-1α, and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase-4, increases the expression of caspase-3 and Bax, as well as activates Nrf2, p38, and ERK pathways to mediate cancer cell death[123]. SFN also activates Nrf2/antioxidant response element/heme oxygenase-1, inhibits STAT3/HIF-1α/VEGF, and ROS dependently inactivates TGF-β pathway and hTERT expression in HCC cells. SFN treatment significantly increases the demethylation of histone H4 on arginine 3 (H4R3me2s) in epidermal squamous cell carcinoma through the alleviation of protein arginine methyltransferase-5 and methylome protein 50 expressions[124].

In lung cancer, SFN upregulates the expressions of p21, p73, p53 upregulated modulator of apoptosis, Bax, cyclin D1, cyclin K, and caspases and downregulates the expressions of EGFR, cyclin B1, and Bcl-2[125]. SFN also suppresses miR-616-5p expression through histone modification, deactivates the GSK3β/β-catenin pathway to inhibit EMT and reduce stem cell-like properties in lung cancer cells, sensitizes lung cancer cells to treatments by upregulating miR-214, and inhibits IL-6/ΔNp63α/Notch pathways[126]. In nasopharyngeal carcinoma, SFN suppresses malignancy by preventing the reactivation of the Epstein–Barr virus lytic cycle, increases the expression of Wnt inhibitory factor 1, inhibits DNA methyltransferase 1, and inhibits the activation of STAT-3 through the upregulation of miRNA-124-3p[127]. Besides, in salivary gland adenoid cystic carcinoma, SFN treatment induces anticancer activities by mediating G2/M arrest, accompanied by the decrease in cyclin B1 and CDK1, the increase in caspases and Bax, and ultimately the inhibition of NF-κ pathway[128]. Overall, the effect of SFN on cancer suppression has been explicitly elaborated in different types of cancers, with the critical cellular markers and processes affected being identified. With the new focus on the drug clearance mechanism and potential side effects, vital information that might be useful in clinical application can be obtained.

2.1.7. 4-methylthiobutyl isothiocyanate (erucin)

Another common ITC compound is erucin. The protective power of this compound in cells is essentially attributed to its H_2S moiety. In addition to other mechanisms, erucin acts by regulating apoptosis and inflammatory processes[129]. In colon cancer, HCC, bladder cancer, prostate cancer, and lung cancer, treatment with erucin suppresses tumor growth and metastasis by promoting AKT and ERK phosphorylation and DNA damage, as well as blocking cell cycle at G2/M phase and p21/53 overexpression, respectively[130]. Erucin induces cell death in KRAS-mutated pancreatic cancer cell line AsPC-1 by suppressing ERK phosphorylation, which is a crucial mechanism to counteract KRAS-associated carcinogenic features associated with MAPK hyperphosphorylation[131]. Besides, treatment with erucin can effectively suppress carcinogenic activities by suppressing telomerase activities in ovarian cancer[132]. In breast cancer, erucin improves microtubule stability, induces cell cycle arrest, mitochondria translocation of cofilin and dynamin-related protein, mitochondria fission, and the downregulation of HER2 and S6 ribosomal protein phosphorylation[133]. Overall, erucin treatment exhibits anticancer activities in different cell types through a variety of mechanisms that are altered in cancer.

2.1.8. Allyl isothiocyanate (AIC)

AIC, a natural anti-inflammatory and anticancer compound, has been shown to have significant anticancer

effects. In breast cancer, AIC induces cell death by activating both mitochondria-dependent and -independent pathways[134]. G2/M arrest, ERK activation, and NF-κB inhibition have also been observed in breast cancer cells following AIC treatment[135]. However, in a recent study, AIC could not potentiate any significant apoptosis and its treatment yielded in the upregulation of antiapoptotic marker Bcl-2 and *MTOR* gene[136]. The reason behind this discrepancy is yet to be determined. Besides, in cervical cancer, oral cancer, lung cancer, and glioma, treatment with AIC significantly attenuates Bcl-2/Bax status, activates caspases, and promotes S/G2/M arrest, thus potentiating its anticancer effect[137]. In bladder cancer, AIC promotes pro-apoptotic activities by facilitating the activation of JNK, the phosphorylation of Bcl-2, and cell cycle arrest[138]. In a recent study, treatment with AIC nanoparticles in bladder cancer cells has demonstrated that AIC nanoparticles inhibit cell proliferation more potently compared to AIC by targeting pro-inflammatory markers, such as IL-6, tumor necrosis factor (TNF)-α, and inducible nitric oxide synthase (iNOS)[138,139]. Treatment with AIC also suppresses EMT events in HCC cells[139]. Moreover, in CRC, the antimetastatic effects of AIC have been reported to be associated with mitotic arrest, Ca^{2+} release, growth arrest and DNA damage inducible protein 153 (GADD153) activation, and the suppression of MMP expression and MAPK pathway[140]. Overall, AIC has shown potential in cancer treatment, although further studies are needed to understand the mechanisms involved and its clearance mechanism.

2.1.9. Benzyl isothiocyanate (BITC)

BITC is another natural H_2S donor and ITC derivative, which is strongly linked with cytoprotection and anti-carcinogenesis. The anticancer effect of BITC has been well-documented in several papers. In bladder cancer, BITC has been shown to reduce the incidence of cancer in mice that are treated with the carcinogenic compound N-butyl-N-(4-hydroxybutyl) nitrosamine and in cellular models through the upregulation of miR-99a-5p through ERK/c-Jun/AP-1 activation, which, in turn, downregulates the expressions of IGF1R, mTOR, and fibroblast growth factor receptor 3 cascades and reduces cell survival[141]. BITC treatment also promotes ROS production, G1 arrest, and protective autophagy through mTOR inhibition[142]. In breast cancer, treatment with BITC can effectively suppress pro-survival activities by targeting p53/liver kinase B1 (LKB1) and p73/LKB1 cascades and overexpressing transcription factor Krüppel-like factor 4 (KLF4)[143]. In addition, BITC can prevent osteoclast differentiation in breast cancer cells by inhibiting runt-related transcription factor 2 and receptor activator of NF-κF ligand[144]. The reduction of XIAP, FOXQ1, STAT-3, AKT, TGF-β, and TNF-α expressions and the elevation of ROS, caspases, FOXO1, and JNK/p38 MAPK activation have been observed in breast cancer cells following BITC treatment[145]. In lung cancer, BITC has been shown to suppress the resistance of cells to gefitinib and promote autophagy, apoptosis, and ROS generation[146]. It has also been suggested that BITC treatment can induce oral cancer cell death by mediating G2/M arrest and DNA damage by elevating pro-apoptotic markers and decreasing antiapoptotic ones[147]. In head-and-neck squamous cell carcinoma, BITC can suppress EMT markers such as vimentin and activate pro-apoptotic markers such as caspase-3 and poly-ADP ribose polymerase (PARP), thus resulting in anticancer activities[148].

Moreover, in HCC, BITC treatment has been reported to have anti-survival effects due to the reduction of MMPs and MAPK pathways[149]. In pancreatic cancer, BITC treatment can suppress the expressions of antiapoptotic proteins such as XIAP, p-PI3K, p-AKT, p-mTOR, p-FOXO1, p-FOXO3a, p-STAT-3, and NF-κB as well as activate MAPK pathways, resulting in increased cellular apoptosis and decreased angiogenesis[150,151]. Besides, BITC has antiproliferative effects when used to treat gastric cancer. These effects are associated with the inhibition of ERK1/2, Ras, iNOS, and COX-2 as well as the activation of death receptors[152]. The above evidence validates the potential of BITC in cancer treatment; however, further investigations are needed to understand the mechanisms of action for this donor and how H_2S moiety participates in ROS generation.

2.1.10. Phenylethyl isothiocyanate (PEITC)

PEITC is a slow-releasing H_2S donor and a member of ITCs. The donor works by regulating the cell cycle and oxidative stress, ultimately causing apoptosis. In oral cancer, PEITC has been reported to suppress the expressions of pro-migration markers, such as MMP-2 and -9, and increase the expressions of tissue inhibitor matrix metalloproteinase (TIMP)-1 and TIMP-2 by inhibiting several pathways, including MAPK, NF-κB, and EGFR signaling cascades[153]. PEITC also induces cell death by activating mitochondria-apoptotic pathways, death receptors, p21/53, and cell cycle arrest[154]. In glioblastoma, PEITC promotes apoptosis, cell cycle arrest, and anti-EMT activities through the activation of intrinsic and extrinsic pathways, along with the downregulation of MMPs, CDC20, cyclin B1, MCL-1, and XIAP expressions[155]. Similarly, PEITC treatment has also been shown to inhibit death receptors and activate TGFβ/Smad2 signaling pathways in cervical cancer[156]. In the treatment of gastric cancer with PEITC, the latter inhibits the expressions of MMPs, FAK, Ras, growth factor receptor-bound protein 2, COX-2, and VEGF

as well as disrupts microtubules to promote apoptosis and anti-migratory events[157]. In colon cancer, PEITC inhibits NF-κB, AKT, ERK, and JNK to mediate anticancer properties[158]. The treatment of ovarian cancer cells with PEITC has revealed that the latter exhibits pro-apoptotic activities through the activation of caspases, p38, and JNK, and the inactivation of AKT/ERK1/2 and CRM1-mTOR/STAT3 pathways[159].

In lung cancer, PEITC treatment promotes G2/M arrest, elevates cleaved caspase-3, PARP, GADD153, endonuclease G, and Bax, and inactivates the Janus kinase 2 (JAK2)/STAT3 pathway, thus facilitating cell death and reducing migration activities[160]. In melanoma, PEITC induces cell death through the activation of mitochondria apoptosis and the elevation of ROS level[161]. Moreover, PEITC administration suppresses Bcl-2 and Bcl-xL, elevates Bak, inhibits Notch 1 and 2 cascades in pancreatic cancer, and inhibits Wnt/β-catenin in CRC[162]. In prostate cancer, PEITC treatment decreases the expressions of CDK1, cyclin B1, CDC25C, α/β-tubulin, surviving, and XIAP, and increases the expressions of miR-194, caspases, p53, and WEE1 to mediate anticancer activities[148]. Furthermore, PEITC induces cell apoptosis in breast cancer cells through the elevation of p53, the suppression of ER-α36, metadherin, HER2, EGFR, and STAT-3 expressions, and the reactivation of cadherin[148,163]. The above data suggests that PEITC has potential in cancer treatment; however, little is known concerning the drug's mode of action and clearance mechanism.

2.1.11. N-acetyl cysteine (NAC)

NAC is a H_2S donor and a precursor for L-cysteine and reduced GSH. It is a cytoprotective compound with potent antioxidant properties[164]. NAC-derived cysteine releases H_2S in the mitochondria, elevating 3-MPST and sulfide quinone oxidoreductase (SQR), which are the potential upstream regulators of sulfane sulfur species[165]. In a recent study, NAC has been shown to serve as a substrate for 3-MPST and SQR in colon cancer cells. However, the event did not significantly alter their viability and rate of proliferation[166]. In contrast, NAC-mediated elevation of 3-MPST activities and intracellular H_2S level exhibits antiproliferative properties in neuroblastoma cells (SH-SY5Y)[167]. Besides, NAC can reverse the anti-tumor effect of xanthatin, including G2/M arrest and ROS-mediated autophagy and apoptosis, in colon cancer cells[168]. In gastric cancer, NAC promotes SJ-89 cell cycle arrest, apoptosis, and DNA damage[169]. Further evidence has shown that NAC treatment can suppress the metastasis and glycolysis of gastric cancer cells, resulting from autophagy inhibition-mediated ROS, through the deactivation of NF-κB and HIF-1α[170]. Cotreatment with NAC, however, may restore pro-cancer properties following treatment with anticancer drugs that initially work by raising ROS levels, such as piperlongumine.

Meanwhile, the combination of NAC with bromelain shows more potency in inhibiting the growth of gastrointestinal cancer by facilitating caspase-dependent apoptosis and autophagy[171]. Moreover, a clinical trial has revealed that the administration of NAC can reduce oxaliplatin-induced neuropathy in CRC and gastric cancer patients[172]. In lung cancer, individual treatment with NAC has pro-cancer effects that are associated with reduced ROS, p53 activity, and DNA damage; however, when administered in combination with other therapeutics, it shows solid anticancer activities[173]. NAC enhances glioblastoma cell death in an antioxidant-independent manner by facilitating lysosomal degradation of Notch 2 cascade, thus resulting in the attenuation of the pathway[174]. In gastric cancer cells, NAC can effectively attenuate ROS-induced apoptosis, triggered by anticancer drugs like curcumin[175].

In human breast cancer MDA-MB-435 cells, treatment with NAC induces cell death and vascular collapse by promoting apoptosis and the production of antiangiogenic mediator angiostatin, as well as shifting estrogen metabolism by inhibiting the formation of DNA adducts[176]. In addition, NAC suppresses cancer proliferation by attenuating Ki67 expression and the glycolysis marker stromal monocarboxylate transporter 4[177]. However, there have been conflicting studies, wherein NAC treatment, combined with other potential anticancer drugs, can either enhance or suppress the drug's cytotoxicity[178]. The mode of action of the treatment plays a key role in determining the synergistic effect of NAC. In a recent clinical trial, oral administration of NAC in breast cancer patients effectively reduced paclitaxel-induced peripheral neuropathy and improved the quality of life in these patients[179]. Moreover, NAC treatment also exhibits anticancer effects in bladder cancer linked with the activation of caspases, cell cycle arrest, and suppression of metastasis through MMP-2 downregulation[180]. In bladder cancer, the co-treatment of cis-dichlorodiammineplatinum and GSH with NAC significantly reduces ROS generation from the initial treatment, suggesting the restoration of carcinogenesis[181].

In prostate cancer, NAC treatment suppresses cancer metastasis through ROS regulation, CYR61 upregulation, NF-κB inhibition, and the partial activation of AKT and ERK1/2[182]. In addition, the pro-inflammatory effects of cisplatin and etoposide (VP-16) may be suppressed by NAC[183]. Besides, in ovarian cancer, the cotreatment of doxorubicin with NAC enhances its anticancer effect, which is associated with ATM/p53 pathway activation and mTOR

inhibition[184]. Furthermore, NAC treatment can inhibit radiotherapy-induced premature ovarian failure through the suppression of nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX4)/MAPK/p53 pathway and the promotion of VEGF, thus conserving ovarian function[185]. In addition, NAC can reduce oxidative injury by increasing GSH peroxidase activity and decreasing the expression of nicotinamide adenine dinucleotide phosphate oxidase subunits (p22 and NOX4). It has also been demonstrated that NAC treatment can effectively attenuate cell invasiveness and proliferation in pancreatic cancer by regulating the cell cycle[186]. The combination of NAC with anticancer drugs, such as bromelain and curcumin, results in potent anticancer activities that are associated with attenuating migration markers such as MMP-2 and -9 as well as suppressing ROS-induced activation of ERK/NF-κB[187].

In HCC, treatment with NAC can restore intracellular GSH levels and IL-2-induced cytotoxicity of mononucleated cells[188]. NAC reduces liver damage and the incidence of post-embolization syndrome following transarterial chemoembolization in HCC patients[189]. In lung cancer, NAC adducts are significantly lowered, and its administration reduces the oxidative stress and senescence caused by the inactivation of transcription factor JunD, in addition to lung emphysema; however, it concurrently promotes the progression of cancer[190]. Briefly, these data suggest that NAC has inhibitory properties on different types of cancers. Its combination with other drugs may further enhance/attenuate the effect, depending on the drug's mode of action. Besides, the cotreatment of NAC with for drugs that initially work by facilitating ROS generation may not be a good option due to the antioxidant properties of nicotinamide adenine dinucleotide (NAD).

2.2. Native compound

2.2.1. Sodium hydrosulfide (NaHS)

NaHS is a fast-releasing H_2S compound and one of the most common donors in H_2S-related research. Being a fast-releasing donor, it produces enormous amounts of H_2S in a remarkably short period of time followed by a subsequent decline in production. Depending on the dose administered and the type of cancer and cell, the drug is known to induce dual effects; thus, there are numerous conflicting reports. The compound also regulates cellular processes, resulting in the modulation of tumor growth and sensitivity to drugs[191]. In a glioblastoma model, treatment with NaHS facilitated tumor growth in the animal model by upregulating HIF-α expression and in C6 cells by activating the p38MAPK/ERK1/2/COX-2 signaling axis[192]. However, another study has suggested that the treatment with NaHS promotes apoptotic activities through the activation of p38 and p53 cascades in C6 cells[193]. Similarly, in colon cancer, NaHS treatment promotes cancer progression and metastasis by upregulating the expressions of SIRT-1, p-AKT, and p-ERK as well as downregulating p21[194]. In a recent study, NaHS reduced cell proliferation in CRC, but it did not induce apoptosis by upregulating Ca^{2+} levels through the activation of transient receptor potential cation channel subfamily V member 1; the effect was only observed in metastatic cells but not in normal cells[195].

In multiple myeloma and oral squamous cell carcinoma, NaHS exhibits pro-cancer effects by promoting the phosphorylation of AKT and ERK1/2 cascades[196]. Moreover, it promotes cancer metastasis through the activation of HSP-90 and JAK2/STAT-3 in esophageal carcinoma EC109 cells; NF-κB, STAT-3/COX-2, and HIF-α/adenosine triphosphate-sensitive potassium channel activation in HCC; and the upregulation of MMP-2/-9 in bladder cancer EJ cells[197]. Alternatively, in lung cancer, treatment with NaHS alleviates carcinogenic activities, including EMT, through TGF-β1/Smad2/Smad3 suppression and the activation of caspase-3, p21, and p53 cascades[198,199].

NaHS also inhibits the proliferation of melanoma cells by blocking PI3K/AKT/mTOR activation and breast cancer cells by inducing G0/G1 arrest and p-p38 MAPK inhibition. In neuroblastoma, treatment with NaHS suppresses adenylyl cyclase and γ-secretase, reduces intracellular cyclic adenosine monophosphate levels and dynamin-like protein expression, and increases ERK phosphorylation[199,200]. These data imply that H_2S has a role in cancer progression; however, the potential of NaHS for cancer treatment is relatively insignificant.

2.2.2. Sodium sulfide (Na_2S)

Na_2S is another fast-releasing H_2S-donating compound that is associated with cancer therapeutics. In CRC patients, Na_2S treatment in human mesenteric arteries results in the relaxation of vessels by targeting potassium ion (K^+) channels[201]. The compound has been reported to selectively kill glioblastoma T98G and U87 cells, while showing no effect in cerebral microvascular endothelial cells (D3), through a mechanism that involves the elevation of ROS levels and the suppression of mitochondria activities, resulting in DNA damage and subsequent cell death[202]. In addition, Na_2S treatment also sensitizes glioblastoma cells to radiotherapy[203]. In an earlier study, the anticancer effect caused by the inhibition of CBS in ovarian cancer was found to be reversible with low doses of Na_2S[204]. Despite the fact that there are only a number of studies on Na_2S, evidence has indicated that Na_2S has protective and

robust anticancer effects. However, its inability to imitate the physiological production of H_2S affects its applicability.

2.2.3. Other metal sulfides

Apart from Na_2S, sulfides of other metals, such as calcium and copper, also have anticancer properties, as witnessed in experimental settings. Although there are no existing studies on individual drug administration containing the aforementioned metal sulfides in cancer; their nanoparticle formulations have been well-documented. Calcium sulfate (CaS) nanoparticles are known to trigger cell cycle arrest and induce apoptosis in lung cancer cells, but no significant effect has been reported in normal cells[205]. Similarly, copper sulfate (CuS) nanoparticles have been reported to possess the ability to target tumor cells and penetrate their nucleus by modifying surface peptides RGD and TAT[206]. In a study, the cotreatment of CuS nanoparticles with 980 nm near-infrared laser irradiation causes cell death by increasing the temperature of the nucleus and destroying the genetic materials. In cervical cancer cells, CuS nanoparticles have been shown to induce a concentration-dependent photothermal destruction with low cytotoxicity[207]. The evidence suggests that metal sulfides are useful as H_2S donors and have a role in cancer suppression; however, further research is needed to illuminate the mechanisms involved and side effects.

2.3. *De novo* design

2.3.1. Morpholin-4-ium 4 methoxyphenyl(morpholino) phosphinodithioate (GYY4137)

GYY4137 is the most common synthetic slow-releasing H_2S donor in research. It is soluble in water and exhibits a strong anticancer effect in both cellular and animal models. In various cellular models of cancer, including prostate, cervical, lung, breast, and ovarian cancer, treatment with GYY4137 can effectively promote pro-apoptotic activities by increasing lactate production, reducing intracellular pH levels, and facilitating G2/M arrest[208]. In CRC, treatment with GYY4137 promotes cell cycle arrest, apoptosis, and necrosis[209]. In addition, drug causes intracellular acidification in both ovarian and CRC cancer, due to uncoupling of sodium-calcium exchanger 1 and sodium-hydrogen exchanger1 channels[210]. Treating colon cancer cells HCT116 with GYY4137 also increase LDHA activity and induce concentration-dependent cell death by inactivating cGMP/VASP, AKT, and p44/42 MAPK (ERK1/2) pathways[187]. Moreover, in HCC, GYY4137 upregulates caspases and blocks STAT-3 activation, thereby inducing G1/S arrest and cell death[211]. In a recent study, GYY4137 has also been shown to protect neuroblastoma cells against lipopolysaccharide-induced elevation of inflammatory activities[212]. The above data suggest that GYY2137 could serve as a potential anticancer drug. However, further research is needed to investigate the mechanism of action, cellular marker, and signaling pathways involved.

2.3.2. 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione (ADT-OH)

ADT-OH is an artificial H_2S donor with significant chemoprotective effects against cancer cells. It is an extraction from amphiphilic block copolymers containing an ester bond linking ADT-OH using isoleucine and glycine linkers[213]. In a recent study, treating melanoma cells with ADT-OH have been shown to inhibit the progression of cancer by downregulating XIAP and Bcl-2 as well as stabilizing Fas-associated protein with death domain and IκB-α, resulting in NF-κB inactivation[214]. Furthermore, connecting ADT-OH with hyaluronic acid forms another novel H_2S donor (HA-ADT), which can produce more H_2S and induce more anticancer effects in breast cancer than commonly used donors, such as NaHS and GYY4137[215]. This effect is associated with the deactivation of PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways. The above evidence supports the use of H_2S in the treatment of cancer and suggests that newly synthetic donors with high efficiency could be the key.

2.3.3. S-propargyl-cysteine (SPRC)

SPRC, also known as ZYZ-802, is a structural analog of S-acetyl cysteine and a crucial substrate for CSE, thus making it an endogenous H_2S donor. Like other H_2S donors, SPRC regulates cellular activities, including inflammation, apoptosis, and oxidative stress. In a mice model of gastric cancer implants, treatment with SPRC significantly reduced tumor weight and volume by promoting pro-apoptotic activities in cancer tissues through the elevation of Bax expression, cell cycle arrest at G1/S phase, and the activation of p53 pathway[216]. The anticancer effects of SPRC can be reversed with peginterferon alfa-2a (PAG) treatment. Likewise, in pancreatic cancer, treatment with SPRC causes the inhibition of cell viability and proliferation by triggering G2/M arrest and apoptosis through the upregulation of p53 and a reduction in JNK degradation through phosphorylation[217]. From the information above, SPRC has shown potential in cancer treatment; however, a dearth of research has limited its applicability in clinical settings.

2.3.4. (10-oxo-10-(4-(3-thioxo-3H-1,2-dithiol-5yl) phenoxy) decyl) triphenylphosphonium bromide (AP39)

AP39 is a compound that targets mitochondria through triphenylphosphonium moiety and releases H_2S inside the

organelle. According to preliminary studies, H_2S induces cytoprotective effects by promoting oxidative stress, apoptosis, and inflammation[217]. Treatment with AP39 has been shown to increase the population of early and late apoptotic cells among colon cancer cells[218]. In addition, it also protects against doxorubicin-induced cardiotoxicity, which is associated with mitochondrial toxicity and a decrease in H_2S level[219]. Despite the lack of vital information on the mechanisms and pathways targeted by this donor in different types of cancers, the available data suggest a potential anticancer effect and protective effect when combined with other drugs.

2.3.5. Ammonium tetrathiomolybdate (ATTM)

ATTM is a slow-releasing inorganic H_2S donor with cytoprotective capability. The chemical formula of ATTM is $(NH_4)_2MoS_4$. ATTM has been shown to exert antioxidant effects at lower concentrations in HaCaT cells[220]. Treating pancreatic cancer cell lines with ATTM dose and time dependently reduces intracellular high affinity copper uptake protein 1, VEGF, and cyclin D1 expressions, thus mediating anticancer activities[221]. In head-and-neck squamous cell carcinoma, ATTM has been reported to suppress resistance to cisplatin by attenuating the progression of cancer by downregulating the expression of ATPase copper transporting beta (ATP7B)[222]. Similarly, in breast cancer, treatment with ATTM reduces the expression of ATP7A, a copper ATPase transporter that is involved in the intercellular movement and sequestering of cisplatin, thereby potentiating cisplatin's nuclear bioavailability, which, in turn, promotes DNA damage, cell cycle arrest, and apoptosis[223]. The safety, tolerance, and anticancer effects of recurrent breast cancer in patients have been witnessed in a clinical study involving the drug[224]. Moreover, treating lung cancer cells with ATTM significantly increase the expression of H_2S-producing enzymes CBS and 3-MPST and promote cancer progression at low concentrations, with an opposite effect at higher concentrations[225]. At lower concentrations, ATTM triggers YTHDF1-dependent PRPF6 m^6A methylation through the upregulation of methyltransferase-like protein 3 and the downregulation of fat mass and obesity associated-protein (FTO). Overall, these data suggest that ATTM shows potential in cancer treatment; however, the information available on the mechanism of action involved is insufficient.

2.3.6. H_2S-releasing nonsteroidal anti-inflammatory drugs (H_2S-NSAIDs)

H_2S-NSAIDs are H_2S-moiety-containing anti-inflammatory drugs with potent anticancer properties. One of the most common H_2S-NSAIDs is ATB-346, a naproxen derivative [2-(6-methoxynapthalen-2-yl)-propionic acid 4-thiocarbamoyl phenyl ester]. In addition to producing H_2S, it inhibits COX-2 activity. The previous studies have shown that treatment with ATB-346 can significantly reduce colonic pre-cancerous lesions in mice, prostaglandin, and whole-blood thromboxane synthesis without causing gastrointestinal injury[226]. The anticancer effects of ATB-346 are associated with the inhibition of C-MYC and β-catenin expressions. Similarly, treating melanoma cells with ATB-346 inhibit pro-survival activities by suppressing NF-κB and AKT pathways[227]. This suggests that the donor ATB-346 has anticancer activities and can be used to treat different types of cancers.

2.4. Hydrogen sulfide-nitric oxide (H_2S-NO) donors

2.4.1. NOSH-aspirin (NBS-1120)

Both NO and H_2S are powerful neuromodulators, and their role in cancer is widely recognized. The two gaseous neuromodulators regulate one another. For the donor to logically contain the moiety for both gasotransmitters, it induces a more substantial regulatory effect. According to a previous study, NBS-1120 exhibits chemoprotective properties in the gastrointestinal tract, which are inextricably linked to its antioxidant and anti-inflammatory effects, thus making it superior to aspirin[228]. Moreover, treating colon cancer cells with NOSH-aspirin significantly facilitate apoptosis, G0/G1 arrest, ROS generation, and NF-κB deactivation[229]. Mechanistically, NOSH-aspirin mediates both S-sulfhydration and S-nitrosylation of p65 NF-κB, along with the denitrosylation and desulfhydration of caspase-3, thereby inhibiting the activation of caspase-3 and NF-κB[230]. According to another study, the compound preferentially inhibits COX-1 over COX-2, and its effect varies with different isomers, with the inhibitory effect in colon cancer ranking as follows: *o*-NOSH-aspirin > *m*-NOSH-sspirin > *p*-NOSH-aspirin[231]. In a mice colon cancer model, the combination of NOSH-aspirin with 5-fluorouracil induced a stronger effect compared to individual treatments and showed no side effects or weight loss in mice[232,233]. In breast cancer, the drug treatment results in tumor suppression through the reduction of proliferating cell nuclear antigen, an increase in cyt c, and ROS generation[234]. Similarly, a recent study has revealed that the treatment with NOSH-aspirin exerts anticancer effects in a mice model of pancreatic cancer by increasing ROS generation, caspase-3 activity, and mutated p53 expression, while suppressing NF-κB and FoxM1 expressions[235]. Overall, the above data suggest that NOSH-aspirin can be used to treat cancer, with minimal side effects and by primarily targeting the cell cycle, COX-1/2, and ROS.

2.4.2. NOSH-sulindac (AVT-18A)

Another H_2S and NO donor is NOSH-sulindac. This compound has been shown to induce apoptosis in cancer cells at a relatively lower concentration than normal cells. The treatment of NOSH-sulindac resulted in over 150 times cell growth inhibition in human breast cancer cells MCF-7, pancreatic cancer cells BxPC-3, and colon cancer cells HT-29 as compared to its treatment in normal lung cells IMR-90, pancreatic epithelial cells ACBRI 515, and normal breast cells HMEpC[236]. Its effect is associated with the suppression of pro-inflammatory TNF-α, oxidative marker MDA, the induction of G2/M arrest, and apoptosis[237]. The effect of this donor on colon cells has been reported to be independent of the cell's ability to produce prostaglandin[238]. As of now, no mechanism has been found to be associated with the inhibitory effect of NOSH-sulindac; hence, the potential of this donor has yet to be determined.

With all the given findings, it is widely recognized that the treatment with H_2S donors (exposure of H_2S) can inhibit the proliferation of cancer cells, induce apoptosis, and promote cell cycle arrest, thus resulting in cancer cell death (Figure 3). However, there is still room for investigation concerning H_2S donors induction, the initiation of cancer cell death signaling, and their causes. Figure 4 is a schematic presentation of exogenous H_2S-based natural and synthesized chemical compounds used in cancer research.

3. Targeting endogenous H_2S for cancer treatment

3.1. CSE inhibitor

CSE is a major contributor to H_2S production in numerous cells. Targeting this marker directly affects cell viability and progression. For example, CSE has been reported to be highly upregulated in breast cancer patients, in which the event positively corresponds to breast cancer metastasis by elevating angiogenic factor VEGF and activating various signaling pathways, such as PI3K/AKT, Ras/Raf/MEK/ERK, and STAT-3[239]. By knocking down CSE in breast cancer cells, MDA-MB-231 significantly suppresses both migration and proliferation activities[240]. Treatment with CSE drug inhibitors, such as I157172 and I194496, potently suppresses CSE activities with pro-cancer events through the promotion of sirtuin 1 and the inhibition of STAT-3, VEGF/FAK/paxillin, PI3K/AKT, and Ras/Raf/MEK/ERK pathways[241]. Similarly, CSE has a pro-cancer effect in gastric cancer; its inhibition prevents cell growth and metastasis through promoting apoptosis and improving anticancer drug sensitivity[242]. SP1-dependent activation of PI3K/AKT pathway in HCC cells has shown that it acts through CSE to enhance tumorigenesis[243,244]. Simultaneously, the inhibition of CSE suppresses EMT markers and EGFR though ERK1/2 inactivation, thus resulting in cancer suppression[245]. Knocking down CSE also increases radiosensitivity and reduces radiation-mediated promotion of EMT by blocking the p38 MAPK pathway[246]. However, a recent study has revealed that the inhibition of CSE in mice negatively regulates the immunosuppressive enzyme indoleamine 2,3-dioxygenase 1, creating an immune-tolerant tumor microenvironment. This event can be reduced by overexpressing CSE or increasing H_2S levels[247]. This negative correlation can also be confirmed in clinical samples. These conflicting results show a need for further studies on cancer and the role of CSE. In colon cancer, the activation of Wnt/β-catenin pathway is associated with the upregulation of CSE expression.

In a study, the proliferation of SW480 cells was significantly reduced by CSE-knockdown, suggesting the enzyme's potential role in colon cancer metastasis[248]. CSE-mediated production of H_2S has been reported to promote the progression of prostate cancer through the activation of Cav3.2 and IL-1β/NF-Kb cascades, whereas CSE inhibition results in anticancer effects in PC-3 cells[249]. Overall, the above data suggest that CSE inhibitors have the potential to be anticancer drugs in certain types of cancers; however, less is still known about their mechanism of action, clinical applicability, and possible side effects.

3.2. CBS inhibitor

CBS is also a key player in cancer activities. Therefore, understanding its inhibition effect on cancer is of paramount importance. It has been previously reported that CBS is highly upregulated in gastric cancer tissues compared to non-cancerous ones. Its inhibition with amino-oxyacetic acid (AOAA) enhances the anticancer effects of 3,3'-diindolylmethane by activating the p38/p53 axis[250]. Similarly, in another study, tissue samples of breast cancer patients exhibited high levels of CBS compared to normal tissues. Further examination had revealed that silencing CBS causes a significant reduction in cell growth and progression of breast cancer cells[251]. The inhibition of CBS also attenuates the antioxidant pathway Nrf2 and sensitizes the cells to doxorubicin[252].

Besides that, CBS modulates cancer cells by regulating nicotinamide phosphoribosyltransferase and ATP activities[253]. In HCC patients, low *CBS* mRNA expression correlates with higher disease progression stages and shorter overall survival[254]. However, the increased expression of CBS as a result of hypoxia-induced radioresistance can be attenuated following treatment with a CBS inhibitor and AOAA in HepG2 cells[255]. CBS has been found to be

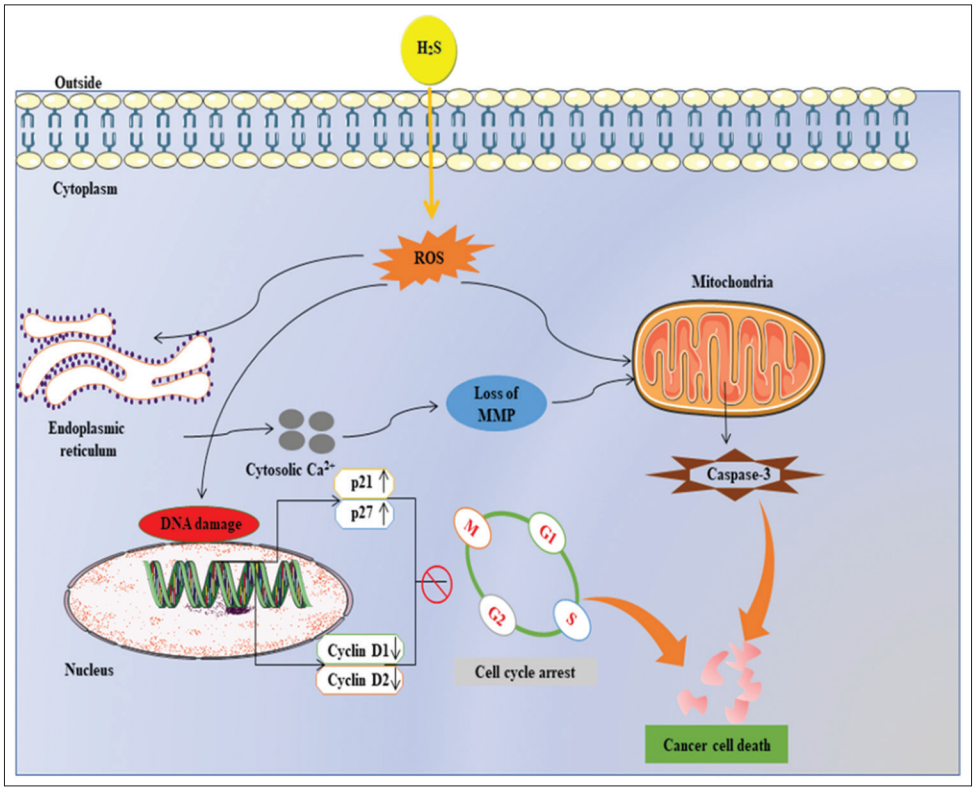

Figure 3. Proposed mechanism of H_2S effect on cell cycle arrest in cancer cells. H_2S increases ROS levels and disrupts Ca^{2+} homeostasis, leading to high intracellular Ca^{2+} with increased expression of p21 and p27, which can result in cell cycle arrest. H_2S: Hydrogen sulfide, ROS: Reactive oxygen species, MMP: Matrix metalloproteinase, G1: Pre-synthetic phase, S: Synthetic phase, G2: Post-synthetic phase, M: Mitotic phase.

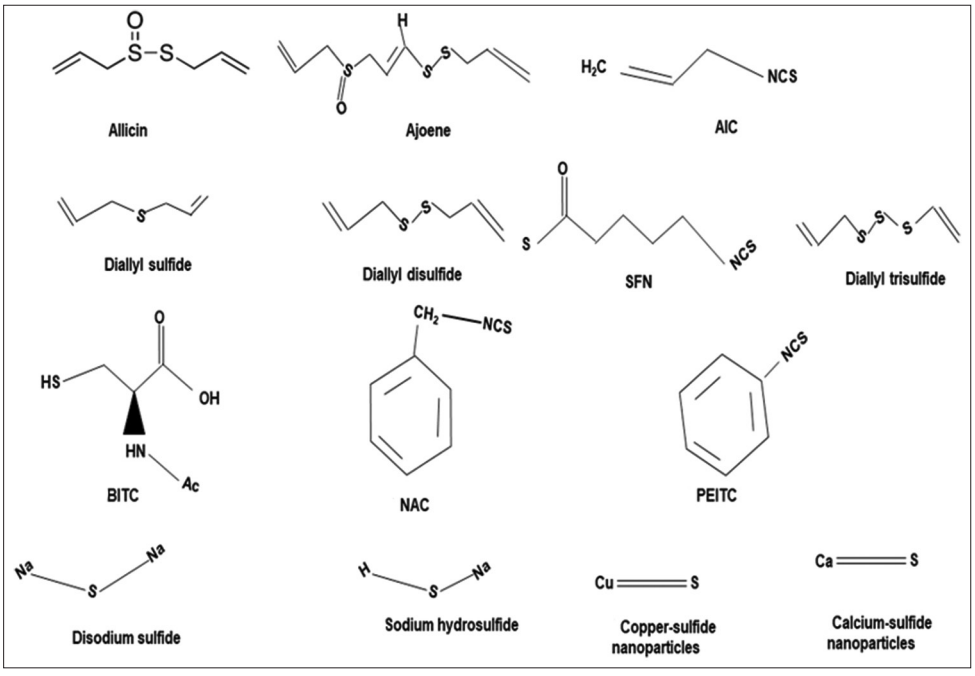

Figure 4. A schematic presentation of exogenous H_2S-based natural and synthesized chemical compounds used in cancer research: (a-i) natural world; (j-n) native compound; (o-w) *de novo* design.

upregulated in hepatoma cells SMMC-7721 and HepG2 but downregulated in BEL-7404 compared to normal cells HL-7702 and QSG-7701[237]. In addition, the silencing of CBS through siRNA or pharmacological inhibitors, AOAA and quinolone-indolone conjugate, effectively induced an anticancer effect in SMMC-7721 by promoting oxidative stress and activating caspase-3.

Besides, treatment with another inhibitor of CBS, CH004, has also been shown to cause cell death in HCC by promoting ferroptosis[256]. High CBS level has been found to be associated with drug resistance in HepG2 cells, and its inhibition increases their sensitivity to doxorubicin and sunitinib; however, in BEL-7404, the elevation of CBS levels enhances the sensitivity to the drugs[257]. This confirms that the effect of CBS in HCC is cell dependent. CBS expression has also been reported to be significantly increased and associated with poor prognosis in renal cancer and cholangiocarcinoma[258], suggesting that the enzyme is involved in cancer activities. However, evidence on its inhibition is still lacking. In ovarian cancer, *CBS* gene silencing reduces migration, angiogenesis, and lipid contents[241]. The inhibition of CBS also activates the JNK pathway and suppresses mitofusin, resulting in mitochondrial morphogenesis reprogramming and the sensitization of cells to erastin[259]. In a recent study, a nanoformulation comprising selenium-containing chrysin has been shown to induce its anticancer effects in ovarian cancer cells by reducing CBS expression, thereby causing oxidative stress[260]. In colon cancer, CBS overexpression is associated with cancer development and treatment with AOAA, and *CBS* gene silencing can significantly reverse pro-cancer activities[261]. AOAA also sensitizes colon cancer cells to oxaliplatin by impairing the antioxidant system and promoting ROS generation. Treatment with AOAA has also been indicated to induce the upregulation of E-cadherin and zonula occludens-1 as well as the suppression of fibronectin, thereby inhibiting the migration and invasion activities of colon cancer cells and promoting mesenchymal-epithelial transition[262]. Other CBS inhibitors that induce apoptosis in colon cancer cells include 2,3,4-trihydroxybenzylhydrazine and sikokianin C[263]. Moreover, treatment with AOAA in multiple myeloma reduces cell cycle progression by triggering G0/G1 arrest and promotes apoptosis through Bcl-2 inhibition and caspase-3 activation[264]. CBS knockdown in glioma cells is to have a fatal outcome, as it results in the progression and metastasis of cancer. These data suggest that CBS plays a role in cancer activities in different types of cells, with its effects varying accordingly; its anticancer effect is selective only to certain types of cancers or cells.

3.3. 3-mercaptopyruvate sulfurtransferase inhibitor

3-MPST in commonly found in cells. It regulates various cellular activities, including bioenergetics, angiogenesis, and the mitochondria electron transport system[265]. In an animal model of colon cancer, treatment with the 3-MPST inhibitor 2-[(4-hydroxy-6-methyl pyrimidin-2-yl)sulfanyl]-1-(naphthalen-1-yl)ethan-1-one (HMPSNE) suppresses H_2S production, CT26 cells proliferation, migration, and oxidative phosphorylation-associated cellular bioenergetics[266]. HMPSNE treatment also suppresses migration- and invasion-promoting markers in colon cancer cells by suppressing Wnt-β-catenin pathway[267]. In human breast cancer cells MCF-7, treatment with another inhibitor, S-Allyl-L-cysteine, has been shown to reduce cell viability by attenuating 3-MPST expression and, subsequently, H_2S level[268]. On the contrary, in neuroblastoma cells, the elevation of 3-MPST activities has shown anticancer properties[167]. The above evidence suggests an involvement of 3-MPST in cancer progression; however, its precise mechanism of action, the pathways involved, and its inhibition effect in different types of cancers are yet to be identified.

4. Translation of H_2S research into therapeutic format

The findings from the aforementioned research on H_2S donors and inhibitors show considerable potential for the development of H_2S-based chemopreventive cancer therapies in the near future. The research community expects substantial outcomes from the preclinical trials on H_2S-based chemopreventive drugs. However, to shape the future of H_2S research in oncology practice, it is highly significant to investigate the biochemistry and pharmacology of H_2S donors and inhibitors as well as characterize their dose-dependent responses to cancer cells. A huge gap remains in understanding how H_2S-producing enzymes respond to the exposure of inhibitors and donors in cancer cells and how they reinforce to generate signals of apoptosis and proliferation in the cancer microenvironment. To reach a large audience across multiple disciplines and promote the innovation of H_2S biomedicine, identifying potential therapeutic H_2S scavengers and donors are as important as assessing their biomedical applications.

5. Conclusion

H_2S is widely recognized for its enormous diagnostic and therapeutic advantages in various diseases, including cancer. Besides its involvement in other pathophysiological illnesses, H_2S plays a significant role in regulating various cellular activities, such as angiogenesis,

cellular bioenergetics, proliferation, apoptosis, EMT, and autophagy, all of which are involved in cancer. The current understanding of H_2S research reveals that both the upregulation and downregulation of H_2S might have anticancer effects, depending on the type of cancer. With the recent advancements in science and technology, researchers have testified that the ability of applied H_2S donor or inhibitor drugs to induce their corresponding effects on H_2S production varies, resulting in pro-cancer or anticancer properties of varying magnitude ranging from none or little to a strong influence depending on the drug type and targeted cells. Besides the individual impact, combining H_2S drugs with other anticancer drugs have been reported to induce significant anticancer effects and sensitize cells to treatments.

Furthermore, by alternating H_2S levels, numerous cellular markers that are associated with cell growth and progression have been reported to be affected, resulting in cancer inhibition or aggravation. Despite the huge potential of these H_2S-based natural, native, and designed chemicals in cancer treatment, little is known about the mechanism of action of these drugs. To shape the future of H_2S research in oncology practice, conclusive investigations are required to assess the drug concentration for treatment and the specificity of both H_2S donors and inhibitors before their use as candidate drugs for cancer treatment in clinical settings.

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Conflict of interest

All the authors declare no conflicts of interest.

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