Role of hydrogen sulfide donors in cancer development and progression

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Abstract

In recent years, a vast number of potential cancer therapeutic targets have emerged. However, developing efficient and effective drugs for the targets is of major concern. Hydrogen sulfide (H$_2$S), one of the three known gasotransmitters, is involved in the regulation of various cellular activities such as autophagy, apoptosis, migration, and proliferation. Low production of H$_2$S has been identified in numerous cancer types. Treating cancer cells with H$_2$S donors is the common experimental technique used to improve H$_2$S levels; however, the outcome depends on the concentration/dose, time, cell type, and sometimes the drug used. Both natural and synthesized donors are available for this purpose, although their effects vary independently ranging from strong cancer suppressors to promoters. Nonetheless, numerous signaling pathways have been reported to be altered following the treatments with H$_2$S donors which suggest their potential in cancer treatment. This review will analyze the potential of H$_2$S donors in cancer therapy by summarizing key cellular processes and mechanisms involved.

Key words: Hydrogen sulfide; H$_2$S donors; Cancer; Signaling pathways; Cellular processes

Introduction

Cancer has remained as one of the most investigated diseases in scientific research, and many potential therapeutic targets have been discovered. However, developing the most effective and highly efficient combination therapy against the extremely resistant metastatic cancer cells is still a challenge. In 2018, the worldwide estimation of cancer new cases was 18.1 and the mortality numbers were 9.6 million [1], which is an increase of more than 28% and 17% respectively from the 2012 report [2]. This enormous increase in new cases demands for the new and effective therapeutic option for the disease. Cellular activities such as autophagy, apoptosis, migration and proliferation that are known to be altered in cancer cells serve as the main therapeutic targets [3-5]. Therefore, the identification of potential compounds that can effectively regulate these activities to bring about anti-cancer properties is essential in determining potential treatments.

Hydrogen sulfide (H$_2$S) is the third gaseous neurotransmitter to be associated with the regulation of pathophysiological processes, next to carbon monoxide (CO) and nitric oxide (NO) [6, 7]. H$_2$S is initially synthesized in the cells by the enzymatic reactions involving cystathionine beta-synthase (CBS), 3-mercaptoppyruvate sulfurtransferase (3-MP-
ST) and cystathionine gamma-lyase (CTH/CSE) enzymes [6, 8, 9]. H_{2}S plays a vital role in the establishment and progression of multiple health disorders ranging from non-cancerous [10, 11] to cancerous [12, 13]. In cancer, H_{2}S participates in both the suppression [12, 14-17] and progression of the disease [13, 18].

H_{2}S donors are naturally or synthetically derived H_{2}S-releasing compounds. Some of the commonly used H_{2}S donors include sodium polysulthionate, 1,2-dithiole-3-thiones, modified non-steroidal anti-inflammatory drugs, sulfide-containing salts, sodium hydrosulfide (NaHS), sodium sulfide, garlic-derived natural sulfides, allyl methyl sulfide, dipropyl disulfide, diallyl sulfide (DAS), diallyl disulfide (DADS), dialyl trisulfide (DATS), Lawesson’s reagents, morpholin-4-ium-4-methoxyphenyl(morpholino) phosphinodithioate (GY4137) and its derivatives, diclofenac derivative, 4-(3-thioxo-3H-1,2-dithio1-5-yl)phenyl ester-2-[(2,6-dichlorophenyl) amino]-benzenecacetic acid, phenol derivative, 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione (ADT-OH), mesalamine derivative, 5-amino-2-hydroxybenzoic acid 4-(5-thioxo-5H-[1,2]dithiol-3-yl)-phenyl ester hydrochloride, naproxen derivative, 2-(6-methoxynaphalen-2-yl)-propionic acid 4-thiocarbamoyl phenyl ester (ATB-346), and the mitochondria-specific H_{2}S donor, 10-oxo-10-(4-(3-carbamoyl phenyl ester (ATB-346). H_{2}S plays a vital role in the body. Both endogenous and exogenous-derived H_{2}S have been shown to participate several physiological activities such as muscle relaxation, water regulation, cytoprotection, and inflammation [30-33]. Low levels of H_{2}S and the downregulation of its producing enzymes are familiar events in cancer cells. The analysis of tissue samples from hepatocellular carcinoma (HCC) patients reveals a significant reduction in CBS levels compared to their surrounding non-cancerous tissues and the decrease could be correlated with poor prognosis [34]. Further downregulation of the CBS enzyme using an inhibitor CH004 induces anti-cancer effects via ferroptosis, an iron-dependent programmed cell death in HepG2 cells [35]. Unlike CBS, CSE is upregulated in many cancer types including HCC, gastric and breast cancer, where its endogenous inhibition also has anti-carcinogenic effects [17, 36, 37]. Alternatively, studies have shown that the supplementation of H_{2}S using donors can also induce strong cytoprotective effects in many cancer types [14, 37-39]. Despite the lack of evidence on the normal range of H_{2}S in different cells and the activities leading to its alteration in cancer cells, the available data suggest that only a certain amount of H_{2}S is required for maintaining cellular activities and any adjustment resulting from either increasing or decreasing the level has an enormous impact on cellular activities involved in cancer modulation.

**Mechanisms involved in H_{2}S-mediated cancer modulation**

One of the primary mechanisms involved in the H_{2}S-induced cancer regulation is through its interaction with cellular transporter/channels. As a neurotransmitter, H_{2}S has been shown to interact with cell transporters [40] and ion channels [41-43], resulting in the downstream regulation of cellular...
activities [43-45]. It has been revealed that the treatment of HEK293 cells with 1 µM-1 mM NaHS inhibits voltage-gated T-type specifically Cav3.2 channels by promoting extracellular binding of zinc (Zn²⁺) [46]. At the downstream, the suppression of T-type channels can result in enhanced antitumor activities and improved sensitivity of cancer cells to drugs [47-49]. Studies also show that H₂S donors can trigger the activation of cellular transporters including ATP-binding cassette transporter A1 (ABCA1) [40] and glutamine transporter-1 (GLT-1) [50] by promoting nuclear translocation of peroxisome-proliferator-activated receptor alpha and inhibiting the extracellular signal-regulated kinase 1/2 (ERK 1/2) respectively. However, depending on the cancer type, the activation of ABCA1 and GLT-1 can either have inhibitory or promoting effects [45, 51-53]. Moreover, by interacting with GLT-1, H₂S donors can directly participate in modulating aerobic glycolysis (Warburg effect) which is a metabolic-hallmark of most cancer cells. Therefore, the impact of the activation of the above transporters by H₂S donors in cancer should be further examined to clarify the mechanism and the subsequent responses. Besides, H₂S can also interact with insulin receptors and toll-like receptors 4 (TLR4), resulting in the inhibition of phosphoinositide 3-kinase (PI3K)/AKT/mTOR [12], nuclear factor-kappa B (NF-κB) [54] and signal transducer and activator of transcription-3 (STAT-3) [55] pathways together with their corresponding cellular responses.

Another key mechanism involved in the regulation of cellular activities is the functional interconnection between H₂S and other gasotransmitters. This potential link between H₂S, CO, and NO serves as a crucial mechanism exploited by H₂S donors in regulating cancer activities. Exclusively, exogenous treatment with donors of either of the three gasotransmitters can reduce cancer progression by facilitating reactive oxygen species (ROS) tolerance, anti-proliferative and pro-apoptotic responses in human breast cancer [56-58]. Moreover, a recent study indicates that treatment with either NO, CO, or H₂S donors (namely S-nitroso-N-acetyl-D,L-penicillamine, carbon monoxide releasing molecule-A1, and GYY4137, respectively) promotes anti-carcinogenic activities in colon cancer cells HCT116 in a dose-dependent manner by regulating AKT, cyclic guanosine monophosphate (cGMP)/VASP, and P44/42 mitogen activated protein kinase (MAPK) pathways [16]. With respect to the link, study shows that the treatment of cancer cells with DAS, DATS, and diallyl tetrasulfide can significantly reduce tumor growth mechanistically by upregulating heme oxygenase-1 (HO-1) expressions through MAPK and PI3K-mediated activation of nuclear factor erythroid-2 related factor-2 (Nrf-2) pathway [59-61]. The downstream effect of HO-1 is the catalysis of heme to biliverdin, a reaction that releases CO as a byproduct [62]. It is also worth noting that treatment with CO donor photo-CORM [Mn (CO)₃] reduces the antioxidant status by inhibiting the bioactivity of H₂S producing enzyme CBS in breast cancer cells [63]. Moreover, it has been reported that both the treatment with 20-100 µM NaHS following the inhibition of long non-coding RNA sONE (an endothelial NO regulator) on breast cancer cells MDA-MB-231 for 72 hours, or the co-treatment of NaHS with 40-100 µM doses of NO donor diethylenetriamine NO adduct (DETA/NO) can reverse the antitumor effects of NaHS by regulating cGMP pathways [64]. Similarly, NaHS treatment also increases the production of NO and its associated cytoprotective pathways in murine brain homogenate and L1210 leukemia cells conceivably via S-nitrosothiol-signaling pathway [65]. In summary, the above data indicate the interaction between H₂S, CO, and NO to play a significant part in regulating cancer activities, which is in addition to its interaction with cell receptors and transporters.

### Role of H₂S donors in cancer

The response of cancer cells to H₂S donors varies substantially depending on the donor type, concentration and cancer types. Here, we will discuss the effects of these donors in cancer by illuminating cancer-promoting activities (including immune response, gene transcription and translation, and cell growth), cancer inhibitory events (such as cell cycle arrest, autophagy, and apoptosis), anti-cancer drug sensitivity and in vivo tumor growth.

### Cancer suppressing activities

**H₂S donor regulates immune responses**

The immune system plays an important role in maintaining normal cellular activities. In the initial stages of cancer, it helps in tumor inhibition by removing immunogenic cancer cells, however, in later stages it is manipulated to facilitate cancer growth and progression [66]. One of the ways in which cancer cells escape from being destroyed by the immune system is through regulatory T cells (Tregs) [67]. By regulating the transforming growth factor-beta (TGF-β), Tregs can markedly promote epithelial-mesenchymal transition (EMT) of HCC cells [68] and suppress the cytotoxicity of the expanded tumor-specific CD8 T cells [69]. High frequency of FOXP3⁺ CD4⁺ CD25⁺ regulatory T cells has been shown to facilitate cancer progression in pancreatic ductal adenocarcinoma [70] and HCC [71]. Though,
the binding of ten-eleven translocation methylcyto-
sine dioxygenases 1 and 2 (Tet 1 and 2) to FOXP3 can help to maintain the stability and functions of Tregs [72, 73]. A substantial reduction in the expressions of Tet genes has been reported in several cancer types including colon and breast cancer and their upregulation promotes tumor-suppressing effects [74-77]. It has been revealed that treatment with H2S donors can stimulate RNA demethylation and Tregs-associated immune responses in CD4+ T cells by increasing the expressions of Tet 1 and Tet 2 genes via the sulfuration of nuclear transcription factor Y subunit beta in H2S-deficient mice model [78]. However, whether H2S donors can deregulate Tet 1 and 2 in cancer types including ovarian cancer [79] and where the Tet 1 and 2 genes are overexpressed need to be further investigated.

Peroxynitrite, an extremely reactive compound formed from the reaction between NO and superoxide radicals, is known to promote DNA damage and trigger autoantibody in cancer patients [80]. Filipovic et al. reports that H2S treatment can effectively prevent the effects of peroxynitrite by reacting with the compound under inflammatory conditions to form sulfanyl nitrite, an NO-releasing compound [81]. Furthermore, treatment with NaHS protects glomerulus mesangial and Jurkat cells against antibody-induced cell lysis and apoptosis by sulfuring the humoral effector molecules thereby reducing antibody binding ability [82]. NaHS also suppresses the activation of the complement alternative pathway (AP), an important effector molecule of innate immunity. Regardless, the effect of the inhibition is still uncertain since both overactivation and underactivation of the pathway have been observed in cancer [83, 84]. In addition, whether the event could impair immune response and expose patients to other infections needs further exploration. Collectively, these data imply an essential role of H2S in regulating immune activities and associated diseases including cancer through the regulation of key immune regulators.

H2S donor mediates gene transcription and translation

The transcription and translation factors are vital entities that regulate the generation of RNA molecules and amino acid sequences respectively [85, 86]. The dysregulation of transcription and translation factors are common events in cancer cells [87, 88]. It has been shown that treatment with H2S donors can effectively regulate numerous transcription factors including NF-κB [32], STAT-3 [55], and Nrf-2 [89-91] that are involved in inflammation, apoptosis, and oxidative stress events. Moreover, GYY4137 treatment can significantly downregulate the expression of transcription factor Krüppel-like factor 5 (KLF-5) [92], which in turn regulates the SRY-box transcription factor-4 [93] and NF-κB [94].

Besides, H2S plays a key role in regulating the post-translational modification of protein via sulfuration [95]. In mouse embryonic fibroblast cells (MEF) and HeLa cells, treatment with 100 µM NaHS significantly increases the phosphorylation of eukaryotic translation initiation factor 2 subunit alpha (eIF2α) partially through the suppression of protein phosphatase 1c as a result of its persulfidation at cysteine (Cys)-127 [96]. Even though the phosphorylation of eIF2α decreases protein synthesis, the incident can result in the promotion of cell migration and ultimately cancer metastasis [97]. Hence, the interaction between H2S and eIF2-α, and its implication in carcinogenic activities needs to be further investigated. Alternatively, treatment with NaHS or GYY4137 could protect against apoptotic and inflammatory responses by sulfuring the p65 subunit of NF-κB at Cys-38 in monocyte/macrophage THP-1 cells, RAW macrophages and human embryonic kidney (HEK-293) cells [98, 99]. In addition, NaHS, GYY4137 or DATS treatments improves antioxidant status through post-translation modification of Kelch-like ECH associated protein 1 (Keap 1), a redox-sensitive protein with the first two molecules of innate immunity. Regardless, the effect of the inhibition is still uncertain since both overactivation and underactivation of the pathway have been observed in cancer [83, 84]. In addition, whether the event could impair immune response and expose patients to other infections needs further exploration. Collectively, these data imply an essential role of H2S in regulating immune activities and associated diseases including cancer through the regulation of key immune regulators.

H2S donor blocks cell cycle

Targeting cell cycle-mediating processes have been identified as a viable therapeutic option for treating numerous disorders including neurodegenerative disorders [105] and cancer [106]. Cell cycle arrest is an important event responsible for evaluating cellular damages and initiating apoptosis [107]. Cell cycle contains 4 main phases, namely Gap 1 (G1), Synthesis (S), Gap 2 (G2), and Mitosis (M) phase, that are closely monitored by the G1/S and G2/M
colon cancer cells [122] by promoting DNA damage and G2/M arrests in pancreatic [120], ovarian [121], and breast cancer cells [14]. Moreover, NaHS treatment prevents cell cycle progression by triggering G0/G1 arrest in breast cancer [112] and non-small cell lung cancer (NSCLC) [113].

It has also been revealed that treatment with DATS can promote DNA damage and G2/M arrest through the activation of ataxia telangiectasia mutated kinase and upregulation of nuclear exportation of cell division cycle 25C protein in thyroid and bladder cancer [114, 115], and by delaying nuclear translocation of CDK1 in prostate cancer [116]. Moreover, DATS increases the expressions of intercellular cyclins (A2 and B1), apoptotic markers (Bcl-2-associated X protein (Bax), p53, cleaved caspase 8, 9, and cytochrome c) and histone 3 phosphorylation in gastric cancer [117, 118]. In osteosarcoma cells, DATS treatment mediates ROS-dependent G0/G1 arrest by suppressing the protein expressions of cyclin D1 and increasing those of p21 and p27 [119]. The protective effects of DATS is induced via the activation of MAPK and AMP-activated protein kinase (AMPK) as well as the inhibition of PI3K/Nrf-2/AKT pathways [117-119].

Besides, treatment with DADS also induces G2/M arrests in pancreatic [120], ovarian [121], and colon cancer cells [122] by promoting DNA-damage and activating mitochondria apoptotic pathways. In summary, H2S donors regulate cell cycle progression by interacting with cell cycle regulators and checkpoints, suggesting the potential of these compounds in cancer treatment.

H2S donor attenuates cell proliferation and viability

Cancer cells are characterized by abnormal/uncontrolled proliferation resulting into their accumulation. The link between cell cycle regulators and signaling pathways plays a crucial role in regulating cell proliferation and viability. H2S donors modulate cell proliferation and viability by interacting with the cell cycle regulators and related signaling pathways [118, 119, 123]. In colon and breast cancer, GYY4137 treatment attenuates pro-proliferation activities by promoting cell cycle arrest, apoptosis, and necrosis [14, 15]. Also, treatment with DATS decreases cell viability and proliferation in gastric cancer [118], osteosarcoma [119], and glioma [123] through the activation of MAPK and suppression of PI3K/AKT cascades, and wingless integrated (Wnt)/beta catenin (β-catenin) pathways respectively. Concomitantly, treatment with DADS downregulates cyclin D1 and c-myc in osteosarcoma [119], and CDK1 and Cyclin B1 in ovarian cancer [121]. As a tumor suppressor, NaHS also inhibits the growth of HepG2 cells by regulating PI3K/AKT/mTOR pathway [38] and that of breast cancer MCF-7 cells via p38 MAPK pathway [112]. Overall, H2S donors regulate cell proliferation and viability in a cell/dose/time-dependent manner by interacting with a wide range of signaling cascades. The above evidences indicate that these donors can serve as a potential candidate in cancer treatment through their ability to regulate key cellular pathways associated with proliferation and viability activities. The summary anti-cancer pathways regulated by H2S donors is depicted in Figure 1.

H2S donor inhibits cell migration and invasion

Migration and invasion are key players in cancer metastasis and progression. Under these processes, an individual or a collective cluster/strand/cords of cancer cell(s) detach from the primary tumor, penetrate the stroma of the surrounding tissue, enter the blood vessels, and eventually be transported into other organs [124]. The whole process is regulated by a comprehensive group of enzymes including extracellular matrix-degrading enzymes, matrix metalloproteinases (MMPs), adhesive enzymes (E-cadherin), desmosomes, and integrins [125]. It has been revealed that treatment of HCC cells with 600-1000 µM NaHS effectively inhibits migration and invasion in a concentration-dependent fashion through the regulation of epidermal growth factor receptor (EGFR)/ERK/MMP-2 and PTEN/AKT pathways [126]. Similarly, in thyroid cancer cells, 200 µM NaHS treatment inhibits migration activities by deactivating the PI3K/AKT/mTOR and MAPK pathways [127]. In lung cancer A549 cells, treatment with 100 µM NaHS significantly reduces nickel-induced EMT and migration by regulating TGF-β1 pathway [128]. Moreover, NaHS decreases the protein levels of MMP-2 in gastric cancer [39], and EMT-inducing snail (SNAIL 1) in breast cancer [112]. A previous study conducted using DAS, DADS, and DATS in colon cancer Caco-2 cells indicates a significant reduction in migration-associated proteins MMP-2, -7, and -9 [129], with DATS showing the highest inhibition rate followed by DADS and DAS. In colon cancer HT29 cells, DATS prevents the angiogenesis and migration by suppressing vascular endothelial growth factor (VEGF), MMPs and
inhibiting p38MAPK, focal adhesion kinase (FAK) and JNK signaling cascades [130]. Similarly, DATS reduces the migration and invasion of glioma cells by impeding the activation of Wnt/β-catenin pathways [123]. Besides, treatment with DADS prevents migration and invasion of breast cancer stem cells by suppressing the glycolytic enzyme pyruvate kinase M2-induced activation of the AMPK pathway as well as by increasing and decreasing the levels of E-cadherin and vimentin, respectively [131]. The treatment with DADS also inhibits Rac1/PAK1/LIMK1/cofilins signaling cascades in colon and gastric cancer [132, 133]. The above data suggest that H₂S donors regulate migration and invasion activities through their interactions with numerous pathways and enzymes (Figure 2).

H₂S donor promotes autophagy

Autophagy is a key process involved in maintenance of cell homeostasis by degrading damaged organelles and misfolded proteins, thereby recycling nutrients and other essential materials [134]. Autophagy is associated with both tumor suppression and progression depending on the tumor stage [135-140]. The mTOR pathway has a decisive role in regulating autophagy, therefore targeting this pathway directly or indirectly through its upstream regulators helps in modulating the process [140]. One of the main events used to confirm the occurrence of autophagy is the conjugation of microtubule-associated protein 1A/B light chain 3, LC3 I to LC3 II, which is incorporated into the complex degradation machinery [141]. A study by Yue et al. shows a significant increase in protein levels of LC3 II accompanied by the inhibition of PI3K/AKT/mTOR pathway following the treatment of MG-63 osteosarcoma cells with DADS [142]. Similarly, in myeloid leukemia cells, treatment with DADS decreases cell viability and increases apoptosis by inactivating the mTOR pathway [143]. Moreover, the administration of NaHS effectively triggers protective autophagy in HCC cells by regulating the mTOR pathway [38]. Collectively, these data identify the interaction of H₂S donors with the mTOR signaling pathway as a crucial event in promoting autophagy and apoptosis hence preventing cancer progression.

H₂S donor induces apoptosis

Apoptosis, a caspase-dependent programmed cell death, is amongst the highly investigated targets in cancer treatment. It helps to maintain normal cell metabolism by destroying specific cells that are not required without affecting their healthy neighbours [144]. So far three major signaling pathways namely intrinsic, extrinsic [145], and perforin/granzyme B pathway [146] are known to induce apoptosis, all of which play an essential role in cancer modulation. Mitochondria, cell surface death receptors/adaptor

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Figure 1. The diagrammatic illustration of the pathways regulated by H₂S donors in cancer suppression. H₂S donors regulate STAT-3, MAPK, AMPK, PI3K-mTOR, p53, ATM-CHK1/2-CDC25C, NF-κB, and Ras-Raf-Mek-Erk pathways together with the intercellular pH and cell cycle regulators resulting into the inhibition of cell cycle progression and promotion apoptosis. (STAT-3: signal transducer and activator of transcription-3; MAPK: mitogen-activated protein kinase; AMPK: AMP-activated protein kinase; PI3K: phosphoinositide 3-kinase; mTOR: mammalian target of rapamycin; p53: tumor protein 53; ATM: ataxia telangiectasia mutated kinase; CHK1/2: checkpoint kinases 1/2; CDC25C: cell division cycle 25 C protein; NF-κB: nuclear factor-kappa B; Raf: rapidly accelerated fibrosarcoma; ERK: extracellular signal-regulated kinase)
proteins and the immune system are the main regulators for each pathway respectively. The activation of cysteine protease enzymes known as caspases is the common objective for all apoptotic pathways which result in the initiation and execution of proteolytic degradation by cleaving specific substrates such as poly adenosine diphosphate-ribose polymerase (PARP) and DNA fragmentation factor [147]. Apoptotic pathways principally rely on pro-apoptotic caspase-2, -8, -9, and -10 for the initiation phase and caspase-3, -6, and -7 for the execution phase [148].

H2S donors regulate apoptosis in cancer cells by interacting with numerous apoptosis-inducing pathways [15, 149]. The treatment with GYY4137 elevates the expressions of apoptotic markers caspase-9 and cleaved PARP in breast cancer MCF-7 cells, colorectal cancer Caco-2 cells [15], and ovarian cancer A2780 cells [150], with little or no effects in normal cell lines IMR90 cells [14] and Ea. hy926 [150]. STAT-3 pathway plays a crucial role in inducing apoptosis, and blocking this pathway is associated with improved apoptotic activities in different cancer types including lung cancer [149], pancreatic cancer [151], and HCC [152]. Treatment with GYY4137 significantly increases apoptotic activities in HCC cells by preventing both interleukin-6 and JAK-2 induced phosphorylation of STAT-3 [55].

Furthermore, treatment with NaHS upregulates the expressions of apoptosis-related genes caspase-3 and Bax and suppresses that of anti-apoptotic marker B cell lymphoma 2 (Bcl-2) by regulating p38 MAPK and p53 pathways [153]. Likewise, treatment of human melanoma cells with ATB-346 promotes cell death by reducing the activities of cyclooxygenase-2 (COX-2) and inhibiting AKT and NF-κB signaling pathways [154]. It has also been shown that the administration of ADT-OH can enhance anti-cancer activities in melanoma by reducing makorin ring finger protein 1 levels and preventing the degradation of IkBα, resulting in the accumulation of apoptotic adaptor protein Fas-associated protein with death domain and inhibition of NF-κB, respectively [155]. In different cancer types, treatment with DATS has been shown to induce cell death by promoting mitochondria-mediated DNA damage [114] and by regulating AMPK [117], c-JUN N-terminal kinases (JNK) [119], PI3K/AKT [120], p38MAPK [156], and NF-κB [157] signaling pathways. Likewise, DADS treatment suppresses cancer progression by facilitating DNA damage [120] and inhibiting PI3K/AKT/mTOR [142, 143] and NF-κB pathways [32]. In addition, compared to NaHS and GYY4137 treatments, breast cancer cells show extremely high apoptotic index when administered with HA-ADT (a conjugate formed with hyaluronic acid (HA) and ADT-OH) [12].

![Diagram](http://www.ijbs.com)

**Figure 2.** The diagrammatic illustration of the mechanism by H2S donors in regulating autophagy and cell migration. H2S reduces the levels of p62 and elevates those of Atg5 and LC3-II to facilitate the formation of autophagosomes resulting in autophagy. Also, H2S suppresses the protein levels of p-PI3K, p-AKT and mTOR resulting in the downstream regulation of p-70S6K expressions and subsequently autophagy. By regulating PI3K, H2S also downregulates the expressions of Rac-1, PAK-1, and cofilin thereby reducing MMP-2, -7, -9, N-cadherin and vimentin levels, and increases TIMP 3 and E-cadherin levels resulting in the inhibition of cell migration. H2S further activates Wnt/β-catenin pathway to suppress migration activities, and inhibits NF-κB and MAPK pathways to reduce migration and invasion activities. (p62: nucleoporin 62; Atg5: autophagy-related protein 5; LC3 II: LC3-phosphatidylethanolamine conjugate; PI3K: phosphoinositide 3-kinase; AKT: protein Kinase B; mTOR: mammalian target of rapamycin; p-70S6K: ribosomal protein S6 kinase beta-1; Rac-1: Ras-related C3 botulinum toxin substrate 1; PAK-1: p21-activated kinase 1; MMPs: matrix metalloproteinases; TIMP 3: tissue inhibitor of metalloproteinase-3; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-kappa B).
The extracellular acidic microenvironment is the key feature that differentiates cancer cells from non-cancer cells [158]. The high rate of glycolysis in cancer cells results in the accumulation of lactic acid, leading to the reduction of intracellular pH (pHi) [159]. Anion exchangers (AEs) and sodium/proton exchangers (NHEs) are key regulators of intracellular acidity recruited to adjust the decreasing pHi via active transportation of proton (H+) to the extracellular environment, making it more acidic compared to the intracellular environment [160, 161]. A previous study indicates that low pHi enhances apoptosis through DNA fragmentation and activation of caspases [162]. It has been revealed that treatment with GYY4137 increases intracellular acidity by promoting glycolysis and inhibiting the activities of NHEs and AEs [150, 163]. However, compared to GYY4137, FW1010 (a structural analogue of GYY4137) promotes pHi-mediated cell death more efficiently [163]. Moreover, synergizing GYY4137 with metformin (glycolysis-inducing type 2 diabetes mellitus drug) or simvastatin (a cholesterol/lipid-lowering drug targeting monocarboxylate transporter-4 (MCT-4)) aggravates the hyperacidity-induced cell death compared to treatment with individual drugs [164]. This confirms that the interaction of donors with glycolysis in cancer suppression, and suggests a new direction of combination therapy comprising of H2S donors and glycolysis regulators (Figure 3). Overall, donor type and concentration play key roles in the regulation of apoptosis, however, slow-releasing donors and garlic-derived donors are more effective and efficient compared to the fast-releasing H2S donors. Regardless, their abilities to induce apoptosis by promoting intracellular acidification and activating both intrinsic and extrinsic apoptotic pathways suggest these donors can be used to target the majority of apoptotic pathways altered in cancer cells.

H2S donor enhances cancer drug sensitivity

Targeting cancer cells with more than one drug (combination therapy) that targets more than one pathway helps to reduce drug resistance and increase the efficiency of the treatment [165]. The combination therapy can be chemotherapy and radiotherapy, chemotherapy and surgery, radiotherapy and surgery, or all three. In addition to their abilities to induce anti-cancer effects in drug resistant cancer cells such as cisplatin-resistant NSCLC A549/DPP cells [113], H2S donors improve the sensitivity and reduce resistance to anti-cancer drugs [118, 166]. The downregulation of metallothionein 2A (MT2A), a stress protein is associated with poor prognosis in gastric cancer patients [167]. It has been reported that DATS treatment can elevate both the mRNA and protein levels of MT2A, thereby improving the sensitivity of the anti-cancer drug, docetaxel (DOC), as well as the survival of gastric cancer patients [166]. In human osteosarcoma cells, treatment with DATS reduces drug resistance by suppressing multidrug resistance protein 1 (P-gp1) [168]. Furthermore, NaHS improves radiosensitivity in breast cancer by increasing tumor oxygen levels [23]. NaHS also decreases hepatotoxicity induced by anti-cancer drug, methotrexate (MTX) [169]. Collectively, cancer cells treated with donor-containing combination therapy demonstrate enhanced sensitivity and reduced drug resistance. Despite the need for further investigation, the data above indicate that H2S donors can regulate sensitivity and resistance-associated genes to enhance the anti-cancer activities of other drugs and further support their potential in cancer treatment.

H2S donor reduces tumor growth in vivo

In vivo xenograft tumor mice model is the most commonly used preclinical tool to determine the drug delivery system and response [170]. Under the assessment, several parameters such as body weight, tumor mass, tumor volume, and protein expressions are analyzed and the results are compared with the control group. It has been shown that treatment of breast cancer tumor mice model with HA-ADT donor can effectively inhibit tumor growth and proliferation [12]. Moreover, the treatment of leukemia xenograft tumor model with 100-300 mg/kg GYY4137 shows a significant reduction in tumor volume with no change in body weight or gross behaviour [14]. GYY4137 donor (50 mg/kg/day) also reduces subcutaneous HepG2 tumor growth by regulating STAT-3 pathway [55]. Besides, treatment with DADS/DATS inhibits in vivo tumor growth by reducing tumor size, weight, and regulating several factors involved in cancer progression [123, 130, 131]. A study by Chandra-Kuntal, et al. also reports a significant reduction in tumor size and the downregulation of p-STAT-3 levels following the treatment of prostate cancer mice model with 2 mg DATS [171]. In colon and gastric cancer mice model, DADS treatment promotes anti-cancer responses by reducing the level of vimentin and increasing that of E-cadherin [132, 133]. Similarly, the treatment of HCC xenograft nude mice model with 0.8-1 mM NaHS can effectively inhibit tumor growth and progression [126]. In summary, the evidence suggests that H2S donors have a dominant anti-cancer effect by reducing tumor volume, weight, growth, and regulating p-STAT-3 levels in a concentration-dependent manner.
Cancer promoting activities

Despite the reported anti-tumor effect of H₂S donors, on numerous occasions cancer promoting activities have been reported in different cancer cells when treated with H₂S donors especially NaHS. Therefore, we further discuss the tumor promoting effects of these donors and the pathways involved.

H₂S donor promotes cell cycle progression

The pro-carcinogenic effects of H₂S are mainly induced by the facilitation of cell cycle progression and the activation of anti-apoptotic pathways. In oral squamous cell carcinoma, treatment with NaHS has been shown to facilitate cell cycle progression by downregulating the protein expressions of the DNA repairing RPA70 and tumor suppressor RB1, while upregulating those of the proliferating cell nuclear antigen (PCNA) and CDK4 [172]. In addition, the treatment decreases the expression of cell cycle-dependent kinase inhibitor 1 and activates the AKT/ERK 1/2 pathways [173]. It has also been reported that treatment of multiple myeloma cells with NaHS reduces the proportion of cells in G0/G1 arrest and increases their proportion in S and G2/M phases [174]. In summary, treatment with NaHS can stimulate cell cycle progression by amplifying the activation of AKT/ERK 1/2 signaling cascades.

H₂S donor increases cell proliferation and viability

In addition to the promotion of cell cycle progression, studies also show that treatment with NaHS promotes cell proliferation and viability in esophageal carcinoma via the activation of heat shock protein 90 (HSP90) and JAK-2/STAT-3 pathways [18, 175]. In HCC cells, NaHS treatment activates EGFR/ERK/MMP-2, PTEN/AKT, STAT-3/COX-2, and NF-κB and inhibits JNK signaling pathways (Figure 4) [126, 176, 177]. Besides, the treatment of oral cancer cells (WSU-HN6, Tca83, and Cal27) with 1000 µM NaHS for 5 hours can enhance cell proliferation by activating COX-2/ERK/AKT pathways [178]. However, conflicting results have been reported in C6 glioma cells where one study shows oncogenic activities induced via the activation of p38MAPK/ERK/COX-2 signaling cascades following 400-1600 µM NaHS treatment [179], while another study conducted on the same cell line (C6) using 250, 500, and 1000 µM NaHS shows anti-oncogenic effects accompanied by the activation of p38MAPK and p53 pathways [154]. With the dose-dependent and fast-releasing nature of NaHS, the above confusion may be caused by the possible loss of H₂S during the preparation of the samples and volatilization of the...
gas in culture plates, since the half-life of the compound is about 5 minutes of which over 80% of H$_2$S is formed within the first 10 seconds after dissolving the crystals [180]. Although, it’s not clear how NaHS could result in stimulation of different MAPK isoforms, leading to the activation or deactivation of apoptotic pathway p53 [181-183]. In addition, it is not well understood as to why the effects of NaHS varies in different cancer types. Together, these data suggest that NaHS can impose pro-proliferating effects on cancer cells by promoting cell cycle progression and regulating the associated pathways.

H$_2$S donor enhances cell migration and invasion

*In vitro* studies have reported that the incubation of endothelial cells with NaHS can significantly promote the migration and proliferation activities by stimulating HIF-α/VEGF, cGMP/protein kinase G as well as ATP-mediated potassium channels (K$_{ATP}$)/p38 MAPK cascades [184-186]. In breast tumor-derived endothelial cells, treatment with NaHS results in VEGF-mediated activation of Ca$^{2+}$ channels and the promotion of cell migration [187]. Besides, treatment of thyroid cancer cells with 25-50 µM NaHS effectively enhances migration and invasion by activating PI3K/AKT/mTOR and MAPK pathways [127]. The H$_2$S donor-mediated cell migration has also been confirmed by elevated levels of MMP-2 and -9 protein levels in bladder cancer and esophageal carcinoma following administration of NaHS [18, 175, 188]. The cell migration-induced activation of AKT pathways have also been reported in multiple myeloma cells following the administration of NaHS [174]. Meanwhile, in EC 109 and PLC/PRF/5 cells, the treatment signals were via HSP90 and NF-κB pathways, respectively [18, 176]. These data suggest that treatment with H$_2$S donors can intensify cancer metastasis through the regulation of PI3K, NF-κB, and MAPK pathways.

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**Figure 4.** The diagrammatic presentation of cancer-promoting pathways regulated with NaHS treatment. H$_2$S donors stimulate HSP90, HIF-1α, AKT, LDHA, JAK-2, MAPK, K$_{ATP}$, cGMP, and NF-κB, but inhibit JNK pathway to exhibit tumor promoting effects. (HSP90: heat shock protein 90; HIF-1α: hypoxia-inducible factor 1 alpha; AKT: protein kinase B; LDHA: lactate dehydrogenase A; JAK-2: janus kinase 2; MAPK: mitogen-activated protein kinase; K$_{ATP}$: ATP-sensitive potassium channels; cGMP: cyclic guanosine monophosphate; NF-κB: nuclear factor-kappa B; JNK: c-Jun N-terminal kinase).
**H₂S donor suppresses apoptosis**

The ability to suppress apoptotic activities is among the key features of cancer cells. Generally, compounds that increase cell apoptosis have great potential in therapeutic application. With respect to H₂S donors, despite the observed potential, conflicting reports show a reduction in apoptosis following the treatment with NaHS. For instance, a previous study indicates that treatment with NaHS reduces the expression of apoptotic marker caspase-3 and Bax but increases that of Bcl-2 via the regulation of HSP90 [18]. Similarly, in multiple myeloma, NaHS treatment increases the expression of Bcl-2 and decreases that of caspase-3 via the stimulation of AKT signaling [174]. In addition, it has been reported that NaHS treatment attenuates the expressions of caspase-9 and -12, and elevates those of VEGF and VEGFR in EC 109 cells [175]. In brief, NaHS can interact with key cell regulators, resulting in enhanced pro-cancer effects.

**H₂S donor stimulates angiogenesis**

The development and growth of new blood vessels from pre-existing ones is known as angiogenesis [189]. It is a crucial process in tumor metastasis as it assures the supply of nutrients and other materials that are required for cell growth. In both normal and cancerous cells, angiogenesis is stimulated by VEGF proteins. A previous study suggests that H₂S treatment can facilitate angiogenic responses such as microvessel sprouting of aortic ring via the regulation of H₂S/NO signaling [186]. It has also been reported that treatment with NaHS induces pro-angiogenic properties by overexpressing HIF-1α and downregulating micro RNA-640 via the vascular endothelial growth factor receptor 2-mTOR pathway [190]. Similarly, a recent study shows that treatment of NSCLC with NaHS stimulates HIF-1α, resulting in VEGF activation and subsequently angiogenesis [191]. Also, the treatment of EC 109 cells with 400 µm of NaHS promotes vascular formation by increasing the expression of VEGF and activating HSP 90 pathway [18]. In brief, these data indicate that treatment with NaHS can promote cancer metastasis through the stimulation of angiogenesis which occurs via the stimulation of VEGF.

**H₂S donor modulates cellular bioenergetics**

Cancer cells undergo several adjustments in energy supply mode so as to sustain the increased requirements. Cancer cells have been reported to undergo aerobic glycolysis in addition to the common mitochondria pathway in order to fulfill the high energy requirements [192]. At lower H₂S concentrations, most cells are reported to consume sulfide as a substrate in mitochondria sulfide-quinone reductase (SQR) of the mitochondria pathway, the event results in a reverse electron transfer in HT-29 colon cells [193]. A recent study indicates that H₂S signals by reprogramming energy metabolism which is in addition to the common pathway involving cysteine persulfidation [194]. The study also demonstrates the dominant role of SQR in inhibiting the anti-proliferative properties of H₂S at high levels. However, the involved mechanism is yet to be elucidated. Besides, it has been shown that the HIF-1α can positively mediate the functioning of glucose transporter-1 (GLUT-1), an important element in glucose transportation [195]. On the downstream, the activation of GLUT-1 promotes the Warburg effect and reduces apoptosis [196]. With respect to H₂S, the activation of HIF-1α mediated by NaHS treatment has been reported in NSCLC [191]. Therefore, it is possible that NaHS treatment could result in the elevation of cellular bioenergetics by enhancing HIF-1α and GLUT-1-mediated aerobic glycolysis. It has also been shown that the treatment of HCT116 colon cancer cells with low concentrations of GYY4137 increases mitochondrial function and glycolysis by persulfidating the Cys-163 of the lactate dehydrogenase A (LDHA) resulting in its stimulation [197]. The activation of LDHA could result in increased glycolysis and Warburg effect [198]. In summary, the above evidences indicate that H₂S donors can induce pro-proliferative effects by modulating cellular bioenergetics via the activations of HIF-1α and LDHA.

**Conclusion**

H₂S donors have consistently been associated with the treatment of numerous cancer types and at different stages. These donors have shown great results in suppressing different cancer types by regulating the associated cellular activities and signaling pathways. However, the alarming inconsistency shown specifically in the case of NaHS (Table 1) needs to be further addressed. Currently, one of the explanations pinpointed is the short-time and high concentration-releasing nature of NaHS resulting in temporary elevation of cellular H₂S levels followed by its subsequent decline which opposes the normal slow-releasing cellular mode and eliminate NaHS as a viable option in clinical settings. Furthermore, limited information on byproducts and clearance mechanism of these donors which raise many questions concerning their applicability. Therefore, it is important to determine the viable range of H₂S donors’ concentration and examine physiological factors such as toxicity and clearance mechanism. In addition, the effects imposed by the
physical and chemical properties of these donors, their possible interactions need further investigation for better understanding of possible side effects. The combination of these donors with other cancer drugs such as docetaxel and cisplatin have presented improved drug sensitivity and reduced resistance [167, 168]. Furthermore, the synergistic effects of H2S donors with metformin/simvastatin have been shown to promote anti-cancer activities by elevating intracellular acidity and impairing pH regulators. 

The available data, it is worth conducting more animal studies and clinical trials to test the hypothesis. The effects of sulfuration-dependent post-translation modifications of proteins also need to be further investigated, since elevating the levels of H2S modifies of proteins also need to be further investigated, since elevating the levels of H2S increases the chance of sulfuration which might affect the primary functions of numerous proteins. In conclusion, H2S donors have shown great potential in cancer treatment individually and in combination with other drugs, with more researches still ongoing, it is possible that these donors could be a great addition to cancer therapy, however more work is needed to be done.

Table 1. The summary of the effects of NaHS in different cancer cell types.

| Cancer types | Cell lines | NaHS doses | Effects on Cancer | References |
|--------------|------------|------------|-------------------|------------|
| Breast cancer | MCF-7      | 5-20 µM, 500 µM | Inhibition        | [14, 112] |
| HCC          | HepG2      | 5-20 µM, 1000 µM | Inhibition        | [14, 38]  |
|              | HLE        | 1000 µM    | Inhibition        | [38]       |
|              | PLC/PRF/5  | 100-500 µM | Promotion         | [13]       |
|              | SMMC-7721  | 10-100 µM  | Promotion         | [126]      |
|              | HuH-7      | 400-1000 µM | Inhibition        |            |
| Thyroid cancer | TPC-1      | 10-50 µM   | Promotion         | [127]      |
|              | TT         | 200 µM     | Inhibition        | [113, 128]|
|              | ARO        | 800 µM     | Inhibition        |            |
| NSCLC        | A549/5A49/DDP | 200-1000 µM | Promotion         | [18, 175] |
| Esophageal cancer | EC 109    | 200-1000 µM | Promotion         | [153, 179]|
|              | C6         | 100-1600 µM | Promotion/Inhibition | [39] |
| Gastric cancer | SGC 7901  | 200-800 µM  | Promotion         | [172, 178]|
| Oral SCC     | GMN        | 200-1000 µM | Promotion         | [174]      |
|              | Cal-27     | 200-1000 µM | Promotion         | [188]      |
| Multiple Myeloma | NCI-H929  | 250-1000 µM | Promotion         |            |
| Bladder Cancer | EJ         | 400 µM     | Promotion         |            |
| Colon Cancer | HCT 116    | 50 - 200 µM | Promotion         | [173, 199]|
|              | SW480      | 1000 µM    | Inhibition        |            |
|              | SW480      | 1000 µM    | Inhibition        |            |

Abbreviations

H2S: hydrogen sulfide; CBS: cystathionine beta-synthase; 3-MPST: 3-mercaptopyruvate sulfurtransferase; CSE: cystathionine gamma-lyase; NaHS: sodium hydrosulfide; DAS: diallyl sulfide; DADS: diallyl disulfide; DATS: diallyl trisulfide; GYY4137: morpholin-4-ium-4-methoxyphenyl(morpholino) phosphinodithioate; ADT-OH: 5-(4-hydroxyphenyl)-3H-1,2-dithiole-3-thione; ATB-346: 2-(6-methoxynaphalen-2-yl)-propionic acid 4-thiocabamoyl phenyl ester; ABCA1: ATP-binding cassette transporter A1; GLT-1: glutamine transporter-1; STAT-3: signal transducer and activator of transcription-3; NF-kB: nuclear factor-kappa B; Nrf-2: nuclear factor erythroid-2 related factor-2; HO-1: heme oxygenase-1; Tregs: regulatory T cells; TGF-β: transforming growth factor-beta; HCC: hepatocellular carcinoma; ROS: reactive oxygen species; PARP: poly adenosine diphosphate-ribose polymerase; eIF2α: eukaryotic translation initiation factor 2 subunit alpha; Keap 1: Kelch-like ECH associated protein 1; CDK: cyclin-dependent kinase; MMPs: matrix metalloproteinases; MT2A: metallothionein 2A; COX-2: cyclooxygenase-2; EGFR: epidermal growth factor receptor; ERK: extracellular signal-regulated kinase; Bcl-2: B cell lymphoma 2; Bax: Bcl-2-associated X protein; PI3K: phosphoinositide 3-kinase; Wnt: wingless integrated; β-catenin: beta catenin; AMPK: AMP-activated protein kinase; MAPK: mitogen activated protein kinase; cGMP: cyclic guanosine monophosphate; VEGF: vascular endothelial growth factor; SQR: sulfide-quinone reductase; LDHA: lactate dehydrogenase A.

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Author Contributions

DDW and XYJ conceived the concept of the review and supervised the project. EEN, AA, MS, SK, SUZ, NHK, TL, QYJ and XZ reviewed literatures and extracted data. EEN drafted the manuscript. DDW,
SFD and XYJ revised the manuscript and provided intellectual input on the review. All authors read and approved the final version of the manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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