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REVIEW

Protective Role of H_2S in High Glucose-Induced Cardiomyocyte and Endothelial Cell Dysfunction: A Mechanistic Review

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Abstract: Hydrogen sulfide (H_2S), recognized as a significant gasotransmitter, has been shown to effectively reduce damage to cardiomyocytes and endothelial cells caused by diabetes. Its protective effects primarily stem from several mechanisms, including S-sulfhydration of proteins, reduction of cell death, alleviation of mitochondrial damage, improvement of ion channel dysfunction, interaction with nitric oxide, and modulation of angiogenesis. H_2S is synthesized by cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3-MST), whose expression is significantly reduced under diabetic conditions, including experimental high-glucose treatment in cells and diabetes mellitus animal models. This review summarizes the protective role of H_2S and its donors in these pathological processes, highlights existing research gaps—including challenges in the targeted delivery of H_2S donors, limited clinical translation, and incomplete mechanistic understanding—and discusses future directions for developing targeted H_2S-based therapeutic strategies.

Keywords: H_2S, diabetic cardiomyopathy, diabetes-induced endothelial cell damage

Introduction

Hydrogen sulfide (H_2S) is a colorless gas characterized by its toxicity, corrosiveness, and flammability, and is prevalent in both environmental and industrial pollutants.[1,2] Recent research has demonstrated that H_2S is integral to cellular signal transduction and the regulation of various biological activities.[3–5] As one of the three recognized gaseous signaling molecules, H_2S significantly influences cardiovascular function, alongside carbon monoxide (CO) and nitric oxide (NO). Hydrogen sulfide (H_2S) is a colorless gas with toxicity and flammability, commonly found in environmental and industrial pollutants. Recent studies have shown that H_2S plays a vital role in cellular signaling and regulation of various biological processes, particularly in cardiovascular function, alongside carbon monoxide (CO) and nitric oxide (NO). H_2S is a weak acid that, when dissolved in water, mainly exists as hydrogen sulfide ions (HS^-) at physiological pH. These highly reactive ions interact with various cellular targets, influencing a range of physiological and pathophysiological processes.[6–9] Researchers are actively investigating small molecule donors for the exogenous delivery and bioavailability of H_2S, driven by its potential as a cardioprotective agent.[10–12] These attributes highlight the critical role of H_2S and its promising applications in physiological and pathophysiological processes, especially within the cardiovascular system.

Diabetes, an endocrine disorder characterized by elevated blood glucose levels, is one of the most common and rapidly escalating conditions globally.[13,14] Studies have demonstrated that diabetes serves as an independent risk factor for patients with heart failure, contributing to cardiac hypertrophy as well as both systolic and diastolic dysfunction.[15,16] Diabetes not only disrupts blood glucose regulation but also significantly impairs vascular endothelial function and cardiac health, contributing to complications such as diabetic nephropathy, diabetic foot, diabetic retinopathy, and diabetic cardiomyopathy.[17–19]

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Despite emerging evidence supporting the cardioprotective and vasoprotective effects of H_2S, its precise molecular mechanisms in mitigating diabetes-induced cardiovascular damage remain insufficiently understood. Current studies focus mainly on its general regulatory roles, but further investigation is needed to clarify how H_2S specifically interacts with key pathological pathways in diabetic cardiomyopathy and vascular complications. This review aims to summarize existing knowledge, identify research gaps, and explore the therapeutic mechanisms of H_2S in diabetes-induced myocardial and endothelial cell damage, providing insights into potential clinical applications and novel intervention strategies.

The Production of Endogenous H_2S

In mammalian cells, H_2S is endogenously produced via both enzymatic and non-enzymatic pathways. Research has identified enzymatic catalysis as the predominant production mechanism, with cystathionine β-synthase (CBS),[20] cystathionine γ-lyase (CSE),[21] and 3-mercaptopyruvate sulfurtransferase (3-MST)[22] being the principal enzymes involved in this process.[23,24] CBS and CSE utilize pyridoxal phosphate (vitamin B6) as a cofactor, with CBS predominantly expressed in the central nervous system and liver,[25] while CSE regulates H_2S levels in the cardiovascular and respiratory systems.[26,27] These enzymes catalyze the conversion of homocysteine to cysteine via the reverse transsulfuration pathway, resulting in the production of H_2S. Meanwhile, 3-MST, requiring zinc, works in mitochondria alongside cysteine aminotransferase (CAT) to generate H_2S.[28] In addition to enzymatic pathways, non-enzymatic mechanisms involving L-cysteine under the action of CAT produce 3-mercaptoacetate (3-MP). This compound, when co-catalyzed by CAT in mitochondria, leads to the generation of H_2S and pyruvic acid. In studies on high glucose conditions, CSE is the most commonly assessed marker of H_2S production due to its predominant expression in the cardiovascular system and its significant downregulation under hyperglycemia.[29,30] In contrast, CBS and 3-MST are less frequently measured, as their expression in the cardiovascular system is lower and their changes under high glucose conditions are less consistent[29] (Figure 1).

The Metabolism of Endogenous H_2S

H_2S is eliminated from the body through various routes: as gaseous molecules via the respiratory tract,[31] as thiosulfates or free sulfates in urine,[32] and as free sulfides in feces through the digestive tract.[33] Primarily, H_2S undergoes metabolism via three main pathways, with the mitochondrial sulfur oxidation pathway being particularly significant for H_2S clearance. In this pathway, sulfur compound quinone oxidoreductase plays a crucial role by catalyzing the oxidation

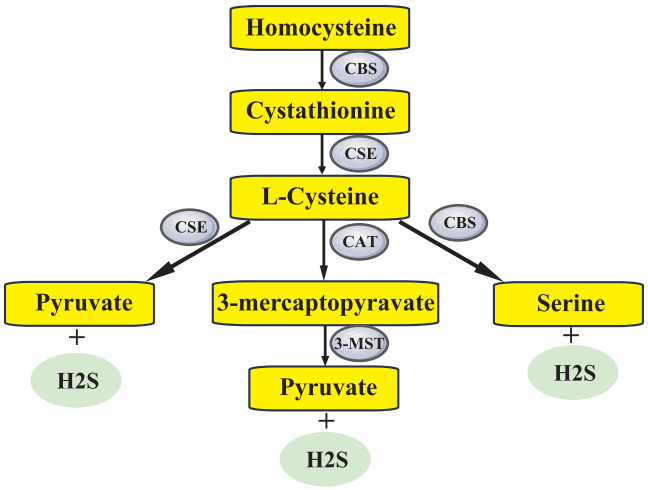

Figure 1 Diagram of H_2S Production Pathways. H_2S is produced through three main enzymatic pathways: the CBS (cystathionine β-synthase) pathway, the CSE (cystathionine γ-lyase) pathway, and the 3-MST (3-mercaptopyruvate sulfurtransferase) pathway. In the CBS pathway, homocysteine is converted to cystathionine and then to L-cysteine, which is further metabolized to generate H_2S. The CSE pathway directly converts L-cysteine into pyruvate while releasing H_2S. In the 3-MST pathway, L-cysteine is first converted into 3-mercaptopyruvate by cysteine aminotransferase (CAT), which is then metabolized by 3-MST to produce H_2S. These pathways collectively regulate endogenous H_2S levels.

of H_2S to thiosulfate. Additionally, other mechanisms, including methemoglobin, metal-containing macromolecules, and sulfur-containing macromolecules, contribute to the clearance of H_2S.[34,35] Methylhemoglobin and myoglobin enhance the binding of hydrogen sulfide to iron, consequently accelerating its oxidation rate by altering iron reactivity.[36] Furthermore, H_2S could undergo metabolism via methylation processes involving glutathione, glycine disulfide, or other molecules containing metals or disulfide bonds.[37]

H_2S S-Sulfidation

S-sulfide hydration denotes the process by which H_2S molecules interact with or modify cysteine residues within proteins. This post-translational modification can significantly impact protein function and stability, thereby playing a crucial role in the regulation of vital biological activities, including intracellular signaling, metabolic pathways, and the pathogenesis of various diseases. Emerging research suggests that H_2S is implicated in protein sulfhydration through these interactions and has the potential to ameliorate myocardial cell damage induced by high glucose (HG) conditions. Sun's study has demonstrated that H_2S can mitigate the inhibition of the interaction between Myosin Heavy Chain 6 (MYH6) and Myosin Light Chain 2 (MyL2) by Muscle-Specific RING Finger Protein 1 (MuRF1) through S-sulfhydration at the Cys44 site of MuRF1. This process consequently reduces the ubiquitination levels of MYH6 and MyL2, thereby alleviating HG-induced myocardial degeneration and damage.[38] Additionally, further investigations have examined the relationship between H_2S and the sulfhydration of ubiquitin-specific protease 8 (USP8). These studies revealed that under conditions of elevated glucose and fat levels, USP8 sulfhydration significantly decreases; however, its expression is notably upregulated following the administration of exogenous H_2S. S-sulfide hydration of USP8 enhances parkin deubiquitination, boosting mitochondrial autophagy in myocardial cells, reducing mitochondrial damage, and improving diabetic cardiomyopathy.[29] Yu's research shows that exogenous H_2S S-sulfhydrates Synovial Apoptosis Inhibitor 1 (Hrd1) at the Cys115 site, lowering VAMP3 ubiquitination and CD36 translocation, which decreases long-chain fatty acid uptake and alleviates diabetic cardiomyopathy.[39] Similarly, Sun et al reported that H_2S enhances the S-sulfhydration levels at the Cys115 site on Hrd1. However, their findings also indicated that Hrd1 inhibits the interaction between Hrd1 and Diacylglycerol O-Acyltransferase 1 (DGAT1) as well as Diacylglycerol O-Acyltransferase 2 (DGAT2) by modulating the ubiquitination levels of DGAT1 and DGAT2. This regulatory mechanism reduces the formation and uptake of lipid droplets in myocardial cells, thereby mitigating diabetic cardiomyopathy.[40] Additionally, Peng's research demonstrates that exogenous H_2S promotes S-sulfhydration at the Cys683 site of SUMO-specific protease 1 (SENP1), leading to enhanced Sumoylation of the ATPase Sarcoplasmic/Endoplasmic Reticulum Ca^{2+} Transporter 2 (SERCA2A). SERCA2A is crucial for calcium reuptake into the endoplasmic reticulum during excitation-contraction coupling in cardiac cells, which improves cardiac contraction-relaxation function and reduces apoptosis in diabetic cardiomyopathy.[30] Zhang et al discovered that exogenous H_2S increases S-sulfhydration of SYVN1 at the Cys115 site, upregulating the ubiquitination of Sterol Regulatory Element-Binding Protein 1 (SREBP1) and downregulating the expression of DGAT1 and 1-Acylglycerol-3-Phosphate O-Acyltransferase 3 (AGPAT3), both key factors in lipid droplet formation, thereby contributing to reduced lipid accumulation.[41] In Wang's study, H_2S-mediated S-sulfhydration of SYVN1 was found to be associated not only with lipid droplet accumulation but also with the regulation of ferroptosis and mitochondrial apoptosis.[42] Specifically, H_2S enhances S-sulfhydration of SYVN1 at the Cys115 site, increasing the ubiquitination of Kelch-like ECH-associated protein 1 (Keap1), which promotes the nuclear translocation of NFE2-like BZIP transcription factor 2 (Nrf2), thereby modulating ferroptosis and apoptosis in diabetic cardiomyopathy.[43] Thus, in diabetic cardiomyopathy, H_2S-mediated S-sulfhydration regulates various target functions and signaling pathways by affecting specific sites on proteins such as MuRF1, USP8, Hrd1, SERCA2A, and SYVN1. However, there is limited research investigating the protective mechanisms of H_2S against HG-induced endothelial cell damage through sulfide hydration. The study by Xie et al demonstrated that H_2S enhances Keap1 sulfide hydration, which promotes the mercaptanization of Keap1 at cysteine residue 151. This modification leads to the dissociation of Nrf2 from Keap1, facilitating the nuclear translocation of Nrf2 and reducing oxidative stress, thereby mitigating HG-induced atherosclerosis.[44] We have summarized the relevant mechanisms and illustrated them in a schematic diagram to provide a clear visualization of how H_2S-mediated S-sulfhydration functions in diabetic cardiomyopathy and HG-induced endothelial cell damage, as shown in Figure 2.

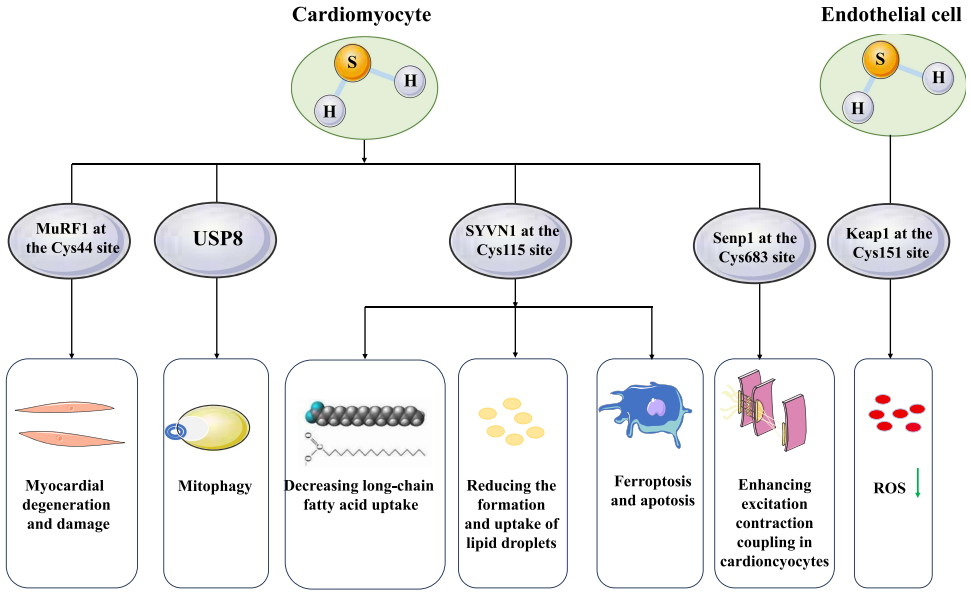

Figure 2 H_2S improves the damage to cardiomyocytes and endothelial cells induced by HG through S-sulfidation.
Abbreviations: MuRF1, Muscle-Specific RING Finger Protein 1; USP8, Ubiquitin-Specific Protease 8; Hrd1, Synovial Apoptosis Inhibitor 1; SENP1, SUMO-specific protease 1; Keap1, Kelch-like ECH-associated protein 1.

H_2S Attenuates HG Induced Mitochondrial Damage in Cells

Mitochondria, the most prevalent organelles in cardiomyocytes and endothelial cells, play a crucial role in energy provision for daily physiological activities.[45,46] However, elevated glucose levels can impair mitochondrial function, metabolism, and quality control mechanisms.[45–47] HG exposure has been shown to alter mitochondrial morphology and upregulate caspase-3, caspase-9, mitochondrial NADPH oxidase 4 (NOX4), and cytochrome c expression, contributing to mitochondrial dysfunction.[48] Yang et al demonstrated that H_2S mitigates HG-induced mitochondrial damage by down-regulating Mitofusin 2 (Mfn2), a key regulator of mitochondrial dynamics.[49] Additionally, H_2S enhances mitochondrial respiratory chain activity and ATP production by restoring NAD levels, upregulating SIRT3, and reducing acetylation of key mitochondrial enzymes such as NADH ubiquinone oxidoreductase, ubiquinol-cytochrome C reductase, and ATP synthase. These mechanisms collectively improve mitochondrial function and energy metabolism.[50] Further studies suggest that H_2S may influence mitochondrial processes, including autophagy, fusion, and fission, which help restore mitochondrial function in cardiomyocytes. Exogenous H_2S has been shown to activate the parkin signaling pathway, increasing the expression of the mitochondrial fusion protein Mfn2 and the fission proteins Fission, Mitochondrial 1 (Fis1) and Dynamin 1 Like (DRP1), thereby promoting mitochondrial autophagy.[29]

Other studies have similarly demonstrated that H_2S ameliorates endothelial cell function by mitigating mitochondrial damage. It inhibits mitochondrial fragmentation and suppresses phosphorylated DRP1 and Fis1 expression, thereby maintaining mitochondrial integrity. Immunoprecipitation and immunostaining analyses further reveal that H_2S facilitates the recruitment of PTEN-induced putative kinase 1 to Parkin, leading to ubiquitination and degradation of Mfn2, ultimately enhancing mitochondrial autophagy.[51] Furthermore, targeting mitochondrial dysfunction with H_2S donors, such as AP39 and AP123, effectively counteracts oxidative stress. These compounds mitigate mitochondrial membrane hyperpolarization, suppress mitochondrial ROS production, and enhance electron transfer at respiratory complex III, thereby improving endothelial cell metabolism.[52] Notably, under hyperglycemic conditions, the generation of mitochondrial reactive oxygen species (ROS) and the enhanced catabolism of H_2S establish a positive feed-forward loop.[53] We have summarized the mechanisms by which H_2S alleviates high glucose-induced mitochondrial damage in cardiomyocytes and endothelial cells in a schematic diagram, as shown in Figure 3.

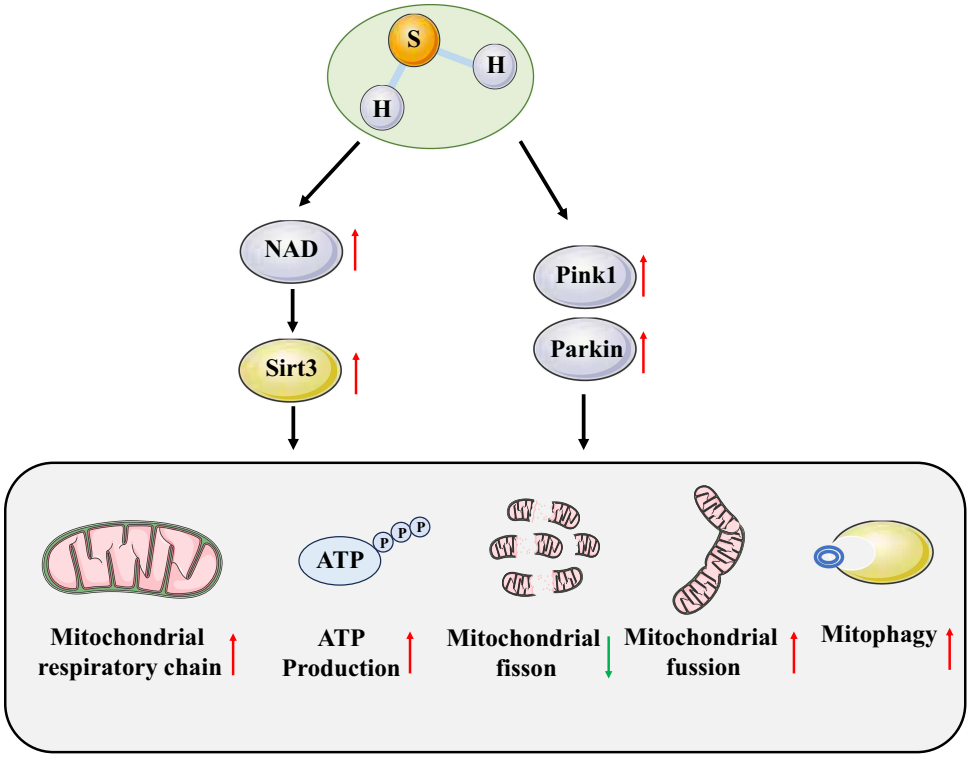

Figure 3 H_2S attenuates HG induced mitochondrial damage in both cardiomyocytes and endothelial cells.
Abbreviations: NAD, Nicotinamide Adenine Dinucleotide; Sirt3, Sirtuin 3; PINK1, PTEN Induced Kinase 1; Parkin, Parkin RBR E3 Ubiquitin Protein Ligase.

H_2S Improves HG Induced Ion Channel Disorders

Beyond its mitochondrial protective role, H_2S also regulates cellular homeostasis by modulating ion channels, which are key to cellular excitability and ion transport. Under hyperglycemia, ion channel dysfunction contributes to oxidative stress and apoptosis. By restoring ion channel function, H_2S helps maintain cardiomyocyte and endothelial integrity, offering broader protection in diabetic complications. Although there is a substantial body of literature addressing the impact of H_2S in various myocardial injury models, Testai et al demonstrated that the H_2S donor Erucin protects the heart from ischemia-reperfusion injury by targeting mitoKv7.4 channels. Their findings revealed that Erucin exerts its cardioprotective effects through the persulfidation of mitoKv7.4, identifying this channel as a novel mitochondrial K^+ channel involved in cardioprotection.[54] Wu et al discovered that CSE-derived H_2S regulates cardiac function by modulating Drp1 activity through S-sulfhydration at cysteine 607, thereby affecting its interaction with voltage-dependent anion channel 1 (VDAC1). This mechanism plays a crucial role in protecting against heart failure.[55] H_2S improves myocardial infarction outcomes by inhibiting I_to channels through direct modification of the Kv4.2 subunit at the Cys320/Cys529 disulfide bond. This regulation reduces the risk of fatal ventricular arrhythmias., research focusing on diabetic cardiomyopathy models remains limited. Liang et al demonstrated that HG conditions significantly reduce the expression levels of ATP-sensitive potassium (K_ATP) channels in cardiomyocytes. However, pre-treatment of cells with NaHS for 30 minutes effectively reverses this reduction, leading to an increase in K_ATP channel expression and a concomitant decrease in cell apoptosis, oxidative stress, and mitochondrial damage. Interventions using diazoxide (a mitochondrial KATP channel opener) or pinacidil (a non-selective KATP channel opener) weaken the protective effect of NAHS on myocardial cells.[56] Researchers also explored the role of H_2S in mitigating ion channel dysfunction in diabetic kidney endothelial cell injury. John et al suggest that under HG conditions, the activation of L-type Ca^{2+} channels lead to intracellular Ca^{2+} influx, which in turn activates cyclophilin D. This activation induces the opening of the mitochondrial permeability transition pore regulator, increasing oxidative stress and contributing to glomerular endothelial cell damage in diabetes. H_2S, however, protects against diabetic kidney injury by blocking N-methyl-D-aspartic acid receptor (NMDA-R1)-mediated Ca^{2+} influx.[57] Thus, by modulating ion channel activity, H_2S exerts protective effects in both

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diabetic cardiomyopathy and diabetic nephropathy endothelial cells, offering a promising therapeutic pathway for improving heart and kidney function.

H_2S Improves HG Induced Cell Death

Apoptosis is a programmed cell death process initiated intrinsically by the cell, proceeding in a spontaneous and orderly manner in response to specific signals or conditions.[58–60] This mechanism facilitates the organized and efficient removal of damaged cells. H_2S has been shown to mitigate myocardial cell apoptosis through various pathways and mechanisms, including the endoplasmic reticulum stress[61,62] or mitochondrial damage[63,64] axis under HG conditions. Excessive endoplasmic reticulum stress causes the buildup of unfolded proteins, speeding up cell apoptosis.[65] Mitochondrial damage, influenced by changes in cytosolic calcium levels, redox status, and ROS, also triggers apoptosis by activating mitochondrial permeability transition pores.[66] Additionally, H_2S has been shown to modulate several critical signaling pathways, including Nuclear Factor kappa-B (NF-κB), Keap1/NRF2, and Wnt/β-catenin, which are integral to antioxidative stress responses, anti-apoptotic mechanisms, and anti-inflammatory processes (Table 1). Furthermore, existing

Table 1 H_2S Improves HG Induced Cardiomyocyte Death

Donor	Model	Pathway	Implication
NaHS	STZ-induced DCM mouse HG-induced NRCM	Nrf2/ARE JNK/AMPK PI3K/Akt	Attenuate inflammation Oxidative stress and apoptosis[69]
NaHS	STZ-induced DCM mouse PA-induced AC16 cell	NA	Attenuate ER stress and apoptosis[70]
SPRC	STZ-induced DCM mouse HG-induced H9C2 cell	Keap1/Nrf2	Attenuate apoptosis[71]
NaHS	STZ-induced DCM mouse HG-induced NRCM	MAPK /ERK1	Protect mitochondria And attenuate apoptosis[72]
NaHS	HG-induced H9C2 cell	AMPK/NF-κB	Attenuate inflammation[73]
Diallyl trisulfide	STZ-induced DCM mouse HG-induced H9C2 cell	IGF1R/Akt	Attenuate apoptosis[74]
NaHS	STZ-induced DCM mouse HG-induced H9C2 cell	ROS/Mfn2	Attenuate ER stress And mitochondrial apoptosis[49]
NaHS	HG-induced H9C2 cell	TLR4/NF-κB	Attenuate inflammation and apoptosis[75]
NaHS	Db/db mice HG+Ole+PA-induced NRCM	USP8/parkin	Upregulated mitophagy[29]
NaHS	HG-induced H9C2 cell HG-induced NRCM	Wnt/β-catenin	Attenuate apoptosis[76]
NaHS	Db/db mice HG+Ole+PA-induced NRCM	SENP1/SERCA2a	Attenuate apoptosis[30]
NaHS	Db/db mice HG+PA-induced HL-1 cell	Syvn1/Nrf2/GPx4	Attenuate ferroptosis And mitochondrial apoptosis [43]
EXERCISE	HFD-induced DCM mouse	CSE/H_2S	Attenuate pyroptosis[77]
NaHS	STZ-induced DCM mouse Db/db mice	CSE/NLRP3	Attenuate necroptosis And oxidative stress[78]
NaHS	HG-induced NRCM Sg/sg mice	E2F1/RORα/Stat3	Attenuate necroptosis[79]
NaHS	HG-induced H9C2 cell STZ-induced DCM rat	Sirt6/AMPK	Attenuate autophagy[80]
NaHS	Db/db mice HG+PA-induced H9C2 cell	Keap1/ROS	Attenuate autophagy[81]
NaHS	STZ-induced DCM rat HG-induced NRCM	ROS/NLRP3	Attenuate pyroptosis[82]

Abbreviations: NRCM, Neonatal Rat Cardiomyocyte; PA, Palmitic acid; Ole, Oleic acid; STZ, Streptozocin; S-Propargylcysteine.

literature indicates that H_2S can regulate the expression of AMP-activated protein kinase (AMPK), a pivotal molecule in the regulation of cellular energy metabolism. AMPK functions as an energy sensor within cells, becoming activated under conditions of stress to facilitate metabolic reprogramming and maintain redox homeostasis.[67] AMPK is vital for diabetes research and cell apoptosis regulation, linked to HG-induced cardiomyocyte apoptosis.[68] These pathways have been shown in other studies to be associated with HG-induced cardiomyocyte apoptosis. H_2S influences multiple signaling pathways, not just one, to regulate cardiomyocyte apoptosis.

Studies have shown that H_2S can mitigate HG-induced myocardial cell damage by reducing other forms of cell death, including pyroptosis, ferroptosis, autophagy, and necroptosis. Liu et al discovered that H_2S decreases pyroptosis via the ROS/ NLR Family Pyrin Domain Containing 3 (NLRP3) pathway by lowering HG-induced ROS, which in turn reduces NLRP3 inflammasome production, a key mediator of pyroptosis. Thus, inhibiting H_2S can decrease ROS and NLRP3 levels, alleviating myocardial cell pyroptosis.[82] Wang et al found that H_2S reduces ferroptosis in heart cells by enhancing Keap1 ubiquitination via Syvn1, promoting Nrf2 nuclear translocation, which regulates ferroptosis.[43] Additionally, Li et al showed that NaHS increases CSE protein expression, activating autophagy through the Sirt6/AMPK pathway, thereby preventing cardiac cell aging and countering HG toxicity. However, the protective effect of NAHS is reversed when a CSE inhibitor dl-propargylglycine is used.[80] H_2S protects myocardial cells through autophagy by modulating Keap1. Specifically, H_2S increases Keap1 expression by inhibiting its ubiquitination level, thereby enhancing the autophagic clearance of ubiquitin aggregates to protect the heart. 1,4-dithiothreitol, a disulfide bond inhibitor, can elevate the ubiquitination level of Keap1, reduce Keap1 expression, and diminish the effects of NaHS on the clearance of ubiquitin aggregates and ROS production in myocardial cells.[81] Studies have also indicated that necroptosis, a novel form of regulated necrotic cell death, contributes to the cardioprotective effects of H_2S. Gong revealed that exogenous H_2S supplementation alleviates necroptosis in diabetic cardiomyopathy by reducing mitochondrial damage, oxidative stress, and inhibiting NLRP3 inflammasome activation.[78] NaHS can increase the expression of E2F transcription factor 1 (E2F1), which subsequently promotes the transcription of RAR-related Orphan Receptor A (RORα) to alleviate necroptosis and oxidative stress, enhance mitochondrial membrane potential, and prevent diabetic cardiomyopathy.[79] We have summarized the relevant findings in Table 1 to provide a clearer and more direct visualization of the target mechanisms of H_2S.

H_2S mitigates HG-induced endothelial cell death, primarily through apoptosis and necroptosis, similar to its effects on cardiomyocytes.[83] Zhou suggested that the H_2S donor AP123 enhances cAMP response element-binding protein (CREB) via the Phosphoinositide 3-kinase (PI3K) pathway, regulating endothelial Nitric Oxide Synthase (eNOS) gene expression and NO release to restore endothelial cell function.[84] Additionally, HG significantly inhibits the PI3K/Akt/eNOS signaling pathway, worsening apoptosis in Human Umbilical Vein Endothelial Cells. Moreover, the inhibitor of the PI3K/Akt/eNOS signaling pathway, LY294002, significantly suppresses the protective effect of H_2S.[85] Liu et al discovered that H_2S protects endothelial cells by enhancing autophagy via the Nrf2/ROS/AMPK pathway and reduces cell adhesion and apoptosis. H_2S also promotes Nrf2 nuclear translocation, mitigating mitochondrial damage and inhibiting HG-induced ROS.[86] Li et al found that dopamine receptors boost the CSE/H_2S pathway, increasing H_2S levels. H_2S inhibits HG-induced cell apoptosis in vascular endothelial cells by downregulating the NF-κB/ NF-kappa-B inhibitor alpha (IκBα) pathway and reduces excessive autophagy by decreasing AMPK activation due to ATP depletion.[87] Additionally, H_2S improves excessive autophagy by reducing AMPK activation induced by ATP depletion, thus protecting endothelial cells induced by HG. Furthermore, Additionally, H_2S significantly reduces necroptosis in HG-induced endothelial cells, a protective effect diminished by the Receptor-interacting protein kinase-3 (RIP3) inhibitor necrostatin-1 or RIP3-siRNA.[88] We have summarized the relevant findings in Table 2 to provide a clearer and more direct visualization of the target mechanisms of H_2S.

H_2S Improves Angiogenesis

Endothelial cell angiogenesis, the process by which new blood vessels sprout from pre-existing vasculature, is essential for the repair of vascular injuries associated with diabetes.[92,93] Vascular damage, prevalent among diabetic patients, frequently results in diminished blood flow and tissue hypoxia.[94] Angiogenesis is critical for the repair and functional recovery of these injuries, with H_2S identified as a significant promoter of endothelial cell angiogenesis.[95] Liu et al

Table 2 H_2S Improves HG Induced Endothelial Cell Death

Donor	Model	Pathway	Implication
NaHS	HG-induced HUVEC	PI3K/Akt/eNOS	Attenuate apoptosis[85]
AP123	HG-induced BAEC	PI3K/CREB/eNOS	Restore endothelial function and attenuate apoptosis[84]
NaHS	Db/db mice HG+PA-induced RAEC	Nrf2/ROS/AMPK	Attenuate autophagy[86]
NaHS	HG-induced HUVEC	NA	Attenuate necroptosis and apoptosis[89]
NaHS	HG-induced HUVEC	NA	Attenuate apoptosis[90]
NaHS	HG-induced HUVEC	NF-κB/IκBα	Attenuate apoptosis[91]
NaHS	HG+PA-induced RAEC	CSE/H_2S	Attenuate apoptosis and mitophagy[51]
NaHS	HG-induced HUVEC	AMPK	Attenuate necroptosis[88]

Abbreviations: HUVEC, Human Umbilical Vein Endothelial Cells; BAEC, Bovine Aortic Endothelial Cell; RAEC, Rat aortic endothelial cell.

underscored the pivotal role of H_2S in facilitating endothelial cell angiogenesis, particularly through the enhancement of angiogenesis and wound healing by restoring Angiopoietin 1/CSE expression.[96] Exogenous H_2S can enhance endothelial cell angiogenesis in diabetic mice by modulating the miR-126-3p/DNA methyltransferase 1 pathway. In cell-based experiments, elevated H_2S levels were primarily achieved through CSE overexpression, which led to increased miR-126-3p transcription and amelioration of diabetes-induced endothelial cell injury.[97] Moreover, microvascular relaxant 3-MP elevates circulating H_2S levels, thereby stimulating endothelial cell angiogenesis by influencing 3-MST to boost H_2S production.[98] Furthermore, lipoic acid acts as an activator of 3-MST, thereby amplifying the pro-angiogenic effects of 3-MP and promoting the restoration of endothelial cell function. In a parallel study, Lin's engineered particles, which are designed for sustained H_2S release, have demonstrated that the H_2S released by these particles enhances endothelial cell proliferation and migration, stimulates angiogenesis, and accelerates the healing of full-thickness wounds in diabetic mice by prolonging the activation of AMPK isoforms AMPK3 and AMPK14.[99]

Interaction Between H_2S and NO

NO is integral to both the functional regulation and pathological processes of endothelial cells. It is synthesized by various cell types via the oxidation of L-arginine, a reaction catalyzed by nitric oxide synthase (NOS). NOS is present in three distinct isoforms: neuronal NOS (nNOS), inducible NOS (iNOS), and eNOS.[100] NO is essential for the maintenance of vascular health and functionality. Within the cardiovascular system, nitric oxide is predominantly synthesized by eNOS.[101] eNOS catalyzes the conversion of L-arginine into NO and L-citrulline.[102] NO primarily facilitates vasodilation, exhibits anti-inflammatory and anti-adhesive properties, and possesses antioxidant capabilities.[103,104] Deficiency in NO can disrupt vascular homeostasis and modify endothelial permeability. Previous research has substantiated the role of NO in HG-induced endothelial cell damage, underscoring the necessity of targeted NO therapy for mitigating endothelial cell injuries. In recent years, researchers have explored the interaction between H_2S and NO in endothelial cells subjected to HG. Treatment with NaHS has been demonstrated to mitigate the elevated activity of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase induced by diabetes, thereby restoring NO levels and reversing diabetes-induced vascular dysfunction, as well as decreasing superoxide production in the mouse aorta.[105] Under HG conditions, bovine aortic endothelial cells exhibit reduced NO levels, decreased eNOS expression, and inhibition of CREB. Treatment with AP123 has been shown to rescue eNOS expression, increased NO levels, and restored the HG environment. Notably, the protective effects of H_2S were significantly diminished by Wortmannin, a specific PI3K inhibitor, highlighting the crucial role of the PI3K pathway in mediating H_2S-induced endothelial protection and the restoration of vasodilation function. This finding suggests that H_2S enhances NO production and protects endothelial cells through the H_2S/PI3K/CREB/eNOS signaling axis.[84] Conversely, Li proposes that H_2S amplifies the protective effects of NO produced by iNOS, rather than eNOS, on endothelial cells. The application of iNOS siRNA and a selective iNOS inhibitor eliminates the protective effects of NaHS against hyperglycemia-induced

upregulation of NOX4 expression, excessive ROS generation, and aberrant matrix laminin expression, thereby aggravating endothelial damage in diabetic nephropathy.[106]

Hydroxylamine (HNO), the one-electron reduction product of NO, has emerged as a promising cardioprotective molecule. It improves myocardial injury by enhancing eNOS activity and reducing oxidative stress, thereby promoting NO production and maintaining vascular relaxation.[107] Additionally, HNO interacts with caveolin-3 to protect cardiomyocytes and reduce ischemia/reperfusion injury. Compared to traditional NO donors, HNO has a lower risk of tolerance, making it a promising candidate for cardiovascular protection.[108] Research has demonstrated that H_2S can interact with NO to form HNO, which plays a crucial role in preserving cardiac function under pathological conditions. HNO has been shown to effectively prevent HG-induced myocardial cell injury in both in vivo and in vitro models. The underlying mechanism involves HNO restoring the interaction between caveolin-3 and eNOS, thereby enhancing NO production, reducing oxidative stress, alleviating mitochondrial dysfunction in myocardial cells, and ameliorating myocardial cell injuries.[109] In conclusion, we posit that H_2S and NO exhibit complementary roles. H_2S can activate NOS to produce NO, and it can also react with NO to generate HNO. These substances are all key targets in protecting endothelial cells or myocardial cells. To better illustrate this interaction, we have created a schematic diagram depicting the relationship between H_2S and NO (Figure 4).

Material Design Based on H_2S

With the progression of technological advancements, an increasing number of research teams are focusing on the design of nanoparticles and materials that incorporate H_2S for targeted delivery or enhanced therapeutic efficacy, grounded in a comprehensive understanding the role of H_2S. These H_2S-based biomaterials are particularly applicable in the treatment of diabetic wound healing. In hyperglycemic environments, where H_2S synthesis is diminished, Lin et al have developed a novel lotion technology to mitigate this challenge. This innovative approach minimizes the degradation of water-unstable active compounds during the emulsification process, resulting in the formation of sodium hydrosulfide-loaded microparticles (NaHS@MPs). These particles act as in-situ storage, continuously releasing H_2S under physiological conditions, which promotes cellular processes like cell proliferation, migration, and angiogenesis by extending ERK1/2 and p38 activation, thus speeding up wound healing in diabetic mice.[99] Additionally, Cao's team developed an antibiotic-free antibacterial protein hydrogel (H_2S hydrogel). The hydrogel produces H_2S gas for diabetes wound healing by combining bovine serum albumin gold nanoclusters (BSA AuNCs) with bis [tetra (hydroxymethyl) phosphonium] sulfate

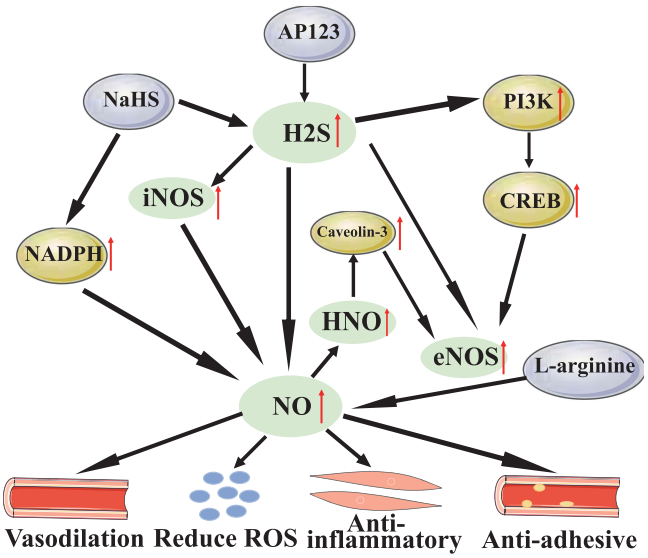

Figure 4 Interaction between H_2S and NO.
Abbreviations: NADPH, Nicotinamide Adenine Dinucleotide Phosphate; iNOS, inducible NOS; eNOS, endothelial Nitric Oxide Synthase; PI3K, Phosphoinositide 3-kinase; CREB, cAMP response element-binding protein.

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(THPS). A Mannich reaction crosslinks the amino group in BSA with the aldehyde group in THPS, creating a stable structure. After THPS hydrolysis, the resulting tris (hydroxymethyl) phosphorus reduces disulfide bonds in BSA to thiol groups, which then catalyze H_2S gas generation by BSA AuNCs. THPS in the H_2S hydrogel disrupts bacterial biofilm and inhibits oxidative stress, aiding cell proliferation, migration, angiogenesis, and wound healing, thus reducing diabetes-related wound injuries.[110] The He team created three quercetin-H_2S donor conjugates that show potential in treating HG-induced insulin resistance, promoting endothelial cell proliferation, wound healing, and tubular formation in vitro.[111]

H_2S Improves Diabetic Nephropathy

In diabetes-induced endothelial damage, diabetic nephropathy is common, and H_2S can treat it. Charlotte et al discovered that Anserine and Carnosine protect against diabetic nephropathy by acting on Heat Shock Protein (Hsp70) in endothelial and proximal tubular epithelial cells, boosting endogenous H_2S expression. This reduces recombinant peptidase activity, decreases Anserine and Carnosine degradation, and enhances endothelial cell function in diabetic nephropathy.[112] Research indicates that GYY4137 can upregulate miR-194 in diabetic glomerular endothelial cells, reducing fibrosis and collagen synthesis. Inhibiting miR-194 worsens fibrosis, while its upregulation by GYY4137 decreases collagen and reactive oxygen species.[113] Kundu et al found that HG levels in kidney glomerular endothelial cells increase Matrix Metallopeptidase 9 (MMP9), decrease H_2S production, induce NMDA-R1, and disrupt connexin-40 and connexin-43. Silencing MMP9 or inhibiting NMDA-R1 preserves connexin-40 and connexin-43. Thus, MMP9 is crucial in diabetes-related renal vascular remodeling, likely via the H_2S/NMDA-R1 pathway.[114] Additionally, HG reduces the regulatory enzymes CBS and CSE, as well as autophagic markers Autophagy Related 5, Autophagy Related 7, Autophagy Related 3, and the LC3B/A ratio, while increasing, the markers of matrix accumulation (galectin-3 and osteopontin) in diabetic nephropathy.

NaHS treatment boosts liver kinase B1 (LKB1)/ STE20-related adaptor (STRAD)/ mouse protein 25 (MO25) complex formation and AMPK phosphorylation in HG cells. H_2S counters HG -induced damage by promoting autophagy and regulating matrix metabolism via the LKB1/STRAD/MO25 pathway.[115] Additionally, HG increases NOX4 expression and activity in renal proximal tubular cells, but H_2S induces iNOS to produce NO, which inhibits NOX4 expression, oxidative stress, and protecting renal epithelial cells from matrix accumulation.[106]

H_2S Improves Other Diabetes-Related Complications Associated with Endothelial Cells

Several studies indicate that H_2S can alleviate endothelial cell complications, enhance wound healing in diabetic rats, and treat diabetes-induced retinopathy. These benefits are linked to granulation tissue formation, anti-inflammatory and antioxidant effects, increased vascular endothelial growth factor[116], and reduced oxidative stress, mitochondrial damage, and MMP9 production. GYY4137, a specific H_2S donor, is particularly effective in preventing retinopathy. H_2S also serves as a potential biomarker for tracking the progression of diabetic retinopathy.[117] H_2S donors protect retinal endothelial cells from apoptosis under HG conditions.[91] Compounds like GYY4137 and AP39 preserve the retinal glycocalyx and endothelial permeability, slowing diabetic retinopathy progression.[118] Moreover, H_2S helps manage diabetic neuropathy by inhibiting apoptosis and inflammation pathways in the spinal cord.[119]

Dose-Response Relationships and Potential Side Effects of H_2S and Its Donors

The use of H_2S-based approaches in therapeutic applications offers several strengths, but also comes with limitations. One of the main advantages of H_2S therapy is its dose-dependent protective effects. At low to moderate doses, H_2S has been shown to improve cardiovascular function, reduce inflammation, and protect against cellular damage. For instance, inhalation of 40–80 ppm H_2S has demonstrated anti-inflammatory effects in animal models, making it a promising candidate for treating conditions like heart failure and acute lung injury.[120–122] Moreover, H_2S can help restore mitochondrial function and regulate ion channels, which are essential for cellular homeostasis.

However, there are notable limitations associated with H_2S-based therapies. High doses of H_2S, such as 100–300 ppm, have been linked to significant side effects, including hypoxemia, pulmonary vasoconstriction, and systemic vasodilation, which can be harmful to the cardiovascular and respiratory systems.[122] Additionally, the rapid dissociation of inorganic H_2S donors, like NaHS and Na_2S, may lead to lower-than-expected concentrations of H_2S, reducing the therapeutic efficacy.[123] The release of potentially toxic by-products, such as formaldehyde and carbon monoxide, from some synthetic H_2S donors (GYY4137), adds another layer of complexity and risk to their clinical use.[124] Therefore, while H_2S-based approaches hold significant therapeutic potential, careful consideration of dose-response relationships and the management of side effects is crucial for their safe and effective clinical application.

Comparative Evaluation of H_2S Donors in Endothelial Dysfunction and Their Translational Potential

Different H_2S donors exhibit distinct therapeutic effects on high glucose-induced endothelial dysfunction, each with unique release mechanisms and pharmacological properties. GYY4137, a slow-releasing H_2S donor, provides sustained H_2S delivery, effectively reducing oxidative stress, inflammation, and apoptosis, making it suitable for long-term management of diabetic vascular complications. AP39, a mitochondria-targeted donor, selectively delivers H_2S to mitochondria, enhancing mitochondrial function and reducing oxidative damage, offering significant potential for addressing mitochondrial dysfunction in diabetic cardiovascular diseases. In contrast, NaHS, an inorganic donor that rapidly releases H_2S, can acutely improve endothelial function by enhancing vasodilation, but its effects are short-lived due to rapid oxidation and degradation, making it more suitable for acute interventions rather than sustained treatment. However, the pharmacokinetics and potential off-target effects of these donors require further investigation. While GYY4137 ensures prolonged H_2S release, its systemic bioavailability and long-term metabolic fate remain unclear. AP39's mitochondria-targeting ability raises questions about its selectivity and possible interactions with other mitochondrial pathways. NaHS, due to its rapid degradation, may lead to transient spikes in H_2S levels, potentially affecting unintended signaling pathways. Further research is necessary to optimize their clinical application and fully understand their therapeutic potential in treating diabetic vascular complications.

Compared to standard treatments, such as antioxidants (eg, NAC, vitamin C), NO donors (eg, nitrates), and anti-inflammatory drugs (eg, aspirin, statins), H_2S donors offer a broader protective effect. While traditional antioxidants primarily scavenge reactive oxygen species (ROS), they have limited efficacy in targeting mitochondrial oxidative stress, whereas AP39 is particularly effective in this regard. NO donors improve vasodilation by increasing NO levels but may lead to tolerance with prolonged use, whereas H_2S enhances eNOS activity and reduces NO degradation without inducing tolerance. Anti-inflammatory drugs mainly inhibit pro-inflammatory pathways like NF-κB but may have systemic side effects, whereas H_2S donors not only suppress inflammation but also regulate oxidative stress, apoptosis, and autophagy, offering a more comprehensive protective effect.

Overall, AP39 holds the greatest potential for clinical translation due to its ability to specifically target mitochondria and mitigate oxidative damage, while GYY4137's sustained H_2S release makes it more suitable for long-term vascular protection. NaHS, though effective in acute settings, may require combination with longer-acting H_2S donors for sustained benefits. Given their multifaceted protective mechanisms, H_2S donors, particularly AP39 and GYY4137, may offer superior therapeutic advantages over conventional treatments, highlighting their potential for clinical application in diabetes-related vascular dysfunction.

Limitation

In the treatment of diabetes-induced cardiovascular complications, the use of H_2S still faces several challenges. First, despite its promising potential, identifying optimal H_2S donors remains a major obstacle. Current mainstream H_2S donors include NaHS, GYY4137, AP39, and AP123, as well as others such as JK-1, JK-2,[125] NSHD-1, NSHD-2, NSHD-6,[126] or garlic extracts.[127] However, no H_2S donor has entered clinical research to demonstrate its efficacy in improving diabetes-induced myocardial or endothelial cell damage, necessitating further evaluation of the clinical prospects of these compounds. Second, although materials have been developed to deliver H_2S stably, ensuring its sustained and effective

release for treating other diabetic complications such as diabetic cardiomyopathy and diabetic nephropathy remains challenging. Therefore, it is crucial to identify or design safe and effective H_2S donor materials to address diabetes-related complications. Furthermore, many existing H_2S donors lack tissue or cell specificity, thus failing to precisely target the desired tissues or cells and potentially causing nonspecific effects. After that, the safety of H_2S donors must be thoroughly assessed in preclinical trials, including evaluating potential side effects and interactions with other medications commonly used by diabetic patients.

Conclusion

Diabetes-induced myocardial and endothelial cell damage serves as the pathological basis for diabetic cardiomyopathy, diabetic microvascular disease, and diabetic nephropathy. Developing effective therapeutic strategies to mitigate these injuries is crucial for improving patient outcomes. As a bioactive gasotransmitter similar to NO and CO, hydrogen sulfide (H_2S) has demonstrated significant protective effects in cardiovascular diseases. Its mechanisms of action primarily involve S-sulfhydration of proteins, which helps mitigate cell death, reduce mitochondrial damage, regulate ion channel function, and promote vascular regeneration.

Despite its promising therapeutic potential, the clinical translation of H_2S-based therapies faces challenges, particularly in optimizing dose-response relationships and minimizing potential side effects. While low-to-moderate doses exhibit protective effects, high concentrations can induce toxicity, such as vascular dysfunction and metabolic disturbances. Additionally, different H_2S delivery methods—including direct inhalation, inorganic sulfides, natural donors, and synthetic compounds—each have distinct advantages and limitations in terms of stability, controlled release, and clinical applicability.

Future research should focus on refining H_2S donor compounds to achieve precise, targeted, and sustained release while minimizing off-target effects. The development of novel prodrugs, enzyme-responsive H_2S donors, and mitochondria-targeted compounds holds promise for enhancing therapeutic efficacy. Furthermore, large-scale clinical trials are necessary to validate the safety, pharmacokinetics, and long-term benefits of H_2S-based treatments. By addressing these challenges, H_2S may emerge as a viable therapeutic strategy for mitigating diabetes-associated cardiovascular and microvascular complications, ultimately improving disease.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare no competing interests in this work.

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