Role of Hydrogen Sulfide in the Treatment of Fibrosis

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Abstract
Hydrogen sulfide (H₂S) is a biological gas, the abnormal metabolism of which has associations with the pathogenesis of fibrosis. The purpose of this paper was to determine the potential of H₂S in the prevention and treatment of fibrosis. The data is obtained mainly from articles found in the PubMed database using the keywords "fibrosis" and "hydrogen sulfide," limiting the results to those published within the last 10 years. Some additional resources have also been used, such as books and articles within journals. Evidence of decreased H₂S enzyme levels in animal models with fibrotic diseases has been found. The protective role of H₂S has been validated by the administration of exogenous H₂S donors in animal models with fibrosis. It is also evident that H₂S is involved in complex signaling pathways and ion channels that inhibit fibrosis development. These findings support the role of H₂S in the treatment of a variety of fibrotic diseases. A randomized controlled trial in fibrosis patients comparing the efficacy of exogenous H₂S and placebo in addition to standard of care can be implemented to validate this further.

Categories: Internal Medicine
Keywords: hydrogen sulfide, fibrosis

Introduction And Background
Fibrotic diseases are a fatal group of disorders affecting many people worldwide [1]. They affect many organs, including the liver, bone marrow, lung, kidney, gastrointestinal tract, skin, eye, and endocardium. They include systemic fibrotic diseases such as systemic sclerosis and organ-specific disorders, including chronic kidney disease (CKD), liver cirrhosis, idiopathic pulmonary fibrosis, and myocardial fibrosis. The underlying etiologies, as well as the molecular mechanism of many fibrotic diseases, are less clear. They all have complex pathogenetic mechanisms of an uncontrolled and progressive accumulation of fibrotic tissue in affected organs, causing their dysfunction [1]. Epithelial or endothelial damage secondary to irritants (e.g., radiation, chronic infections, toxins) triggers fibrosis’ pathogenesis. Dysfunction of the coagulation cascade and immune system causes chronic production of proteolytic enzymes, fibrogenic cytokines, growth factors, and angiogenic factors, ultimately resulting in fibrosis [2].

Local fibroblasts get attracted to the injury site by platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-ß), and tumor necrosis factor alpha (TNF-α) [3]. Later, they differentiate into myofibroblasts, which play a crucial role in fibrogenesis [4]. Myofibroblasts are the activated repair cells needed to restore tissue integrity after injury by producing and organizing the extracellular matrix (ECM) [3,4]. Malfunction of myofibroblasts is considered responsible for excessive synthesis, deposition, and remodeling of extracellular matrix proteins in fibrosis [3,4]. It results in the loss of cellular homeostasis and the disruption of typical tissue architecture, eventually causing organ fibrosis [2]. Currently, anti-fibrotic drugs (e.g., pirfenidone, nintedanib) are the only effective therapy. They are not curative but only manage to slow the rate of progression of common fibrotic diseases, such as idiopathic pulmonary fibrosis [5].

Hydrogen sulfide (H₂S) is considered the third biological gas after nitrous oxide and carbon monoxide. It acts as a gaso-neurotransmitter. It influences cellular signaling pathways and the sulfhydration of target proteins [6]. H₂S is produced endogenously by activating two major H₂S-generating enzymes (cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE)) [7]. It involves many physiological processes in the cardiovascular, neuronal, immune, respiratory, gastrointestinal, liver, and endocrine systems. It also has potent properties, such as inhibiting inflammation and oxidative stress in several organs [7,8]. Abnormal metabolism of H₂S causes damage to the structure and function of many organs [7]. All the above findings lead us to propose the association of H₂S with fibrosis pathogenesis and the potential to help treat fibrosis.

Methodology
In this review, data from clinical trials and reviews relevant to the role of H₂S in the treatment of fibrosis are displayed. The idea of this study is to reveal the role of H₂S in the prevention and treatment of fibrosis. The
Hydrogen sulfide in myocardial fibrosis

protective role of H
animal hepatic fibrosis. These findings suggest that H
of pro-fibrogenic properties and reduced oxidative stress by H
induces cell cycle arrest and apoptosis in activated hepatic stellate cells (HSCs) and attenuates carbon
al. found that in many liver diseases, such as hepatic fibrosis and hepatic cirrhosis, malfunction of hepatic
hepatic fibrosis, the metabolic levels of H
mercaptopyruvate sulfurtransferase (MST)) are all present in the liver. CSE and CBS play a significant role in
endogenous H
stellate cells (HSCs) transform into myofibroblast-like cells. These cells can proliferate and produce
Diverse stimuli, such as ethanol, viral infection, and toxins, can cause hepatic fibrosis. The activated hepatic
stellate cells (HSCs) transform into myofibroblast-like cells. These cells can proliferate and produce
extracellular matrix (ECM) deposition and fibrogenesis [9,10]. This progressive disease leads to chronic
kidney disease, a common global health challenge [11]. H2S plays a physiological role in maintaining the
kidney’s normal function and is found in discrete parts of the kidney [7,12]. Dugbartey discussed the
protective mechanisms of H2S in experimental models of chronic kidney disease (CKD) [11]. H2S under
hypoxic conditions acts as an oxygen sensor in the renal medulla and restores oxygen balance [11]. It also increases medullary flow [11]. Han et al. revealed the experimental data showing H2S deficiency leading to
renal fibrosis [13]. Wang et al. demonstrated that H2S stimulates tubular cell regeneration, reduction in
apoptosis, autophagy, and hypertrophy, which improved vascular remodeling and high blood pressure [14].
According to Qian et al., the reduction of endogenous H2S contributes to diabetic injury [15]. The supply of
exogenous H2S protects tissues from diabetic damage through anti-apoptosis and anti-fibrosis mechanisms,
inhibited oxidative stress, and inflammation [15]. Sun et al. provided evidence from experimental studies
suggesting the involvement of the H2S signaling pathway in the treatment of diabetic nephropathy [16].

Hydrogen sulfide donor molecules, such as GYY4137, have led to significant decreases in inflammation,
fibrosis, and the expression of epithelial-mesenchymal transition markers following urinary obstruction
[17]. Sodium hydrosulfide (product of the half-neutralization of H2S with sodium hydroxide) protects against
unilateral ureteral obstruction (UUO)-induced renal damage by attenuating fibrosis, oxidative stress, and
inflammation [18]. H2S also exerts a preventive effect on UUO-induced kidney damage in rats by reducing
oxidative stress [19].

There is a reduction in the levels of H2S production by renal cells in pathological conditions, including
diabetic nephropathy [15,16]. The benefits of H2S donors in kidney injury have been evident [15]. In CKD
patients and animal models, plasma H2S level has been reported to be markedly reduced [12]. Aging-induced
kidney changes have been shown to alleviate following H2S administration, probably by inhibiting signaling
pathways leading to matrix protein synthesis [20]. It exhibits potent antioxidant, anti-inflammatory, and
anti-fibrotic properties in several experimental kidney disease models [12]. It also suppresses inflammation
and oxidative stress, inhibiting activation of fibrosis-related cells and cytokine expression [14]. These
findings suggest that H2S and its transsulfuration pathway may be a potential target for developing
therapeutics for fibrosis-related diseases [21].

Hydrogen sulfide in hepatic fibrosis

Diverse stimuli, such as ethanol, viral infection, and toxins, can cause hepatic fibrosis. The activated hepatic
stellate cells (HSCs) transform into myofibroblast-like cells. These cells can proliferate and produce
extracellular matrix, leading to the destruction of the architecture of the liver parenchyma and cirrhosis [12].
The liver helps maintain plasma H2S homeostasis by regulating its production and elimination [7]. Three
endogenous H2S-producing enzymes (cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS), and 3-
mercaptopuruvate sulfortransferase (MST)) are all present in the liver. CSE and CBS play a significant role in
hepatic H2S production. In human hepatic fibrosis and cirrhosis, as well as in animal and cellular models of
hepatic fibrosis, the metabolic levels of H2S and its producing enzymes were recorded to change [12]. Mani et
al. found that in many liver diseases, such as hepatic fibrosis and hepatic cirrhosis, malfunction of hepatic
H2S metabolism may be involved [22]. Fan et al. validated that exogenous H2S inhibits proliferation and
induces cell cycle arrest and apoptosis in activated hepatic stellate cells (HSCs) and attenuates carbon
tetrachloride (CCL4)-induced hepatic fibrosis and ECM gene expression [23]. Zhang et al. displayed hindrance
of pro-fibrogenic properties and reduced oxidative stress by H2S-associated mechanism in HSCs [24].

The results mentioned above support the involvement of endogenous H2S in the pathogenesis of human and
animal hepatic fibrosis. These findings suggest that H2S may be implicated in hepatic fibrosis, and the
modulation of H2S production may represent a therapeutic remedy for liver fibrosis. To further prove the
protective role of H2S in hepatic fibrosis, more research is needed.

Hydrogen sulfide in myocaridal fibrosis
Any mechanical stretch or inflammatory stimuli can cause the proliferation and activation of cardiac fibroblasts resulting in cardiac fibrosis. It is associated with the excessive formation of extracellular matrix within the myocardium [25,26]. Locally released angiotensin II can stimulate cardiac fibroblast proliferation and increase collagen production by activating the angiotensin II type 1 (AT1) receptor [27]. Aldosterone can also induce cardiac fibrosis by exhibiting pro-inflammatory effects and directly promoting cardiac fibroblast proliferation and collagen synthesis [28]. Interstitial fibrosis is a partial manifestation of cardiac remodeling. It eventually leads to chronic heart failure [12]. H\textsubscript{2}S could protect against endoplasmic reticulum stress-induced endothelial-to-mesenchymal transition through the Src pathway [29]. There is evidence of H\textsubscript{2}S causing a reduction in fibronectin and galectin-3, the inhibition of which prevents cardiac remodeling by interfering with myocardial fibrogenesis [30]. It also inhibits the local renin-angiotensin-aldosterone system (RAAS) [12]. H\textsubscript{2}S exhibits angiogenic and anti-inflammatory actions. It also preserves mitochondrial function and reduces apoptosis [31]. H\textsubscript{2}S suppresses potassium channel (K\textsuperscript{+} channel) activity, attenuating atrial fibroblast proliferation and differentiation toward myofibroblasts [32]. GYY4137, a slow-releasing H\textsubscript{2}S donor, causes enhanced early postischemic endogenous natriuretic peptide activation [33]. It preserves cardiac function and attenuates adverse remodeling [33]. It may also exert postischemic cardioprotective effects, such as pro-angiogenesis, anti-apoptosis, anti-hypertrophy, and anti-fibrosis [33]. Meng et al. also supported the protective role of GYY4137 in myocardial fibrosis, which is by inhibiting oxidative stress, blocking the TGF-β1/Smad2 signaling pathway, and decreasing the expression of α-smooth muscle actin (α-SMA) [34]. Pan et al. provided strong evidence that exogenous H\textsubscript{2}S prevented cardiac remodeling through ECM accumulation inhibition and increased vascular density [35].

Endogenous H\textsubscript{2}S and its producing enzymes were involved in cardiac fibrosis development [36-40]. In different animal models of cardiac fibrosis, endogenous H\textsubscript{2}S levels and H\textsubscript{2}S enzyme expressions were reduced [36-40]. Exogenous H\textsubscript{2}S has demonstrated a protective effect in various animal models of cardiac fibrosis [32-34,41]. Liposomal formulations, which release H\textsubscript{2}S slowly within tissues, have exhibited enhanced cardioprotective effects in vivo via the inhibition of the TGF-β1/Smad signaling pathway [41]. Overall, all the above studies have shown the protective role of H\textsubscript{2}S in myocardial fibrosis.

**Hydrogen sulfide in pulmonary fibrosis**

Idiopathic pulmonary fibrosis is one of the most common interstitial lung diseases with debilitating dyspnoea symptoms and cough. Scarring of alveolar walls, airways, or vasculature causes irreversible lung function impairment. The significant derangement of ventilatory function and gas exchange contributes to chronic respiratory insufficiency with a severely impaired quality of life, ultimately leading to respiratory failure and death. It is a fatal disease with limited effective therapeutic options. H\textsubscript{2}S is produced endogenously in the respiratory system, and it targets epithelial cells, fibroblasts, airway, and pulmonary artery smooth muscle cells [42]. A decrease in H\textsubscript{2}S-producing enzymes and endogenous H\textsubscript{2}S levels is associated with pulmonary fibrosis development [7]. The inhibition of proliferation, migration, and differentiation of human lung fibroblasts have shown protective effects against pulmonary fibrosis [12]. The metabolism of H\textsubscript{2}S in the lungs may serve as a biomarker for specific respiratory diseases [42]. Hence, it may prove useful for the prevention and treatment of selective chronic respiratory diseases, including fibrosis.

The studies mentioned above show that endogenous H\textsubscript{2}S in the respiratory tract regulates essential functions, such as airway tone, pulmonary circulation, cell proliferation or apoptosis, fibrosis, oxidative stress, and inflammation [43]. Chronic inflammation can result from high concentrations of H\textsubscript{2}S (50-500 ppm), which can lead to pulmonary fibrosis [8].

The mechanisms of H\textsubscript{2}S in preventing fibrosis of different organs are listed in Figure 1. The abovementioned observations from the articles included in this review are shown in Table 1. Table 2 presents the comparison of current treatments of fibrosis with H\textsubscript{2}S.
### FIGURE 1: The main mechanisms of hydrogen sulfide in different organs preventing fibrosis

MMP, matrix metalloproteinase; EMT, epithelial–mesenchymal transition

<table>
<thead>
<tr>
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<th>Conclusion</th>
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<tbody>
<tr>
<td><strong>Renal fibrosis</strong></td>
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<tr>
<td>Han et al. [13]</td>
<td>$H_2S$ deficiency leads to fibrosis.</td>
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<td>$H_2S$ resulted in improved vascular remodeling and high blood pressure.</td>
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<tr>
<td>Qian et al. [15]</td>
<td>Reduced endogenous $H_2S$ contributes to diabetic injury; exogenous $H_2S$ protects tissues from diabetic damage.</td>
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<td>Sun et al. [16]</td>
<td>The $H_2S$ signaling pathway is involved in the treatment of diabetic nephropathy.</td>
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<tr>
<td>Dursun et al. [19]</td>
<td>$H_2S$ has preventive effect on UUO-induced kidney damage in rats by reducing oxidative stress.</td>
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<tr>
<td>Lee et al. [20]</td>
<td>Aging-induced kidney changes are alleviated following $H_2S$ administration by inhibiting signaling pathways leading to matrix protein synthesis.</td>
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<td><strong>Hepatic fibrosis</strong></td>
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<tr>
<td>Song et al. [12]</td>
<td>The metabolic levels of $H_2S$ and its producing enzymes were recorded to change in hepatic fibrosis.</td>
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<td>Mani et al. [22]</td>
<td>Hepatic $H_2S$ metabolism’s malfunction may be involved in many liver diseases.</td>
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<td>Fan et al. [23]</td>
<td>Exogenous $H_2S$ inhibits proliferation and induces cell cycle arrest and apoptosis in activated HSCs and attenuates CQ-induced hepatic fibrosis and ECM gene expression.</td>
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<tr>
<td>Zhang et al.</td>
<td>Diallyl trisulfide hinders pro-fibrogenic properties and reduces oxidative stress by an $H_2S$-associated mechanism in HSCs.</td>
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<td>Author(s)</td>
<td>Summary</td>
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<td>Ying et al. &lt;sup&gt;[29]&lt;/sup&gt;</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;S could protect against endoplasmic reticulum stress-induced EMT through the Src pathway.</td>
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<td>Snijder et al. &lt;sup&gt;[30]&lt;/sup&gt;</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;S causes a reduction in fibronectin and galectin-3, the inhibition of which prevents cardiac remodeling by interfering with myocardial fibrogenesis.</td>
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<td>Shen et al. &lt;sup&gt;[31]&lt;/sup&gt;</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;S exhibits angiogenic and anti-inflammatory actions; it also preserves mitochondrial function and reduces apoptosis.</td>
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<td>Sheng et al. &lt;sup&gt;[32]&lt;/sup&gt;</td>
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<td>Lilyanna et al. &lt;sup&gt;[33]&lt;/sup&gt;</td>
<td>GYY4137, a slow-releasing H&lt;sub&gt;2&lt;/sub&gt;S donor, cause enhanced early postischemic endogenous natriuretic peptide activation; it may also exert postischemic cardioprotective effects.</td>
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<td>Pan et al. &lt;sup&gt;[35]&lt;/sup&gt;</td>
<td>Exogenous H&lt;sub&gt;2&lt;/sub&gt;S prevented cardiac remodeling through ECM accumulation inhibition and increased vascular density.</td>
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<td>Tran et al. &lt;sup&gt;[41]&lt;/sup&gt;</td>
<td>Liposomal formulations, which release H&lt;sub&gt;2&lt;/sub&gt;S slowly within tissues, have exhibited enhanced cardioprotective effects in vivo via the inhibition of the TGF-β1/Smad signaling pathway.</td>
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<td>Song et al. &lt;sup&gt;[12]&lt;/sup&gt;</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;S inhibits the local RAAS.</td>
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<td>Chen et al. &lt;sup&gt;[42]&lt;/sup&gt;</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;S metabolism in the lungs is associated with respiratory diseases.</td>
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<td>Zhang et al. &lt;sup&gt;[7]&lt;/sup&gt;</td>
<td>A decrease in H&lt;sub&gt;2&lt;/sub&gt;S-producing enzymes and endogenous H&lt;sub&gt;2&lt;/sub&gt;S levels is associated with pulmonary fibrosis development.</td>
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<tr>
<td>Bazhanov et al. &lt;sup&gt;[43]&lt;/sup&gt;</td>
<td>Endogenous H&lt;sub&gt;2&lt;/sub&gt;S in the respiratory tract regulates essential functions.</td>
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</table>

**TABLE 1: Brief observation of articles included in this review**

H<sub>2</sub>S, hydrogen sulfide; UUO, unilateral ureteral obstruction; HSCs, hepatic stellate cells; CCl<sub>4</sub>, carbon tetrachloride; ECM, extracellular matrix; EMT, endothelial-to-mesenchymal transition; α-SMA, α-smooth muscle actin; RAAS, renin-angiotensin-aldosterone system.
### Fibrosis Current treatments Possible role of H₂S

**Renal**
- RAAS blocker, ETA R antagonist, TGF-β inhibitor, inflammation modulators, SGLT2 inhibitor
- RAAS inhibitors, inflammation modulators, TGF-β inhibitors, endothelin inhibitors, β-blockers, ivabradine, loop diuretics, sildenafil

Exogenous H₂S can protect the kidneys by inhibiting signaling pathways leading to matrix protein synthesis [20]. H₂S donor molecules led to significant decreases in inflammation, fibrosis, and the expression of EMT markers [17].

**Myocardial**
- Treating the underlying disorder, liver transplantation for patients with advanced stages of liver fibrosis
- Nintedanib and pirfenidone are associated with very high morbidity and mortality

Exogenous H₂S prevents cardiac remodeling through ECM accumulation inhibition and increased vascular density [35]. Liposomal formulations, which release H₂S slowly within tissues, have exhibited enhanced cardioprotective effects in vivo via the inhibition of the TGF-β1/Smad signaling pathway [41]. QYY4137, a H₂S donor, can cause enhanced early postischemic endogenous natriuretic peptide activation. It may also exert postischemic cardioprotective effects [33].

**Hepatic**
- Nintedanib and pirfenidone are associated with very high morbidity and mortality

Exogenous H₂S inhibits proliferation and induces cell cycle arrest and apoptosis in activated hepatic stellate cells [23]. It also hinders pro-fibrogenic properties and reduces oxidative stress by H₂S-associated mechanisms in HSCs [24].

**Pulmonary**
- Nintedanib and pirfenidone are associated with very high morbidity and mortality

Endogenous H₂S in the respiratory tract regulates essential functions [43]. The association of H₂S metabolism in lungs with respiratory diseases can be used to prevent this from occurring [42].

### TABLE 2: Comparison of current treatments of fibrosis with hydrogen sulfide

<table>
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<tr>
<th>Fibrosis</th>
<th>Current treatments</th>
<th>Possible role of H₂S</th>
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### Conclusions

In this review, the role of H₂S in fibrotic diseases, a major fatal irreversible group of disorders for which no current treatment has proved effective in stopping the progression, is discussed. It has been demonstrated that H₂S plays a protective role in developing fibrosis in the lung, liver, kidney, and heart. This protective effect in fibrosis has been established by the administration of exogenous H₂S donors in animal models. H₂S inhibits fibrosis development by involving targeted signaling pathways and suppressing the K⁺ channel activity. These results imply that the H₂S-producing enzymes or H₂S itself might be a potential therapeutic target for fibrosis. To better understand the potential role of H₂S in the treatment of fibrotic disorders, a randomized controlled trial comparing the efficacy of H₂S and placebo in addition to the current standard of care should be performed.

### Additional Information

**Disclosures**

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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remodeling, preserves cardiac function and modulates the natriuretic peptide response to ischemia

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