International Journal of
Molecular Sciences

MDPI

Editorial

Hydrogen Sulfide (H_2S)-Donor Molecules: Chemical, Biological, and Therapeutical Tools

Angela Corvino * and Giuseppe Caliendo

Department of Pharmacy, School of Medicine, "Federico II" University of Naples, Via D. Montesano, 49, 80131 Naples, Italy; caliendo@unina.it
* Correspondence: angela.corvino@unina.it

This Special Issue aims to gather new research on hydrogen sulfide (H_2S)-releasing compounds (Figure 1) as cutting-edge pharmacological tools and to advance the understanding of the critical role that H_2S plays in physiological and pathological processes.

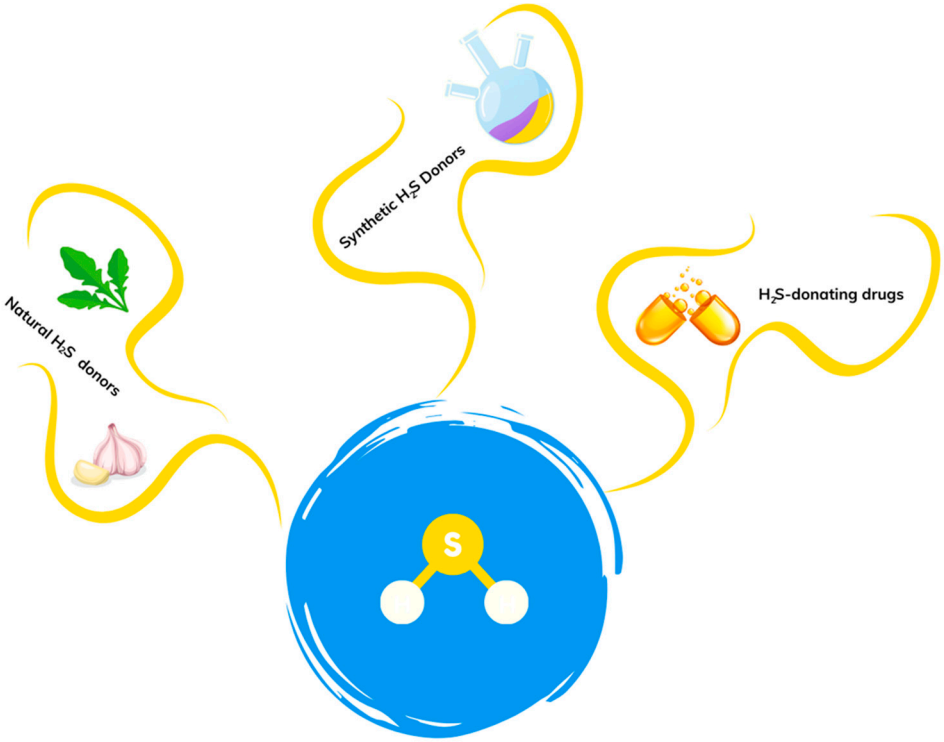

Figure 1. Different sources of H_2S: natural and synthetic H_2S donors, and H_2S-donating drugs.

Over the past two decades, H_2S has emerged as the third recognized endogenous gasotransmitter [1,2] with several positive effects in different physiological and pathophysiological processes, such as inflammation, hypertension, oxidation, metabolic disorders, neuromodulation, and tumor progression [3–5].

Among the natural sources of H_2S, there are polysulfides, which include garlic-derived compounds, and isothiocyanates, derived from vegetables belonging to the Brassicaceae family [6,7].

In addition to plants from the Alliaceae and Brassicaceae families, Citi and colleagues (contribution 1) performed a qualitative and quantitative analysis of the organosulfur compounds contained in mushroom extracts using an amperometric approach. Their studies confirmed the H_2S-releasing capabilities of fungus extracts.

check for updates

Citation: Corvino, A.; Caliendo, G. Hydrogen Sulfide (H_2S)-Donor Molecules: Chemical, Biological, and Therapeutical Tools. *Int. J. Mol. Sci.* **2024**, *25*, 7932. https://doi.org/10.3390/ijms25147932

Received: 5 July 2024
Accepted: 17 July 2024
Published: 20 July 2024

Moreover, the authors reported the pharmacological effects of natural H_2S-donating compounds, including antioxidant properties, anti-inflammatory effects, regulation of the immune system, cardioprotection, and systemic metabolism's regulation.

Interestingly, it has been demonstrated that natural isothiocyanates, including sulforaphane and erucin, significantly prevent and reduce the onset and spread of cancer [8]. In particular, several studies have proven the anti-tumor action of erucin (4-(methylthio)butyl isothiocyanate) [9].

Brancaleone et al., 2023 (contribution 2), investigate the anti-cancer properties of erucin in an in vitro model of triple-negative breast cancer. Erucin was found to significantly inhibit MDA-MB-231 cell proliferation by inducing apoptosis and autophagy in a concentration-dependent manner. Furthermore, the authors proved that erucin reduced intracellular ROS generation, boosting the activation of critical antioxidant genes and stopping MDA-MB-231 cell movement, invasion, and colony formation.

Moreover, to further define the physio-pathological functions of H_2S, synthetic H_2S-donating compounds have been developed.

In this regard, 4-methoxy-phenyl(morpholino)phosphinodithioate morpholinium salt, named GYY4137, is the earliest synthesized and characterized H_2S donor molecule [10]. Due to its capability to gradually release H_2S, it is the most widely studied H_2S donor to elucidate the involvement of H_2S signaling pathway in specific physio-pathological conditions [11–14].

More recently, Berenyiova and colleagues (contribution 3), through the intraperitoneal application of GYY-4137, investigated the involvement of NO and H_2S pathways in fructose-fed spontaneously hypertensive rats with metabolic disorders. They found that the slow H_2S-releasing donor activated the endogenous sulfide pathway in the thoracic aorta, with a consequent positive pro-relaxant and anti-contractile effect.

Ishkaeva et al., 2023 (contribution 4), develop novel synthetic H_2S donating molecules. These compounds are derived from the combination of glutathione with different H_2S donors, dithiophosphates.

The kinetics of H_2S generation from the new compounds indicated that the donors were continuously releasing H_2S, with the dithiophosphate of reduced glutathione releasing more H_2S than oxidized glutathione. The compounds that effectively increased intracellular H_2S prevented C2C12 myoblasts from proliferating at submillimolar doses, in contrast to NaHS. Overall, these studies revealed glutathione dithiophosphates as redox-modulating H_2S donors with a long-acting profile.

As well as being used as pharmacological tools for further studies on the functions of H_2S in the body, some of the H_2S-releasing moieties have been largely combined with different drugs already used in the clinic to obtain novel multi-target molecular hybrids [15].

In the study by Sparaco et al., 2022 (contribution 5), new molecular hybrids between antiglaucoma drugs, such as brinzolamide, betaxolol, and brimonidine, and H_2S donors were designed and synthesized.

All new compounds were proven to release H_2S both in aqueous solutions and in the intracellular environment of human primary corneal epithelial cells. Moreover, their findings indicated two brinzolamide derivatives and one brimonidine H_2S donor as the best hybrids, characterized by a significant and long-lasting production of the gasotransmitter. Their findings allow for more intensive glaucoma therapy to be provided.

Conflicts of Interest: The authors declare no conflicts of interest.

List of Contributions

1. Citi, V.; Passerini, M.; Calderone, V.; Testai, L. Plants and Mushrooms as Possible New Sources of H_2S Releasing Sulfur Compounds. *Int. J. Mol. Sci.* **2023**, *24*, 11886.
2. Bello, I.; Smimmo, M.; d'Emmanuele di Villa Bianca, R.; Bucci, M.; Cirino, G.; Panza, E.; Brancaleone, V. Erucin, an H_2S-Releasing Isothiocyanate, Exerts Anticancer Effects in Human Triple-Negative Breast Cancer Cells Triggering Autophagy-Dependent Apoptotic Cell Death. *Int. J. Mol. Sci.* **2023**, *24*, 6764.

3. Berenyiova, A.; Cebova, M.; Aydemir, B.G.; Golas, S.; Majzunova, M.; Cacanyiova, S. Vasoactive Effects of Chronic Treatment with Fructose and Slow-Releasing H_2S Donor GYY-4137 in Spontaneously Hypertensive Rats: The Role of Nitroso and Sulfide Signalization. *Int. J. Mol. Sci.* **2022**, *23*, 9215.
4. Ishkaeva, R.A.; Khaertdinov, N.N.; Yakovlev, A.V.; Esmeteva, M.V.; Salakhieva, D.V.; Nizamov, I.S.; Sitdikova, G.F.; Abdullin, T.I. Characterization of Glutathione Dithiophosphates as Long-Acting H_2S Donors. *Int. J. Mol. Sci.* **2023**, *24*, 11063.
5. Sparaco, R.; Citi, V.; Magli, E.; Martelli, A.; Piragine, E.; Calderone, V.; Andreozzi, G.; Perissutti, E.; Frecentese, F.; Santagada, V.; Caliendo, G.; Severino, B.; Corvino, A.; Fiorino, F. Design, Synthesis and Evaluation of Novel Molecular Hybrids between Antiglaucoma Drugs and H_2S Donors. *Int. J. Mol. Sci.* **2022**, *23*, 13804.

References

1. Wang, R. Two's company, three's a crowd: Can H_2S be the third endogenous gaseous transmitter? *FASEB J.* **2002**, *16*, 1792–1798. [CrossRef] [PubMed]
2. Szabo, C. A timeline of hydrogen sulfide (H_2S) research: From environmental toxin to biological mediator. *Biochem. Pharmacol.* **2018**, *149*, 5–19. [CrossRef] [PubMed]
3. Powell, C.R.; Dillon, K.M.; Matson, J.B. A review of hydrogen sulfide (H_2S) donors: Chemistry and potential therapeutic applications. *Biochem. Pharmacol.* **2018**, *149*, 110–123. [CrossRef] [PubMed]
4. Cirino, G.; Szabo, C.; Papapetropoulos, A. Physiological roles of hydrogen sulfide in mammalian cells, tissues, and organs. *Physiol. Rev.* **2023**, *103*, 31–276. [CrossRef] [PubMed]
5. Andrés, C.M.C.; Pérez de la Lastra, J.M.; Andrés Juan, C.; Plou, F.J.; Pérez-Lebeña, E. Chemistry of Hydrogen Sulfide-Pathological and Physiological Functions in Mammalian Cells. *Cells* **2023**, *12*, 2684. [CrossRef] [PubMed]
6. Gu, X.; Zhu, Y.Z. Therapeutic applications of organosulfur compounds as novel hydrogen sulfide donors and/or mediators. *Expert Rev. Clin. Pharmacol.* **2011**, *4*, 123–133. [CrossRef] [PubMed]
7. Citi, V.; Martelli, A.; Testai, L.; Marino, A.; Breschi, M.C.; Calderone, V. Hydrogen sulfide releasing capacity of natural isothiocyanates: Is it a reliable explanation for the multiple biological effects of Brassicaceae? *Planta Med.* **2014**, *80*, 610–613. [CrossRef] [PubMed]
8. Melchini, A.; Traka, M.H. Biological Profile of Erucin: A New Promising Anticancer Agent from Cruciferous Vegetables. *Toxins* **2010**, *2*, 593–612. [CrossRef] [PubMed]
9. Singh, D.; Arora, R.; Bhatia, A.; Singh, H.; Singh, B.; Arora, S. Molecular targets in cancer prevention by 4-(methylthio)butyl isothiocyanate—A comprehensive review. *Life Sci.* **2019**, *241*, 117061. [CrossRef] [PubMed]
10. Li, L.; Whiteman, M.; Guan, Y.Y.; Neo, K.L.; Cheng, Y.; Lee, S.W.; Zhao, Y.; Baskar, R.; Tan, C.H.; Moore, P.K. Characterization of a novel, water-soluble hydrogen sulfide-releasing molecule (GYY4137): New insights into the biology of hydrogen sulfide. *Circulation* **2008**, *117*, 2351–2360. [CrossRef] [PubMed]
11. Star, B.S.; van der Slikke, E.C.; Ransy, C.; Schmitt, A.; Henning, R.H.; Bouillaud, F.; Bouma, H.R. GYY4137-Derived Hydrogen Sulfide Donates Electrons to the Mitochondrial Electron Transport Chain via Sulfide: Quinone Oxidoreductase in Endothelial Cells. *Antioxidants* **2023**, *12*, 587. [CrossRef] [PubMed]
12. Chen, X.; Xiao, L.; Yu, S.; Ren, Z.; Wang, W.; Jia, Y.; Liu, M.; Wang, P.; Ji, D.; Yu, Y.; et al. GYY4137, a H_2S donor, ameliorates kidney injuries in diabetic mice by modifying renal ROS-associated enzymes. *Biomed. Pharmacother* **2023**, *162*, 114694. [CrossRef] [PubMed]
13. Zhou, K.; Luo, W.; Gui, D.D.; Ren, Z.; Wei, D.H.; Liu, L.S.; Li, G.H.; Tang, Z.H.; Xiong, W.H.; Hu, H.J.; et al. Hydrogen sulfide attenuates atherosclerosis induced by low shear stress by sulfhydrylating endothelium NFIL3 to restrain MEST mediated endothelial mesenchymal transformation. *Nitric Oxide* **2024**, *142*, 47–57. [CrossRef] [PubMed]
14. Shayea, A.M.F.; Renno, W.M.; Qabazard, B.; Masocha, W. Neuroprotective effects of a hydrogen sulfide donor in streptozotocin-induced diabetic rats. *Int. J. Mol. Sci.* **2023**, *24*, 16650. [CrossRef] [PubMed]
15. Corvino, A.; Scognamiglio, A.; Fiorino, F.; Perissutti, E.; Santagada, V.; Caliendo, G.; Severino, B. Pills of Multi-Target H_2S Donating Molecules for Complex Diseases. *Int. J. Mol. Sci.* **2024**, *25*, 7014. [CrossRef] [PubMed]