Overview: Impact of Hydrogen Sulphide on Some Advanced Molecular Modulators Involved in Cardiac Hypertrophy

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Abstract:

Pressure overload (aortic stenosis) induced myocardial hypertrophy is allied with a poor prognosis in humans. It leads to the development of cardiac arrhythmias, diastolic dysfunction, and ultimately congestive heart failure. Heart failure is a global pandemic disease, affecting an estimated 26 million people worldwide and more than 4 million in India. This poses a huge burden to both individuals and society. However, there is limited knowledge regarding the underlying molecular mechanisms. Therefore, we hypothesized that the various cellular signaling pathway is playing a key role in myocardial hypertrophy. In this review, we were highlighting that drug-like H_2S can target these cellular signaling pathways and hold promise as a potential lead for therapeutic intervention. Furthermore, it includes the concerns associated with H_2S based therapy. In literature, clinical trials suggest that H_2S based therapy is beneficial in cardiac hypertrophy and other diseases. The realization of the biological importance of H_2S in numerous cells, tissues, and organs is now shedding light on the pathogenesis of various human diseases and paving the way for innovative therapeutic interventions.

Keywords: *Aortic stenosis; cellular Signaling; H_2S; myocardial hypertrophy; Heart failure.*

1. Introduction

Hydrogen sulfide (H_2S) is an endogenous gas that regulates many physiological and/or pathological processes in the human body. Modulation of H_2S levels could have potential therapeutic value in the medical and pharmaceutical fields**.** [1] In recent years, notably, H_2S has also been reported to be effective not only as cardioprotective in cardiovascular diseases, [2, 5] such as myocardial ischemia/reperfusion (I/R) injury, heart failure, cardiac hypertrophy, [6] atherosclerosis, [7,9] and hypertension pressure. [9] Moreover, it is also effective in the treatment of Alzheimer's disease, gastric ulcer, and inflammation. [11,13]

Literature shows that the physiological roles of H2S have been recognized, and there is emerging evidence that this endogenous gaseous substance can modulate inflammatory processes, antioxidants, activation of potassium adenosine triphosphate (KATP) channel, inhibition of the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and angiotensin-converting enzyme (ACE) inhibitors. [14,15]

Cardiovascular diseases are silent killers. It is generally agreed that prevention is better than cure. Lifestyle modifications are very important for preventing cardiovascular disease. The dietary habits of the Indian population have changed over the last few decades. Notably, natural food is replaced by fast food and some of the vital nutraceuticals are absent or consumed in low quantity resulting in increased incidences of cardiovascular diseases.

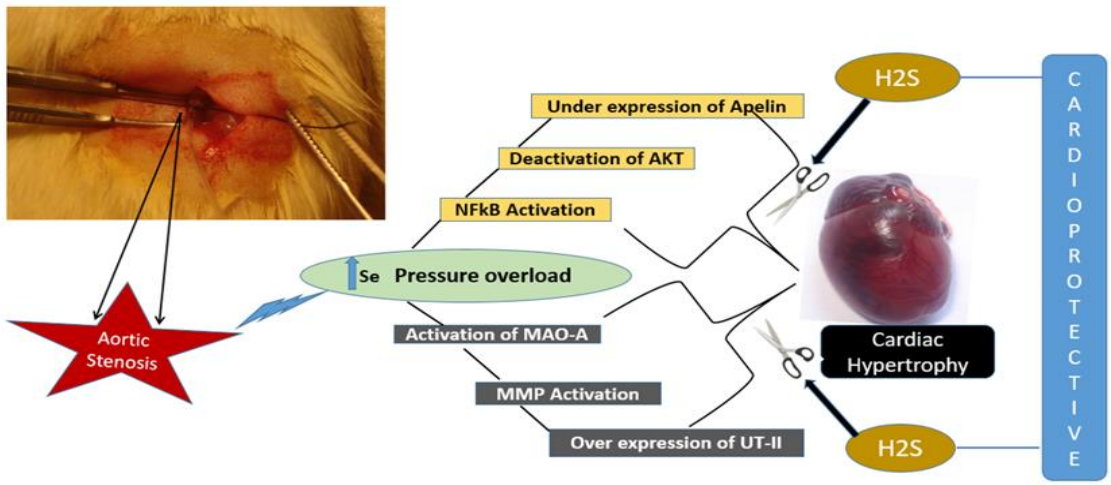

Figure 1. Graphical Abstract

2. H_2S as cardioprotective

Despite some recent improvements in diagnosis and treatment, Heart failure is a global pandemic affecting an estimated 26 million people worldwide and in India, more than 4 million, posing a huge burden to both individuals and society. [16] It is a predictor of cardiovascular morbidity and mortality, independent of hypertension and coronary diseases. [17]

Cardiomyocytes have the capacity to adapt in response to mechanical and neurohumoral stimuli. Under sustained stimulation, for a longer period, the adaptive response leads to cardiac hypertrophy. [18,19] Although, hypertrophy of the heart muscle is initially beneficial during

early growth, but prolonged hypertrophy is potentially deleterious, causing dilated cardiomyopathy and heart failure. [20]
The process of cardiac hypertrophy involves various effectors and signaling molecules. The recent studies are focusing on:

2.1. Monoamine oxidases (MAOs)
MAOs are mitochondrial flavoproteins responsible for the oxidation of monoamines. During this process, they generate hydrogen peroxide (H2O2) as by-products. Based on substrate specificity and inhibitor sensitivity, two isoforms of MAO have been identified, MAO-A and MAO-B. However, MAO-A appears to be the predominant isoform in the myocardium of several species. [21] It has been also found that pharmacological or genetic inhibition of MAO-A prevents maladaptive remodeling and left-ventricular dysfunction in mouse hearts subjected to pressure overload. [22] Overexpression of MAO-A in mouse hearts causes oxidative stress-mediated mitochondrial damage and cardiomyocyte necrosis, leading to ventricular dysfunction. [23] Moreover, the important role of MAO as a relevant source of reactive oxygen species (ROS) and contributing to the development of cardiomyopathy was demonstrated by Umbarkar et al, 2015. [24] Cardiomyocytes upon exposure to H2O2 play a crucial role in urotensin–II (UII) promotes the activation of extracellular signal-regulated kinases (ERK) leading to cardiac hypertrophy.

2.2. Urotensin-II (U-II)
It is a cyclic undecapeptide (H-Glu-Thr-ProAsp-c {Cys-Phe-Trp-Lys-Tyr-Cys}-Val-OH) with an intramolecular ring structure connected by two cysteine residues, [25] has been identified as a vasoactive peptide. [26] Literature shows that UT-induced hypertrophic response was associated with the up-regulation of atrial natriuretic factor (ANP) and brain natriuretic factor (BNP) as well as inflammatory cytokines, such as interleukin-6. [27] Besides its hypertrophic effects, U-II acts as a fibrotic factor, inducing the mRNA synthesis of pro-collagen type I and III and fibronectin mRNA in rat neonatal cardiac fibroblasts. [28] Several recent reports have revealed the vasoconstrictive effect of U-II, which testifies to its potential significance in cardiovascular physiology and contribution to cardiovascular diseases. [29,30]

2.3. Serine/threonine kinase Akt/PKB
It exists as three isoforms in mammals. Akt1 has a wide tissue distribution like hearts, whereas Akt2 is found predominantly in muscle and fat cells while Akt3 is expressed in testes and the brain. [31] Literature shows that Akt is a crucial target for inducing cardiac hypertrophy through the regulation of multiple biological processes including cell survival, proliferation, growth, glycogen metabolism survival, transcription, angiogenesis, and protein synthesis. [32,34] Upon exposure to various growth factors, hormones, cytokines, and pressure overload activates Akt signaling cascade. It is associated with various transducer mechanisms and leads to PIP3 generates at the plasma membrane. by binding their cognate receptor tyrosine kinase (RTK), cytokine receptor, integrins, B and T cell receptors, or G-protein-coupled receptors and triggering activation of the lipid kinase phosphoinositide 3-kinase (PI3K), which generates PIP3 at the plasma membrane.[35,36] The mechanism of Akt at the molecular level promotes cell survival directly by its ability to phosphorylate and inactivate several pro-apoptotic targets,

including Bad, Bim, Bax, and the forkhead (FoxO1/3a) transcription factors. [37,40] The Akt signaling cascade is activated by receptor tyrosine kinases, integrins, B and T cell receptors, cytokine receptors, G-protein-coupled receptors, and other stimuli that induce the production of phosphatidylinositol (3,4,5) trisphosphates (PIP3) by phosphoinositide 3-kinase (PI3K). Studies in cardiac-specific inducible protein kinase B (AKT1) transgenic mice show decreased angiogenesis during pathological remodeling and report that both heart size and cardiac function are angiogenesis-dependent. The study further reported that the disruption of coordinated cardiac hypertrophy and angiogenesis plays a role in the pathogenesis of heart failure.

2.4. Matrix metalloproteinase (MMPs)

It is an active biological substance in cell proliferation, migration, differentiation during embryogenesis, angiogenesis, and apoptosis. MMPs act not only on extracellular Metrix (ECM) proteins but also on various cytokines and growth factors. In the literature, nearly 30 MMPs have been identified and are mainly classified as collagenases, gelatinases, stromelysins, and membrane types. They are involved in host defense as well as tissue remodeling. [41,43] Notably, MMPs are associated with myocardial remodeling due to their action as proteolysis of ECM. [44,45] For example, Collagenases (MMP-1, MMP-8, and MMP-13), stromelysins (MMP-3, MMP-10, MMP-11, and MMP-12), gelatinases (MMP-2 and MMP-9), and membrane-type matrix metalloproteinase (MT1-MMP to MT6-MMP). [46-47] Tyagi and colleagues have demonstrated that myocardial latent MMPs can be activated by chemically induce oxidative stress leading to cardiac hypertrophy and heart failure. [48] In response to persistence, overload induced by stenosis/hypertension activation of myocardial MMPs (especially MMP-2) is playing a crucial role in cardiac hypertrophy.

2.5. Stress nuclear factor-κB:

Literature shows that in response to mechanically & chemically stress nuclear factor-κB (NF-κB)/Rel proteins include NF-κB2 p52/p100, NF-κB1 p50/p105, c-Rel, RelA/p65, and RelB has been activated. [49] Which are important factors in releasing proinflammatory cytokines, LPS, growth factors, and antigen receptors activate an IκB kinase (IKK) complex (IKKβ, IKKα, and NEMO), which phosphorylates IκB proteins. [50,51] These proteins function as dimeric transcription factors that regulate the expression of genes influencing a broad range of biological processes leading to cardiac hypertrophy and heart failure. [52] The post-translational modification of nuclear factor-κB (NF-κB) serves as an example of the difference in functional effects between S-nitrosylation and S-sulfhydration. NF-κB is a transcription factor that regulates the expression of many inflammations and apoptosis-responsive genes. [53]

2.6. Apelin/APJ expression

Currently, in experimental models of heart failure, a reduction in myocardial apelin/APJ expression has been reported. It may be due to the pressure overload-induced HF model, and apelin knockout (KO) mice lead to severely impaired heart contractility which results in cardiac hypertrophy and heart failure.[54,55] Moreover, Iwanaga et al reported that the cardiac apelin/ APJ pathway is markedly downregulated in Dahl salt-sensitive hypertensive (DS) rats with

HF.[56] Reduction in myocardial apelin/APJ expressions was restored by angiotensin II (Ang II) type 1 receptor (AT1R) blocker in end-stage HF with severe left ventricular (LV) dysfunction. [57] However, the effect of exogenous apelin on the apelin/APJ pathway in end-stage HF is unknown. The literature showed that cardiomyocyte's specific deletion of APJ, which improves cardiac function and suppressed cardiac hypertrophy in pressure overload models. [58]

2.7. Sirtuins

Sirt1 is a gene widely expressed in the heart. This is activated in response to pressure overload and oxidative stress leads to cardiac hypertrophy. [59] Notably, phenylephrine (an -adrenergic agonist) is induced the upregulation and activation of Sirt1 as well as inhibition or downregulation of AMPK, foremost to attenuated cardiac hypertrophy. [60] Resveratrol and overexpression of Sirt1 attenuate phenylephrine-induced hypertrophy in cardiomyocytes. [61,62] A recent study demonstrated that Sirt1 critically regulates Akt activation by deacetylation at lysine residues in the pleckstrin homology domains of Akt. Acetylation of Akt and phosphoinositide-dependent protein kinase 1 (PDK1) blocks the binding of Akt and PDK1 to PIP3. [63] Deacetylation of Akt by Sirt1 enhances the binding of Akt and PDK1 to PIP3 and promotes their activation, thereby leading to cardiac hypertrophy. [64]

It has been evident that the productions of excessive reactive oxygen species play a key role in cardiac hypertrophy and heart disease. [65,66] The literature shows that in the heart, (Ang II) is playing a crucial role in the development of cardiac fibrosis via induction of fibroblast proliferation and collagen disposition leads to the progress of cardiac cell hypertrophy. [67,68]

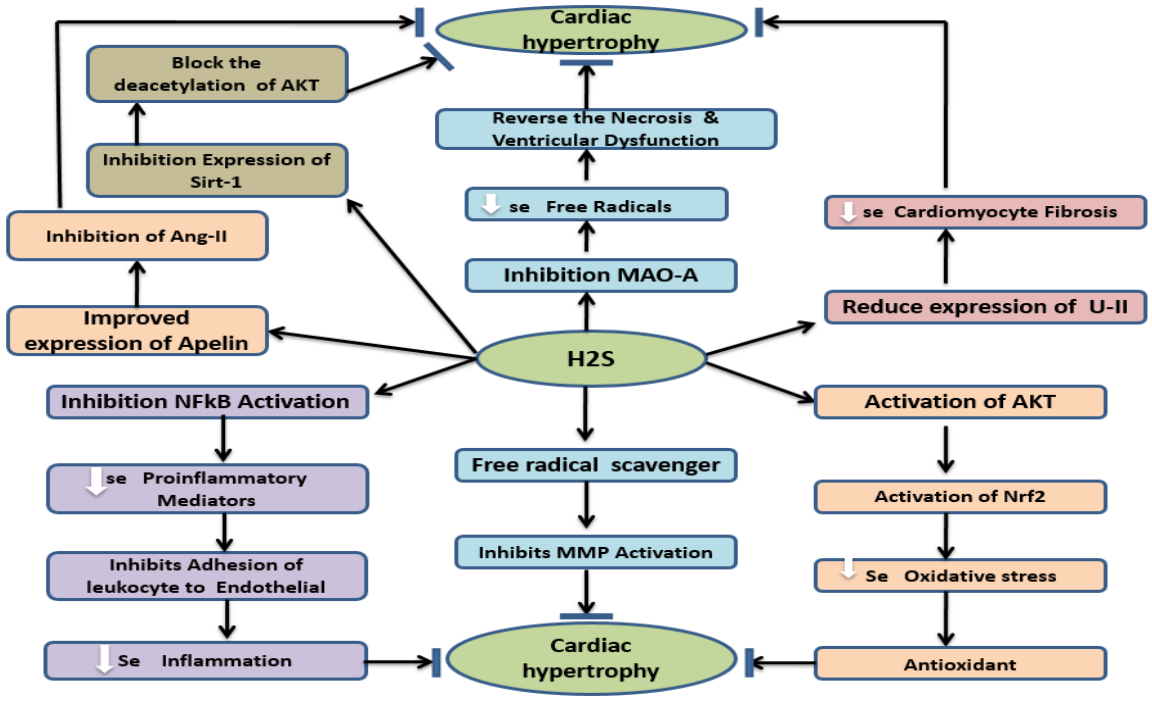

Figure 2. A proposed scheme summarizing all described molecular pathways and cells involved in cardiac hypertrophy and heart failure

3. H_2S-based therapeutics

Regulations of these effectors are the key for many drugs to control hypertrophy act as cardioprotective drugs including H_2S. [69,70]

Over the past decade, so many scientists had focused on exploiting the potent anti-inflammatory and cytoprotective actions of H_2S (Table 1).

The main drug, which acts through the release of H2S, is used to target pain and inflammation, with the primary benefit of reduction in gastrointestinal ulceration that is normally caused by NSAIDs. [71]

3.1. Preclinical studies of orally administered SG-1002 in relevant animal models of pressure overload heart failure and high-fat diet-induced cardiac hypertrophy result in a more sustained and consistent increase in H_2S and sulfane Sulphur levels. Such replenishment of H_2S levels is significantly effective in decreasing infarct size, improving cardiac function; increasing angiogenesis, decreasing inflammation, and downregulating oxidative stress. [72] In addition, attenuated the endoplasmic reticulum stress by upregulation of endothelial NO synthase (eNOS) mediated signaling. [73] Noteworthy, it was also noted as biologically active by improving the coronary artery vascular reactivity against the Yucatan minipig model of severe hind limb ischemia. [74]

3.2. In the field of medicine, a new approach subcellular-targeted delivery of the H_2S-releasing group has been developed the compounds AP39 and AP123 by investigators. In 2014, mitochondria were introduced as first-class subcellular-targeted H_2S donors due to having a critical role in determining whether a cell survives or dies. [75] H_2S has conferred benefits to mitochondria by acting as an electron donor and downregulating the antioxidant response pathway. Szczesny, B. et al. the University of Exeter has patented (WO2013045951 A1) such H_2S-releasing compounds for the treatment of humans, animals, and the authors propose that the compounds would be useful for the treatment of disorders such as hypertension and hemorrhagic shock, as well as conditions characterized by inflammation and edema. [76] AP39 is the most advanced of these compounds (Table 1). It has been shown to elevate H_2S levels within endothelial mitochondria, protect cells against oxidant-induced damage, and prevent damage to mitochondrial DNA in vitro (Szczesny et al., 2014). Further, followed in vivo studies and demonstrated that AP39 is cardioprotective against acute cardiac arrest, myocardial, and renal I/R injury. [77,79]

3.3. Moore et al. developed the H_2S donor GYY4137, which is now widely used as a research tool to study the effects of H_2S. Compared with conventional H_2S donors, GYY4137 releases H_2S more slowly. [80,81] GYY4137 has been shown to exert antihypertensive actions in spontaneously hypertensive rats (SHRs), [82] and to reduce inflammation through its ability to reduce circulating levels of various pro-inflammatory cytokines and mediators.

In this regard, GYY4137 has been shown to be an effective anti-inflammatory agent in the murine adjuvant-induced arthritis model. [83] Nowadays, GYY4137 as an H_2S donor has been used in more than 100 publications due to its properties as a slow-release profile, which helps better mimics the physiological H_2S production. [84]

3.4. Moreover, the use of hybrid drugs is a novel concept in the field of biomedical that exert beneficial effects beyond H_2S production. For example, hybrids such as Zofenopril (Menarini), act as H_2S releasing angiotensin-converting enzyme (ACE) inhibitors. Bucci et al. demonstrated that a large component of the anti-hypertensive effects of this drug occurs independently of ACE inhibition and are instead attributable to the H_2S released by this drug. [85] Noteworthy, studies of Zofenopril in a porcine model have shown a protective effect against MI/R injury in mice by improving endocardial blood flow. [86] Literature showed that given the positive candidate preclinical data for Zofenopril as well as recently, ATB-346 an H_2S-releasing nonsteroidal anti-inflammatory drug (NSAID) was successfully used for the treatment of osteoarthritis. Therefore, it cannot be denied that H_2S-releasing hybrid drugs will undergo further development for the treatment of cardiovascular disease. [87]

3.5. N-acetylcysteine (Mucolytic) is one of the most widely used antioxidants for the treatment of cystic and pulmonary fibrosis. It is also noted as an antidote for acetaminophen-induced liver damage. In mitochondria, NAC is desulfurated to H_2S and followed by sulfane sulfur species demonstrated by the investigator. [88] Moreover, it has been shown to elicit marked anti-inflammatory effects in rodents. [89] Despite its widespread use, the roles of H_2S in mediating its above-mentioned clinical effects have not yet been established.

3.6. Oltipraz is belonged to dithiolethione class and is chemically known as organosulfur compound. [90,91] It is noted in rodent models as a crucial role to inhibit the formation of cancers in the bladder, blood, colon, kidney, liver, lung, pancreas, stomach, and trachea, skin, and mammary tissue and also acts as a schistosomicide. [92,93] Notable, Oltipraz has shown significant side effects, including neurotoxicity and gastrointestinal toxicity due to the release of superoxide radicals. It subsequently failed to show the efficacy of Oltipraz when demonstrated in Clinical trials. [94]

3.7. ATB-346 is the most promising cardiovascular safe molecule, which is a derivative of the naproxen NSAID family. Literature showed, in animal studies that ATB-346 was significantly more potent as well as longer than naproxen in terms of suppressing cyclooxygenase (COX) activity during phase 1 clinical trial. [95] Noteworthy, a low dose of ATB-346 (250 mg; equimolar to 160 mg naproxen), given once daily, would provide significant pain relief in patients with osteoarthritis was performed in the phase 2a trial. [96]

3.8. GIC-1001 is a novel and orally administered, a colonic analgesic drug developed as an alternative to intravenous (i.v.) sedative during full colonoscopy. Notable, GIC-1001 in a mouse model of colorectal distension tested and nociceptive response to all injuries showed to significantly reduce with a dose-dependent manner.[97] Literature showed that the phase I study completed; (ClinicalTrials.gov Identifier: NCT01738425) in terms of better efficacy in the animal model and the safety of its use in humans. In addition, GIC-1001 was subjected to a phase II study, demonstrating a clinically significant pain reduction (ClinicalTrials.gov Identifier: NCT01926444).

Table 1. H_2S-based therapeutics in development

Institution (location)	Clinical Indications	Lead Drug	Comment	Stage of Development
Sulfa GENIX (New Orleans, Louisiana, USA)	Oxidative stress	SG-1002	Polyvalent sulfur	Phase II for heart failure
University of Exeter (Exeter, UK)	Inflammation, oxidative stress	AP39	Mitochondrion targeted H2S release	Preclinical
National University of Singapore	Hypertension, Inflammation, Cancer	GYY4137	Slow-releasing H2S donor	Unknown
Antibe Therapeutics (Toronto, Ontario, Canada)	Osteoarthritis	ATB-346	Naproxen Derivative	Phase II
	Acute pain	ATB-352	Ketoprofen Derivative	Preclinical
	Veterinary (pain)	ATB-338	Diclofenac Derivative	Preclinical
	Thrombosis	ATB-350	Aspirin Derivative	Preclinical
GI Care Pharma (Montreal, Quebec, Canada)	Colonic pain	GIC-1001	Trimebutine salt; licensed from Antibe Therapeutics	Phase II for analgesia during colonoscopy*
Sova P'ceuticals (La Jolla, California, USA)	Pain, metabolic disorders	Unknown	Inhibitor of CSE activity	Unknown
City University of New York (New York, USA)	Cancer	NBS-1120	Aspirin Derivative	Preclinical

4. Conclusion

The endogenous H_2S has very rapidly emerged as an exciting signaling molecule in many physiological aspects of the human body. This gaseous molecule impacts cells and cellular organelles throughout the body and freely diffuses across cellular membranes resulting in a universal biological expression. Although, the multiple therapeutic effects induced by H_2S resulted from the wide variety of targets involved in the managing of cardiovascular diseases. Mechanistic discovery of H_2S is underway and much has been accomplished in regards to the aforementioned such as antioxidant, anti-inflammatory and ACE inhibitors signaling and combat the disease process in humans. In this review, we summarized the information on currently available H_2S donors as potential cardioprotective modulators. It is a notion that the importance of H_2S in biomedical research, there is not only a useful research tool but also a potential therapeutic agent. Many donor moieties have been developed that release H_2S both in vitro and in vivo. In addition, all the donors have both pros and cons. A major biochemical hurdle is that H_2S release from many donors (i.e. sulfide salts, GYY4137, and DTTs) is not controllable and in other cases, it is not able to mimic biological/endogenous H_2S generation.

In conclusion, H_2S is a potential therapeutic molecule, and the development of useful donors is critical. In our opinion, future efforts should be focused on developing controllable H_2S donors and different H_2S releasing mechanisms should be exploited that aid in the management of cardiac hypertrophy.

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References:

[1] Gadalla, M.M., Snyder, S.H. Hydrogen sulfide as a gasotransmitter. J Neurochem. 2010; 113 (1): 14–26.
[2] Polhemus, D.J., Lefer, D.J. Emergence of Hydrogen Sulfide as an Endogenous Gaseous Signaling Molecule in Cardiovascular Disease. Circ Res. 2014; 114(4): 730–737.
[3] Huang, S., Li, H., Ge, J. A Cardioprotective Insight of the Cystathionine γ-Lyase/Hydrogen Sulfide Pathway. IJC Heart Vasc 2015; (7): 51–57.
[4] Meng, G., Ma, Y., Xie, L., Ferro, A., Ji, Y. Emerging Role of Hydrogen Sulfide in Hypertension and Related Cardiovascular Diseases. Br J Pharmacol. 2015; 172(23): 5501–5511.
[5] Yu, X.H., Cui, L.B., Wu, K., Zheng, X.L., Cayabyab, F.S., Chen, Z.W., et al. Hydrogen Sulfide as a Potent Cardiovascular Protective Agent. Clin Chim Acta. 2014; (437): 78–87.
[6] Calvert, J.W., Elston, M., Nicholson, C.K., Gundewar, S., Jha, S., Elrod, J.W., et al. Genetic and Pharmacologic Hydrogen Sulfide Therapy Attenuates Ischemia-Induced Heart Failure in Mice. Circulation. 2010; 122(1): 11–19.
[7] Xu, S., Liu, Z., Liu, P. Targeting Hydrogen Sulfide as a Promising Therapeutic strategy for Atherosclerosis. Int J Cardiol. 2014; 172(2): 313-317.
[8] Van Den Born, J.C., Mencke, R., Conroy, S., Zeebregts, C.J., Van Goor, H., Hillebrands, J.L. Cystathionine Gamma-Lyase Is Expressed in Human Atherosclerotic Plaque Microvessels and Is Involved in Micro-Angiogenesis. Sci Rep. 2016; (6): 1–13.
[9] Du, C., Lin, X., Xu, W., Zheng, F., Cai, J., Yang, J., et al. Sulfhydrated Sirtuin-1 Increasing Its Deacetylation Activity Is an Essential Epigenetics Mechanism of Anti-Atherogenesis by Hydrogen Sulfide. Antioxid Redox Signal. 2019; 30 (2): 184–197.
[10] Yang, G., Wu, L., Jiang, B., Yang, W., Meng, A.K., Zhang, W.M., et al. H2S as a Physiologic Vasorelaxant: Hypertension in Mice with Deletion of Cystathionine Gamma-Lyase. Science. 2008; 322(5901): 587–590.
[11] Cao, L., Cao, X., Zhou, Y., Nagpure, B.V., Yang, Y., Moore, P.K., et al. Hydrogen Sulfide Inhibits ATP-Induced Neuroinflammation and aβ1–42 Synthesis by Suppressing the Activation of STAT3 and Cathepsin S.Brain Behav. Immun. 2018; (73): 603–614.

[12] Wang, X.H., Wang, F., Cao, Y.J., Cao, L.D, Han, Q., Liu, C.F., et al. Dysregulation of Cystathionine γ-Lyase (CSE)/Hydrogen Sulfide Pathway Contributes to Ox-LDL-Induced Inflammation in Macrophage. Cell Signal. 2013; 25 (25): 2255–2262.
[13] Wallace, J.L., Dicay, M., McKnight, W., Martin, G.R. Hydrogen Sulfide Enhances Ulcer Healing in Rats. FASEB J. 2007; 21(14): 4070–4076.
[14] Zhao, W., Zhang, J., Lu. Y., Wang, R. The vasorelaxant effect of H2S as a novel endogenous gaseous KATP channel opener. EMBO J. 2001; 20(21): 6008–6016.
[15] Kelleher, Z.T., Matsumoto, A., Stamler, J.S., Marshall, H.E. NOS2 regulation of NF-κB by S-nitrosylation of p65. J. Biol. Chem. 2007; 282(42): 30667–30672.
16. Savarese, G., Lund, L. H. Global Public Health Burden of Heart Failure. Card Fail Rev. 2017; 3(1): 7–11.
[17] Koren, M.J., Devereux, R.B., Casale, P.N., Savage, D.D., Laragh, J.H. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991; 114(5): 345-352.
[18] Tzanidis, A., Hannan, R.D., Thomas, W.G. Direct actions of urotensin II on the heart: implications for cardiac fibrosis and hypertrophy. Circ Res. 2003; 93(3): 246–53.
[19] Yang, H., Schmidt, L.P., Wang, Z., Yang, X., Shao, Y., Borg, T.K. Dynamic myofibrillar remodeling in live cardiomyocytes under static stretch. Sci Rep. 2016; (6): 20674.
[20] You, J., Wu, J., Zhang, Q., Ye, Y., Wang, S., Huang, J. Differential cardiac hypertrophy and signaling pathways in pressure versus volume overload. Am J Physiol Heart Circ. 2018; 314(3): H552–H562.
[21] Kaludercic, N., Carpi, A., Menabo, R., Di, L.F., Paolucci, N. Monoamine oxidases (MAO) in the pathogenesis of heart failure and ischemia/reperfusion injury. Biochim Biophys Acta. 2011; 1813(7): 1323–1332.
[22] Kaludercic, N., Takimoto, E., Nagayama, T., Feng, N., Lai, E.W., Bedja, D. Monoamine oxidase A-mediated enhanced catabolism of norepinephrine contributes to adverse remodeling and pump failure in hearts with pressure overload. Circ Res. 2010; 106(1): 193–202.
[23] Velayutham, M., Villamena, F.A., Fishbein, J.C., Zweier, J.L. "Cancer chemopreventive oltipraz generates superoxide anion radical,". Arch Biochem Biophys. 2005; 435(1): 83–8.
[24] Umbarkar, P., Singh, S., Arkat, S., Bodhankar, S. L. Monoamine oxidase-A is an important source of oxidative stress and promotes cardiac dysfunction, apoptosis and fibrosis in diabetic cardiomyopathy. Free Rad Biol and Medicine. 2015; (87): 263-273.
[25] Russell, F.D., Kearns, P., Toth, I., Molenaar, P. Urotensin-II converting enzyme activity of furin and trypsin in human cells in vitro. J Pharmacol Exp Ther. 2004; 310(1): 209–14.
[26] Ames, R.S, Sarau, H.M., Chambers, J.K., Willette, R.N., Aiyar, N.V., Louden, C.S., et al. Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14. Nature. 1999; 401(7650): 282–6.
[27] Johns, D.G., Naselsky, D., Herold, C.L., Maniscalco, K., Sarov Blat, L., Steplewski, K., et al. Urotensin II-mediated cardiomyocytes hypertrophy: effect of receptor antagonist and role of inflammatory mediators. Naunyn Schmiedebergs Arch Pharmacol. 2004; 370(4): 238–50.
[28] Douglas, S.A., Ohlstein, E.H. Human urotensin-II, the most potent mammalian vasoconstrictor identified to date, as a therapeutic target for the management of the cardiovascular disease. Trends Cardiovasc Med. 2000; 10(6): 229–37.

[29] Douglas, S.A., Tayara, L., Ohlstein, E.H., Halawa, N., Giaid, A. Congestive heart failure and expression of myocardial urotensin II. Lancet. 2000; 359(9322): 1990–7.
[30] Kassiri, Z., Khokha, R. Myocardial extra-cellular matrix and it's regulation by metalloproteinases and their inhibitors. Thromb Haemost. 2005; 93(2): 212-9.
[31] Song, M.S., Salmena, L., Pandolfi, P.P. The functions and regulation of the PTEN tumor suppressor. Nat Rev Mol Cell Biol. 2012; 13(5): 283–296.
[32] Sussman, M.A., Volkers Mand, F.K. Myocardial AKT: the omnipresent nexus. Physiol Rev. 2011; 91(3): 1023–1070.
[33] Song, G., Ouyang, G., Bao, S. The activation of Akt/PKB signaling pathway and cell survival. J Cell Mol Med. 2005; 9(1): 59–71.
[34] Yu, J.S., Cui, W. Proliferation, survival and metabolism: the role of PI3K/AKT/mTOR signalling in pluripotency and cell fate determination. Development. 2016; 143 (17): 3050–3060.
[35] Naga Prasad, S.V., Esposito, G., Mao, L., Koch, W.J., Rockman, H.A. Gbetagamma-dependent phosphoinositide 3-kinase activation in hearts with in vivo pressure-overload hypertrophy. J Biol Chem. 2000; 275(7): 4693–4698.
[36] Alessi, D.R., James, S.R, Downes, C.P., Holmes, A.B., Gaffney, P.R., Reese, C.B., et al. Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase B alpha. Curr Biol. 1997; 7(4): 261–269.
[37] Stephens, L., Anderson, K., Stokoe, D., Erdjument, B.H., Painter, G.F., Holmes, A.B., et al. Protein kinase B kinases that mediate phosphatidylinositol 3,4,5-trisphosphate-dependent activation of protein kinase B. Science. 1998; 279(5351): 710–714.
[38] Fu, Z., Tindall, D.J. FOXOs, cancer and regulation of apoptosis. Oncogene. 2008; 27(16): 2312–2319.
[39] Dijkers, P.F., Medema, R.H., Lammers, J.W., Koenderman, L., Coffer, P.J. Expression of the pro-apoptotic Bcl-2 family member Bim is regulated by the forkhead transcription factor FKHR-L1. Curr Biol. 2000; 10(19): 1201–1204.
[40] Stahl, M., Dijkers, P.F., Kops, G.J., Lens, S.M., Coffer, P.J., Burgering, B.M. The forkhead transcription factor FoxO regulates transcription of p27Kip1 and Bim in response to IL-2. J Immunol. 2002; 168(10): 5024–5031.
[41] Belo, V.A., Parente, J.M., Tanus-Santos, J.E., Castro, M.M. Matrix metalaloproteinase (MMP)-2 decreases calponin-1 levels and contributes to arterial remodeling in early hypertension. Biochem Pharmacol. 2016; (118): 50–58.
[42] Parente, J.M., Pereira, C.A., Oliveira-Paula, G.H., Tanus-Santos, J.E., Tostes, R.C., Castro, M.M. Matrix metalloproteinase-2 activity is associated with divergent regulation of calponin-1 in conductance and resistance arteries in hypertension-induced early vascular dysfunction and remodelling. Basic Clin Pharmacol Toxicol. 2017; 121(4): 246–256.
[43] Wang, Xi., Khalil, R.A. Matrix Metalloproteinases, Vascular Remodeling, and Vascular Disease. Adv Pharmacol. 2018; (81): 241-330.
[44] Page-McCaw, A., Ewald, A.J., Werb, Z. Matrix metalloproteinases and the regulation of tissue remodeling. Nat Rev Mol Cell Bio.l 2007; 8(3): 221–233.
[45] Dabek, J., Kulach, A., Gasior, Z. The role of matrix metalloproteinases in acute coronary syndromes. Eur J Intern Med. 2007; 18(6): 463-6.

[46] Nagase, H., Visse, R., Murphy, G. Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res. 2006; 69(3): 562–573.
[47] Amin, M., Pushpakumar, S., Muradashvili, N., Kundu, S., Tyagi, S.C., Sen, U. Regulation and involvement of matrix metalloproteinases in vascular diseases. Front Biosci. 2016; (21): 89–118.
[48] Tyagi, S.C., Ratajska, A., Weber, K.T. Myocardial matrix metalloproteinase(s): localization and activation. Mol Cell Biochem. 1993; 126(1): 49-59.
[49] Hayden, M.S., Ghosh, S. Shared principles in NF-kappaB signaling. Cell 2008; 132(3): 344–362.
[50] Israel, A. The IKK complex, a central regulator of NF-κB activation. Cold Spring Harb. Perspect Biol. 2010; 2(3): a000158.
[51] Freund, C., Schmidt-Ullrich, R., Baurand, A., Dunger, S., Schneider, W., Loser, P. Requirement of nuclear factor-kappaB in angiotensin II- and isoproterenol-induced cardiac hypertrophy in vivo. Circulation. 2005; 111(18): 2319–2325.
[52] Zelarayan, L.A., Renger, C., Noack, C., Dietz, R. NF-kappaB activation is required for adaptive cardiac hypertrophy. Cardiovasc Res. 2009; 84(3): 416–424.
[53] Perkins, N.D. Post-translational modifications regulating the activity and function of the nuclear factor kappa B pathway. Oncogene. 2006; 25(51): 6717–6730.
[54] Kuba, K., Zhang, L., Imai, Y., Arab, S., Chen, M., Maekawa, Y. Impaired heart contractility in Apelin gene-deficient mice associated with aging and pressure overload. Circ Res. 2007; 101(4): e32 – 42.
[55] Charo, D.N., Fajardo, G., Kawana, M., Kundu, R.K., Sheikh, A.Y, Finsterbach, T.P, et al. Endogenous regulation of cardiovascular function by apelin-APJ. Am J Physiol Heart Circ Physiol. 2009;(297): H1904–H1913.
[56] Iwanaga, Y., Kihara, Y., Takenaka, H., Kita, T. Down-regulation of cardiac apelin system in hypertrophied and failing hearts: Possible role of angiotensin II-angiotensin type 1 receptor system. J Mol Cell Cardiol. 2006; 41(5): 798 – 806.
[57] Fukushima, H., Kobayashi, N., Takeshima, H., Koguchi, W., Ishimitsu, T. Effects of olmesartan on Apelin/APJ and Akt/endothelial nitric oxide synthase pathway in Dahl rats with end-stage heart failure. J Cardiovasc Pharmacol. 2010; 55(1): 83 – 88.
[58] Parikh, V.N., Liu, J., Shang, C., Woods, C., Zhao, M., Charo, D.N., et al. Apelin and APJ orchestrate complex tissue-specific control of cardiomyocytes hypertrophy and contractility in the hypertrophy-heart failure transition. Am. J. Physiol. Heart Circ. Physiol. 2018; 315(2): H348–H356.
[59] Matsushima, S., Sadoshima, J. The role of Sirtuins in cardiac disease. Am J Physiol Heart Circ Physiol. 2015; 309(9): 1375–1389.
[60] Gu, X.S., Wang, Z.B., Li, J.P., Lei, L., Su, DF, Zheng, X. Resveratrol, an activator of SIRT1, up-regulates AMPK and improves cardiac function in heart failure. Genet. Mol Res. 2014; 13(1): 323–335.
[61] Suzuki, K., Koike, T. Resveratrol abolishes resistance to axonal degeneration in slow Wallerian degeneration (WldS) mice: activation of SIRT2, a NAD-dependent tubulin deacetylase. Biochem Biophys Res Commun. 2007; 359(3): 665–671.

[62] Desquiret, D.V., Gueguen, N., Leman, G., Baron, S., Nivet, A.V. Resveratrol induces a mitochondrial complex I-dependent increase in NADH oxidation responsible for Sirtuins activation in liver cells. J Biol Chem. 2013; 288(51): 36662–36675.
[63] Pillai, V.B., Sundaresan, N.R., Gupta, M.P. Regulation of Akt signaling by sirtuins: its implication in cardiac hypertrophy and aging. Circ. Res. 2014; 114(2): 368–378.
[64] Sundaresan, N.R., Pillai, V.B., Samant, S., Vasudevan, P., Gupta, M.P. The deacetylase SIRT1 promotes membrane localization and activation of Akt and PDK1 during tumorigenesis and cardiac hypertrophy. Sci Signal. 2011; 4(182): 46.
[65] Maulik, S.K., Kumar, S. Oxidative stress and cardiac hypertrophy: A review. Toxicol Mech Methods. 2012; 22(5): 359–366.
[66] Peoples, J.N., SarafGhazal, A.N., Pham, T.T., Kwong, J.Q. Mitochondrial dysfunction and oxidative stress in heart disease. Exp Mol Med. 2019; 51(12): 1–13.
[67] Forrester, S.J., Booz, G.W., Sigmund, C.D., Coffman, T.M., Rizzo, V., Eguchi, R.S. Angiotensin II signal transduction: an update on mechanisms of physiology and pathophysiology. Physiol Rev. 2018; 98 (3): 1627–738.
[68] Dostal, D.E. The cardiac renin-angiotensin system: novel signaling mechanisms related to cardiac growth and function. Regul Pept. 2000; 91(1-3): 1-11.
[69] Szabo, C. Hydrogen sulfide and its therapeutic potential. Nature Rev. Drug Discov. 2007; 6(11): 917–935.
[70] Wallace, J.L., Caliendo, G., Santagada, V., Cirino, G. Markedly reduced toxicity of a hydrogen sulfide releasing derivative of naproxen (ATB-346). Br J Pharmacol. 2010; 159(6): 1236–1246.
[71] Wallace, J.L. THU0474 A Phase 1 Clinical Trial of ATB-346, A Gastrointestinal-Ssafe Nonsteroidal Anti-Inflammatory Drug. Annals of the Rheumatic Diseases. 2015; 74 (Suppl 2): 371.3-372.
[72] Kondo, K., Bhushan, S., King, A.L., Prabhu, S.D., Hamid, T., Koenig, S., et al. H_2S protects against pressure overload-induced heart failure via upregulation of endothelial nitric oxide synthase. Circulation. 2013; 127(10): 1116-1127.
[73] Barr, L.A., Shimizu, Y., Lambert, J.P., Nicholson, C.K., Calvert, J.W. Hydrogen sulfide attenuates high fat diet-induced cardiac dysfunction via the suppression of endoplasmic reticulum stress. Nitric Oxide. 2015; (46):145-56.
[74] Donnarumma, E., Rushing, A.M., Boisvert, S.F., Scarborough, A.L., Polhemus, D.J., Trivedi, R.K., et al. The Novel H2S Pro-Drug, SG-1002, Preserves Coronary Artery Vascular Reactivity in the Setting of Critical Limb Ischemia in Swine. Circulation. 2016; (134): A19028.
[75] Trionnaire, L.S., Perry, A., Szczesny, B., Szabo, C., Winyard, P.G. The synthesis and functional evaluation of a mitochondria-targeted hydrogen sulfide donor, (10-oxo-10-(4-(3-thioxo-3H- 1,2-dithiol-5-yl) phenoxy) decyl) triphenylphosphonium bromide (AP39). Med. Chem. Commun. 2014; 5(6): 728–736.
[76] Szczesny, B., Módis, K., Yanagi, K., Coletta, C., Le Trionnaire, S., Perry, A., et al. AP39, a novel mitochondria-targeted hydrogen sulfide donor, stimulates cellular bioenergetics, exerts cytoprotective effects and protects against the loss of mitochondrial DNA integrity in oxidatively stressed endothelial cells in vitro. Nitric Oxide. 2014; (41): 120–130.
[77] Ahmad, A., Olah, G., Szczesny, B., Wood, M.E., Whiteman, M., Szabo, C.. AP39, a mitochondrially targeted hydrogen sulfide donor, exerts protective effects in renal epithelial

cells subjected to oxidative stress in vitro and in acute renal injury in vivo. Shock. 2016; (45): 88–97.
[78] Chatzianastasiou, A., Bibli, S.I., Andreadou, I., Efentakis, P., Kaludercic, N., Wood, M.E., et al. Cardioprotection by H2S donors: nitric oxide-dependent and independent mechanisms. J Pharmacol Exp Ther. 2016; (358): 431–440.
[79] Karwi, Q.G., Bornbaum, J., Boengler, K., Torregrossa, R., Whiteman, M., Wood, M.E., et al. AP39, a mitochondria-targeting hydrogen sulfide (H2 S) donor, protects against myocardial reperfusion injury independently of salvage kinase signalling. Br J Pharmacol. 2017; (174): 287–301.
[80] Li, L., Whiteman, M., Guan, Y.Y., Neo, K.L., Cheng, Y., Lee, S.W., et al. Characterization of a novel, water-soluble hydrogen sulfide-releasing molecule (GYY4137): new insights into the biology of hydrogen sulfide. Circulation. 2008; (117): 2351–2360.
[81] Rose, P., Dymock, B.W., Moore, P.K. GYY4137, a novel water-soluble, H2S-releasing molecule. Methods Enzymol. 2015; (554): 143–167.
[82] Li, L., Tellez, M.S., Tan, C.H., Whiteman, M., Moore, P.K. GYY4137, a novel hydrogen sulfide-releasing molecule, protects against endotoxic shock in the rat. Free Radic Biol Med. 2009; 47(1): 103-13.
[83] L, Li., Keeble, M.S., Tellez, P.G., Wood, M.E., Moore, P.K., Whiteman, M. The complex effects of the slow-releasing hydrogen sulfide donor GYY4137 in a model of acute joint inflammation and in human cartilage cells. J Cell Mol Med. 2013; 17(3): 365-76.
[84] Szabo, C., Papapetropoulos, A. International union of basic and clinical pharmacology. CII: pharmacological modulation of H2S levels: H2S donors and H2S biosynthesis inhibitors. Pharmacol Rev. 2017; (69): 497–564.
[85] Bucci, M., Vellecco, V., Cantalupo, A., Brancaleone, V., Zhou, Z., Evangelista, S., et al. Hydrogen sulfide accounts for the peripheral vascular effects of zofenopril independently of ACE inhibition. Cardiovasc Res. 2014; (102): 138–147.
[86] Donnarumma, E., Ali, M.J., Rushing, A.M., Scarborough, A.L., Bradley, J.M., Organ, C.L., et al. Zofenopril protects against myocardial ischemia-reperfusion injury by increasing nitric oxide and hydrogen sulfide bioavailability. J Am Heart Assoc. 2016; (5): e003531.
[87] Wallace, J.L., Vaughan, D., Dicay, M., MacNaughton, W.K., De Nucci, G. Hydrogen sulfide-releasing therapeutics: translation to the clinic. Antioxid Redox Signal. 2018; (28): 1533–1540.
[88] Ezeriņa, D., Takano, Y., Hanaoka, K., Urano, Y., Dick, T.P. N-acetyl cysteine functions as a fast-acting antioxidant by triggering intracellular H2S and sulfane sulfur production. Cell Chem Biol. 2018; 25(4): 447–459.e4.
[89] Zanardo, R.C., Brancaleone, V., Distrutti, E., Fiorucci, S., Cirino, G., Wallace, J.L. Hydrogen sulfide is an endogenous modulator of leukocyte-mediated inflammation. FASEB J. 2006; 20(12): 2118–2120.
[90] Prince, M., Li, Y., Childers, A., Itoh, K., Yamamoto, M., Kleiner, H.E. "Comparison of citrus coumarins on carcinogen-detoxifying enzymes in Nrf2 knockout mice," Toxicol Lett. 2009; 185(3): 180–6.
[91] Ansari, M.I., Khan, M.M., Saquib, M., Khatoon, S., Hussain, M.K. "Dithiolethiones: a privileged pharmacophore for anticancer therapy and chemoprevention," Future Medicinal Chemistry. 2018; 10(10): 1241–1260.

[92] Zhang, Y., Gordon, G.B. "A strategy for cancer prevention: stimulation of the Nrf2-ARE signaling pathway". Mol. Cancer Ther. 2004; 3(7): 885–93.
[93] Iida, K., Itoh, K., Kumagai, Y. "Nrf2 is essential for the chemopreventive efficacy of oltipraz against urinary bladder carcinogenesis," Cancer Res. 2004; 64(18): 6424–31.
[94] Villeneuve, C., Guilbeau-Frugier, C., Sicard, P., Lairez, O., Ordener, C., Duparc, T. p53-PGC-1alpha pathway mediates oxidative mitochondrial damage and cardiomyocyte necrosis induced by monoamine oxidase-A upregulation: role in chronic left ventricular dysfunction in mice, Antioxid. Redox Signaling. 2013; 18(1): 5–18.
[95] Wallace, J.L., Rory, I., Blackler, W., Chan, M.V., Da Silva, G.J., Elsheikh, W., et al. Anti-inflammatory and cytoprotective actions of hydrogen sulfide: translation to therapeutics. Antioxid Redox Signal. 2015; 22(5): 398-410.
[96] Wallace, J.L., Vaughan, D., Dicay, M., MacNaughton, W.K., De Nucci, G. Hydrogen sulfide-releasing therapeutics: translation to the clinic. Antioxid Redox Signal. 2018; (28): 1533–1540.
[97] Cenac, N., Castro, M., Desormeaux, C., Colin, P., Sie, M., Ranger, M. A novel orally administered trimebutine compound (GIC-1001) is anti-nociceptive and features peripheral opioid agonistic activity and hydrogen sulphide-releasing capacity in mice. Euro. J. Pain. 2015; (20): 723–730.