Hepatic Medicine: Evidence and Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Literature Review on the Regulatory Effects of Hydrogen Sulfide in Non-Alcoholic Fatty Liver Disease (NAFLD)

Shan Zhou[1], Baoyi Sun[1], Zongyuan Xuan[1], Guanning Zhong[1], Xiaolei Sun[2], Jun Yan[1]

[1]Department of Forensic Medicine, Medical School of Nantong University, Nantong, Jiangsu, People's Republic of China; [2]Department of Pathogenic Biology, Medical School of Nantong University, Nantong, Jiangsu, People's Republic of China

Correspondence: Jun Yan, Email forensicyan@ntu.edu.cn

Introduction: This paper reviews the regulatory effects of hydrogen sulfide (H_2S) in non-alcoholic fatty liver disease (NAFLD). The research background indicates that NAFLD has become one of the most common chronic liver diseases worldwide, with a complex pathogenesis involving insulin resistance and lipid metabolism disorders. Hydrogen sulfide, as an important gaseous signaling molecule, exerts protective effects in NAFLD through multiple pathways, including antioxidant, anti-inflammatory, lipid metabolism regulation, apoptosis inhibition, and insulin resistance improvement. This article provides a detailed summary of the research overview of NAFLD, the biological characteristics of hydrogen sulfide, its mechanisms of action in NAFLD, empirical studies, and evaluates and prospects current research, aiming to provide a new theoretical basis and experimental support for the treatment of NAFLD.

Purpose: This literature review aims to systematically synthesize the regulatory roles of hydrogen sulfide (H_2S) in non-alcoholic fatty liver disease (NAFLD). It provides a comprehensive overview of NAFLD research, the biological characteristics of H_2S, the mechanisms underlying H_2S's action in NAFLD, and relevant empirical studies. Additionally, the review evaluates the current state of research and prospects future directions, with the goal of offering novel theoretical foundations and experimental support for NAFLD treatment.

Patients and Methods: It adopts a comprehensive literature analysis approach. Analyze literature on NAFLD pathogenesis, H_2S (synthesis/function), and NAFLD treatments (in vitro, animal models, clinical studies).

Results: NAFLD links to insulin resistance/inflammation; H_2S protects against NAFLD by mitigating inflammation, oxidative stress, and lipid accumulation, while improving insulin sensitivity and inhibiting apoptosis. However, its precise mechanisms, stage-specific effects, and therapeutic safety require further clinical validation.

Conclusion: Hydrogen sulfide (H_2S), a gaseous signal, exerts multi-mechanistic protective effects in NAFLD. Current limitations include unclear signaling mechanisms and lack of targeted delivery systems. Future research should focus on stage-specific mechanisms, optimized H_2S donors, and combination therapies for NAFLD treatment.

Keywords: hydrogen sulfide, H_2S, non-alcoholic fatty liver disease, NAFLD, regulatory mechanisms, antioxidant, anti-inflammatory, lipid metabolism

Introduction

Research Background and Significance

Non-alcoholic fatty liver disease (NAFLD) is a manifestation of metabolic syndrome in the liver and has become one of the most common chronic liver diseases globally, with a prevalence rate as high as 32.4%.[1] It is characterized by abnormal lipid accumulation in the liver and is closely associated with metabolic syndrome, obesity, and insulin resistance. With the increasing incidence of obesity and metabolic syndrome, NAFLD not only affects liver health but also significantly increases the risk of cirrhosis, liver cancer, and cardiovascular events, imposing a heavy burden on both patients' health and the economy. However, current treatment strategies for NAFLD are limited in effectiveness. Therefore, in-depth research into its pathogenesis and exploration of new therapeutic targets are of great significance.

Received: 16 October 2025
Accepted: 23 December 2025
Published: 27 December 2025

Hydrogen sulfide (H_2S), as the third gaseous signaling molecule after nitric oxide (NO) and carbon monoxide (CO), plays an important role in physiological and pathological processes.[2] Studies have shown that H_2S is involved in regulating intracellular redox status, inflammatory responses, energy metabolism, and lipid metabolism, and has protective effects on various diseases. In recent years, the role of H_2S in the occurrence and development of NAFLD has gradually attracted attention, and exploring its regulatory mechanisms in NAFLD may provide possibilities for developing new therapeutic strategies.

Overview of Non-Alcoholic Fatty Liver Disease Research

NAFLD is a metabolic stress-induced liver injury closely related to insulin resistance and genetic susceptibility. Its pathological features include excessive fat deposition in hepatocytes, with a wide disease spectrum ranging from simple steatosis (NAFL) to non-alcoholic steatohepatitis (NASH), NASH-related liver fibrosis, cirrhosis, and hepatocellular carcinoma. The pathophysiological mechanisms of NAFLD involve multiple cellular pathways and molecular factors, mainly including insulin resistance, lipid metabolism disorders, chronic inflammatory responses, and mitochondrial dysfunction.[3]

Insulin Resistance and Lipid Metabolism Disorders

Insulin resistance is one of the core pathophysiological mechanisms of NAFLD. Insulin resistance leads to decreased sensitivity of the liver and peripheral tissues to insulin, thereby causing lipid metabolism disorders. Excessive deposition of fatty acids in the liver is a major characteristic of NAFLD, which is closely related to insulin resistance.[4] In addition, overconsumption of nutrients and gastrointestinal dysbiosis can also exacerbate lipid metabolism abnormalities.[5]

Chronic Inflammatory Responses

NAFLD is considered a chronic low-grade inflammatory state. The increase in pro-inflammatory factors and abnormalities in cytokine signaling play important roles in the occurrence and development of the disease. For example, the activation of Kupffer cells and apoptosis of hepatocytes can trigger inflammatory responses, further leading to the development of non-alcoholic steatohepatitis (NASH).[6,7]

Mitochondrial Dysfunction

Mitochondrial dysfunction in the liver plays an important role in the pathogenesis of NAFLD. Abnormal mitochondrial function can lead to decreased fatty acid oxidation capacity, thereby exacerbating fat deposition in hepatocytes. In addition, mitochondrial dysfunction can also cause oxidative stress, further aggravating hepatocyte injury.[8] In the pathogenesis of NAFLD, insulin resistance leads to increased hepatic lipid synthesis and deposition, which is an important link in the development of the disease. Meanwhile, mitochondrial dysfunction induces oxidative stress and lipid peroxidation, further worsening hepatic steatosis and inflammation. Moreover, the expression and release of inflammatory factors promote hepatic inflammatory responses, accelerating the progression of NAFLD to NASH and liver fibrosis.

Biological Characteristics and Physiological Functions of Hydrogen Sulfide

Hydrogen sulfide (H_2S) is a colorless, flammable, and toxic gas. However, in biological organisms, it functions as an important gaseous signaling molecule with a wide range of biological functions. H_2S is mainly synthesized in mammals from L-cysteine through the catalysis of cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3-MST). Its biosynthesis and metabolic mechanisms are complex, involving multiple enzymes and regulatory pathways.

Biosynthesis of H_2S

Hydrogen sulfide is primarily synthesized through the following four enzymatic pathways in the body (as shown in Figure 1).

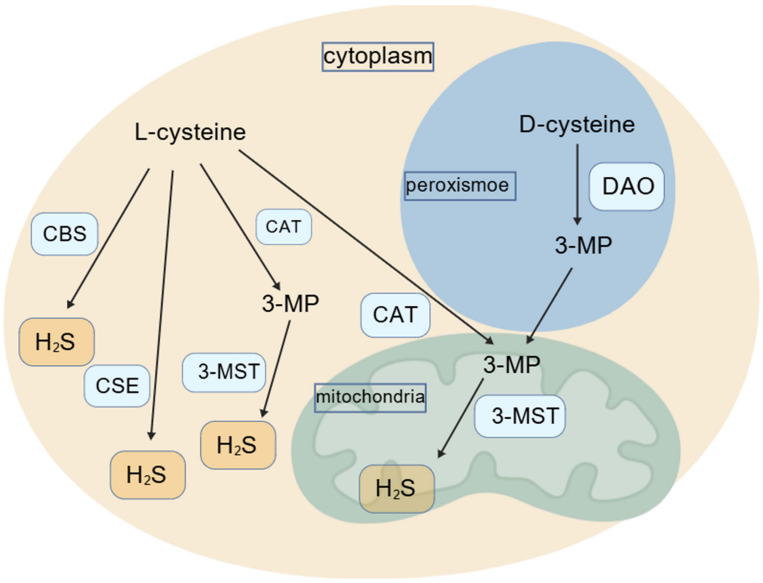

Figure 1 Endogenous Hydrogen Sulfide Production Pathways.
Notes: The figure illustrates four enzymatic pathways of H_2S synthesis in mammals: (1) CBS catalyzes cysteine and homocysteine to generate H_2S; (2) CSE decomposes cystathionine to produce H_2S; (3) 3-MST converts 3-mercaptopyruvate to H_2S in the nervous system; (4) DAO oxidizes D-cysteine to 3-mercaptopyruvate, which is metabolized to H_2S by mitochondrial 3-MST (predominantly in the brain and kidneys).

Cystathionine β-Synthase (CBS)

CBS is one of the main enzymes for H_2S synthesis, utilizing cysteine and homocysteine as substrates to generate cystathionine and H_2S.

Cystathionine γ-Lyase (CSE)

CSE generates cysteine, α-ketobutyrate, and H_2S by breaking down cystathionine, representing another important pathway for H_2S synthesis.

3-Mercaptopyruvate Sulfurtransferase (3-MST)

3-MST catalyzes the generation of H_2S from 3-mercaptopyruvate, mainly functioning in the nervous system.[9]

DAO/3-MST Pathway

Kimura[10] first identified a fourth pathway for H_2S generation in the body. In the presence of DAO, D-cysteine is oxidized to generate 3-mercaptopyruvate (3-MP), ammonia (NH_3), and hydrogen peroxide (H_2O_2). Subsequently, 3-MP enters the mitochondria and is metabolized to H_2S by 3-MST. Since DAO is mainly distributed in the brain and kidneys, this H_2S generation pathway is believed to exist only in these two organs.

Metabolism of H_2S

The metabolism of hydrogen sulfide mainly occurs through the following pathways.

Oxidative Metabolism

H_2S can be oxidized in the body to form thiosulfate, sulfite, and sulfate, which are eventually excreted in urine.

Methylation Metabolism

H_2S can be methylated to form methanethiol and dimethyl sulfide, which are further metabolized and excreted.

Binding with Metal Ions

H_2S can bind with metal ions such as iron and copper to form insoluble sulfides, thereby reducing its toxicity. H_2S can

https://doi.org/10.2147/HMER.S574921

freely permeate biological membranes and exert effects on a series of biological targets, participating in the regulation of intracellular redox status, inflammatory responses, energy metabolism, and lipid metabolism.[9]

Physiological Functions of H_2S

Anti-Inflammatory and Anti-Apoptotic Effects

Hydrogen sulfide protects cells from damage by inhibiting inflammatory responses and apoptosis. For example, SPRC (a garlic-derived compound) can slowly release hydrogen sulfide, enhancing anti-inflammatory and anti-apoptotic effects.[11]

Metabolic Regulation

Hydrogen sulfide plays an important role in regulating energy and lipid metabolism. It can regulate insulin secretion and oxidative stress, thereby influencing the energy balance and metabolic state of cells. Additionally, hydrogen sulfide can delay cell aging and maintain cell function by regulating the generation of persulfides. It also promotes fatty acid β-oxidation and inhibits lipid synthesis, reducing lipid accumulation in the liver. Studies have shown that H_2S can shift the metabolism of free fatty acids (FFAs) from lipid accumulation to β-oxidation, thereby improving lipid metabolism disorders.[12,13]

Signal Transduction in the Central Nervous System

In the central nervous system, hydrogen sulfide regulates homeostasis and cell signaling, playing an important physiological role. It is considered an emerging gaseous neurotransmitter that can regulate neuronal transmission and cell function.[14,15]

Antioxidant Effects

Hydrogen sulfide delays cell aging and maintains cell function by scavenging reactive oxygen species (ROS) and regulating the generation of persulfides. Studies have shown that persulfidation is an evolutionarily conserved modification that prevents cysteine oxidation, preserving protein function. Hydrogen sulfide can activate ATP-sensitive potassium channels in endothelial cells, dilate blood vessels, inhibit adhesion between endothelial cells and leukocytes, reduce oxidative stress, and maintain vascular homeostasis.[16]

In summary, H_2S, as an important gaseous signaling molecule, participates in cell signaling, regulating physiological and pathophysiological processes of cells through various mechanisms. Its roles in energy metabolism, anti-inflammatory, anti-apoptotic, neuronal transmission, and vascular regulation make it an important target for the study of non-alcoholic fatty liver disease (NAFLD) and lipid metabolism. Future research can further explore the potential applications of hydrogen sulfide in disease treatment.

Current Treatment Strategies for NAFLD

At present, the treatment of NAFLD mainly includes lifestyle interventions and pharmacological treatments. Lifestyle interventions such as dietary adjustments, increased physical activity, and weight loss are the foundation of NAFLD management. In terms of pharmacological treatment, insulin sensitizers, antioxidants, lipid-lowering drugs, etc., are used to improve metabolic disorders and alleviate liver injury.[17]

Pharmacological Therapies

Biguanides

Biguanides are the first-line drugs for the treatment of type II diabetes, especially for overweight and obese patients. Metformin is the most commonly used biguanide, which improves insulin resistance by reducing hepatic glucose production and increasing peripheral tissue sensitivity to insulin.[18,19] Additionally, metformin has cardiovascular protective effects and can reduce the risk of diabetic complications.

Thiazolidinediones (TZDs)

TZDs improve insulin sensitivity by activating peroxisome proliferator-activated receptor γ (PPAR-γ). These drugs

increase glucose uptake in adipose tissue and muscle, thereby reducing blood glucose levels.[20] Common drugs include rosiglitazone and pioglitazone.

GLP-1 Receptor Agonists

GLP-1 receptor agonists increase insulin secretion, inhibit glucagon secretion, and delay gastric emptying by mimicking the action of the gut hormone GLP-1. These drugs not only improve glycemic control but also help with weight loss.[21] Common drugs include exenatide and liraglutide.

Vitamin E

Vitamin E, as an antioxidant, is thought to improve insulin sensitivity and reduce oxidative stress in some studies, although its role in diabetes treatment requires further research.[22] Vitamin E is usually used as an adjunctive therapy to improve the overall health of patients with metabolic syndrome.[23]

Gut Microbiota and Its Metabolites

Regulating the structure and function of the gut microbiota is closely related to the prevention and treatment of NAFLD.[24] Taking a combination of Bifidobacterium can increase the number of beneficial bacteria in the gut. Through the mutual restraint between different bacterial species, the structure of the gut microbiota is optimized. This helps reduce the functional damage caused by endotoxins produced by harmful bacteria such as Escherichia coli and Enterococcus to various organs and tissues, and aids in restoring the gut's immune barrier function, thereby alleviating liver inflammation and enhancing the overall therapeutic effect.[25] Additionally, gut microbiota regulation as an adjunctive therapy can effectively improve liver function, serum adiponectin, fasting insulin, blood lipids, BMI levels, and Fibroscan controlled attenuation parameters in patients with non-alcoholic fatty liver disease.[26]

Other Treatment Strategies

Other relevant literature has explored various treatment strategies for non-alcoholic fatty liver disease (NAFLD), including lifestyle changes, the application of bioactive substances, and pharmacological treatments.[27] In terms of lifestyle adjustments, particular emphasis is placed on the Mediterranean diet and regular physical exercise. The Mediterranean diet promotes weight loss and alleviates NAFLD symptoms by restricting the intake of high-calorie, high-sugar, and high-fat foods; while physical exercise helps significantly reduce liver fat content and the risk of progression from NAFLD to non-alcoholic steatohepatitis (NASH). In the exploration of bioactive substances, peptides, alkaloids, polyphenols, silymarin, and other components are mentioned for their potential value in NAFLD treatment. These substances exert multiple effects through antioxidant, anti-inflammatory, and lipid metabolism regulation.[28] In terms of pharmacological treatments, the application status and research progress of statins, peroxisome proliferator-activated receptor (PPAR) agonists, cenicriviroc, and farnesoid X receptor (FXR) agonists are detailed.[29]

Challenges and Prospects for H_2S-Based Therapies

Multiple reports have highlighted the diverse regulatory effects of hydrogen sulfide (H_2S) in NAFLD. There is ongoing research and development of H_2S-related drugs. However, given the transient release and oxidative susceptibility of H_2S, its practical application faces many challenges. These challenges have spurred researchers to develop donors that can achieve controlled, sustained, and targeted release of H_2S. Currently,[30] some compounds that simulate endogenous H_2S release have attracted widespread attention. These include the pioneering H_2S donor compound GYY4137 in the field of H_2S donors; the naproxen H_2S donor derivative ATB-34 with anti-inflammatory effects, which can be used as a sedative for colonoscopy; the H_2S donor of mebeverine maleate for colonoscopy sedation; the biological GIC-1001; and the cardioprotective SG1002.[31]

Association Between NAFLD and H_2S Levels

In non-alcoholic fatty liver disease (NAFLD), the accumulation of triglycerides in hepatocytes is the main pathological change, leading to hepatic steatosis. The main causes can be summarized into four aspects: excessive uptake of free fatty acids from the blood by the liver; enhanced de novo synthesis of fatty acids; weakened fatty acid oxidation; and impaired

https://doi.org/10.2147/HMER.S574921

output of triglycerides from the liver in the form of lipoproteins. When the liver's capacity to take up triglycerides exceeds its clearance capacity, triglycerides accumulate in hepatocytes, leading to NAFLD. Hydrogen sulfide has dual effects on adipose tissue and the liver. On one hand, hydrogen sulfide accelerates the storage of fatty acids in adipose tissue and inhibits lipid synthesis in the liver. On the other hand, hydrogen sulfide increases fatty acid breakdown and oxidation in the liver, alleviating lipid accumulation in the liver. The activity of CSE directly affects the generation of H_2S, and its expression levels are usually reduced in patients with NAFLD. Supplementation with H_2S or its precursors can restore its function.[9,32]

Non-alcoholic steatohepatitis (NASH) is a disease characterized by hepatic steatosis, fibrosis, and inflammation in the absence of other liver-damaging factors such as excessive alcohol consumption or drugs. The protective effects of hydrogen sulfide on NASH may be realized through antioxidant stress, anti-inflammatory, and anti-fibrotic mechanisms. In an MCD-induced NASH rat model, the hepatoprotective effects of endogenous hydrogen sulfide were observed. Specifically, the expression of CBS and CSE was significantly reduced, leading to decreased liver hydrogen sulfide levels, resulting in increased liver fat accumulation, oxidative stress, and expression of inflammatory factors in mice. Administration of exogenous hydrogen sulfide donors significantly improved liver function, reduced liver lipid deposition, and decreased hepatocyte apoptosis.[31]

In liver fibrosis, it has been reported in CCl4-induced liver fibrosis models that the protein expression of CSE and CBS is inhibited, leading to decreased H_2S content. Exogenous H_2S donors (such as NaHS) can improve liver function and reduce liver fibrosis. Moreover, H_2S alleviates oxidative stress and inflammatory responses through various mechanisms, inhibits the activation of hepatic stellate cells, reduces collagen deposition, and thereby alleviates liver fibrosis.[33]

Research Review on the Mechanisms of Action Between Non-Alcoholic Fatty Liver Disease and Hydrogen Sulfide

In recent years, numerous studies have made significant progress in exploring the mechanisms of hydrogen sulfide in NAFLD through in vitro and in vivo experiments. The following is a detailed analysis of its specific effects and regulatory mechanisms.

Role in Hepatic Inflammation

Hydrogen sulfide alleviates liver inflammation through various mechanisms, including antioxidant and anti-inflammatory effects. H_2S can scavenge reactive oxygen species (ROS) and nitrogen radicals in the body, reducing oxidative stress-induced hepatocyte damage. Studies have shown that exogenous H_2S donors can significantly reduce oxidative stress levels in NAFLD models, protecting hepatocytes from lipid peroxidation damage. Additionally, H_2S inhibits the expression and release of inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), thereby alleviating liver inflammation and reducing the severity of NAFLD.[34] H_2S exerts its anti-inflammatory and anti-fibrotic effects by activating signaling pathways such as AMPK and Nrf2.[12,35]

Role in Hepatic Fibrosis

Liver fibrosis is a key step in the progression of NAFLD to cirrhosis, and H_2S exhibits significant anti-fibrotic effects in this process.

Inhibition of Fibrosis-Related Gene Expression

H_2S downregulates the expression of pro-fibrotic factors such as TGF-β, reducing collagen deposition and thereby inhibiting fibrosis.[36,37]

Promotion of Hepatocyte Regeneration

H_2S enhances the regenerative capacity of hepatocytes, repairing damaged tissues and thereby slowing the progression of fibrosis.[9,38]

Epigenetic Regulation

H_2S may also regulate the expression of genes related to inflammation and fibrosis through mechanisms such as DNA methylation and histone modification.[9,38] H_2S can enhance the binding ability of NFYB transcription factor to the promoter regions of Tet1 and Tet2 genes by directly mediating the sulfhydryl modification of its thiol group, thereby up-regulating the expression levels of TET1/2. Subsequently, TET enzymes catalyze the oxidation of 5mC to 5hmC, promoting the active demethylation process at key gene loci such as Foxp3.[39]

Metabolic Pathway Regulation

H_2S improves liver metabolic functions by influencing lipid and carbohydrate metabolism, indirectly reducing the risk of fibrosis.[9,40]

Regulation of Lipid Metabolism

Hydrogen sulfide plays an important role in regulating lipid metabolism. Studies have shown that H_2S promotes fatty acid β-oxidation, thereby reducing lipid accumulation in the liver. Additionally, H_2S regulates the expression of lipid metabolism-related genes, such as peroxisome proliferator-activated receptor γ (PPARγ) and sterol regulatory element-binding protein 1c (SREBP1c), improving the balance of lipid metabolism in the liver and thereby alleviating the steatosis of non-alcoholic fatty liver disease (NAFLD).[41] In methionine choline-deficient (MCD) induced non-alcoholic steatohepatitis (NASH) models, H_2S donors (such as NaHS) significantly reduced liver triglyceride and cholesterol levels by increasing PPARα expression and decreasing SREBP-1c gene expression, thereby alleviating steatosis. Moreover, H_2S activates the AMPK-mTOR signaling pathway to promote fatty acid β-oxidation and reduce lipid accumulation in the liver. In high-fat diet (HFD) induced NAFLD models, H_2S donors significantly reduced hypertriglyceridemia and improved NAFLD by activating hepatic autophagy flux and the AMPK-mTOR signaling pathway.[42] H_2S can also regulate other mechanisms in lipid metabolism. For example, by inhibiting the expression of 3-mercaptopyruvate sulfurtransferase (MPST) to reduce H_2S generation, SREBP-1c is upregulated, promoting fat synthesis. Conversely, inhibiting MPST can reduce free fatty acid (FFAs) levels and increase H_2S generation, thereby improving lipid metabolism.[43]

Inhibition of Cell Apoptosis

Apoptosis of hepatocytes is an important mechanism in the progression of NAFLD. Studies have shown that H_2S can inhibit the apoptotic process of hepatocytes, protecting them from death signals. H_2S regulates the expression of apoptosis-related genes such as B-cell lymphoma-2 (Bcl-2) and Bcl-2 associated X protein (Bax), thereby inhibiting hepatocyte apoptosis and alleviating the condition of NAFLD.[44]

Regulation of Autophagy

Autophagy is a self-degradation process within cells that is important for maintaining cell homeostasis and responding to stress stimuli. Studies have shown that H_2S can induce autophagy in hepatocytes, promoting the clearance and regeneration of damaged organelles, thereby alleviating the condition of NAFLD. H_2S regulates the expression of autophagy-related genes such as microtubule-associated protein 1 light chain 3 (LC3) and autophagy-related gene 5 (Atg5), thereby promoting autophagy in hepatocytes and improving liver function.[45]

Improvement of Insulin Resistance

Insulin resistance is an important mechanism in the development of NAFLD. Studies have shown that H_2S can enhance insulin signaling pathways, improving insulin resistance and thereby alleviating the condition of NAFLD. H_2S regulates the expression of insulin signaling-related genes such as insulin receptor substrate 1 (IRS1) and protein kinase B (Akt), thereby enhancing insulin sensitivity, promoting glucose uptake and utilization, and improving metabolic abnormalities in NAFLD.[46,47]

In summary, H_2S exerts protective effects in various tissues and organs, including the cardiovascular system, nervous system, digestive system, and liver. In the liver, H_2S alleviates hepatocyte damage through antioxidant and anti-inflammatory effects, improves hepatic steatosis by regulating lipid metabolism, protects hepatocyte survival by

inhibiting apoptosis, and promotes the clearance and regeneration of damaged organelles by inducing autophagy. Additionally, H_2S enhances insulin signaling pathways, improving insulin resistance and thereby alleviating the condition of NAFLD.

Discussion

Research Evaluation and Prospects

Research Evaluation

Current research on the role of H_2S in NAFLD has made significant progress, yet several limitations persist. For instance, although H_2S is known to modulate multiple signaling pathways—such as AMPK, Nrf2, and TGF-β—the precise molecular mechanisms and cross-talk among these pathways remain incompletely understood.[12,35–37] Existing studies often focus on single pathways in isolation, and integrative models are lacking.

Moreover, individual differences in H_2S metabolism and response have been observed but are underexplored. For example, variations in the expression of H_2S-synthesizing enzymes (CBS, CSE, 3-MST) due to genetic or epigenetic factors may influence disease progression and treatment efficacy.[9,38] Clinical and preclinical studies also suggest that H_2S levels fluctuate across NAFLD stages, with lower endogenous H_2S in advanced fibrosis, yet how these changes affect therapeutic outcomes is not well characterized.[31,33]

These gaps highlight the need for more stratified research—considering disease stage, genetic background, and metabolic phenotype—to clarify H_2S's role in NAFLD and inform personalized treatment approaches.

Future Prospects

1. Stage-specific mechanism exploration: Investigate H_2S's regulatory differences in NAFLD stages (eg, whether it inhibits lipogenesis in NAFL and fibrosis in NASH) using clinical samples and stratified animal models.

2. H_2S donor optimization: Develop biomaterial-based targeted delivery systems (eg, liver-specific nanoparticles) to achieve on-demand H_2S release at lesions, reducing systemic toxicity.

3. Combination therapy development: Combine H_2S donors with:

3.1 Lifestyle interventions: Mediterranean diet + H_2S donors to synergistically improve insulin resistance;

3.2 Existing drugs: Metformin + H_2S donors to enhance hepatic lipid metabolism;

3.3 Gut microbiota modulators: Bifidobacterium + H_2S donors to amplify anti-inflammatory effects.

Conclusion

Hydrogen sulfide exerts protective regulatory effects in NAFLD via antioxidation, anti-inflammation, lipid metabolism modulation, apoptosis inhibition, autophagy induction, and insulin resistance improvement, making it a promising therapeutic target. However, current research is limited by unclear multi-signaling pathway crosstalk, unelucidated stage-specific and individual differences, and unvalidated H_2S donor safety/efficacy in large-scale clinical trials. Future studies should focus on stage-specific mechanisms, targeted donor development, and evidence-based combination therapies to advance H_2S-based NAFLD treatments and address the global burden of this disease. However, current research has limitations: the specific regulatory mechanisms of H_2S in multiple signaling pathways remain unclear, and its differential roles across individuals and NAFLD stages need further exploration. Additionally, the safety, efficacy, and targeted delivery of H_2S donor drugs (to avoid gas toxicity and achieve controlled release at lesions) require validation through large-scale clinical trials.

Abbreviations

H_2S, Hydrogen sulfide; NAFLD, Non-Alcoholic Fatty Liver Disease; CBS, Cystathionine β-synthase; CSE, Cystathionine γ-lyase; DAO, D-amino acid oxidase; 3-MST, 3-mercaptopyruvate sulfurtransferase; CAT, Cysteine aminotransferase; 3-MP, 3-mercaptopyruvate; TNF-α, Tumor necrosis factor-α; IL-6, Interleukin-6; PPAR, Peroxisome proliferator-activated receptor; SREBP1c, Sterol regulatory element-binding protein 1c; AMPK, Adenosine 5'-monophosphate-activated protein kinase; Nrf2, Nuclear factor erythroid 2-related factor 2; TGF-β, Transforming growth factor-β; IRS1, Insulin receptor substrate 1; Akt, Protein kinase B; LC3, Microtubule-associated protein 1 light chain 3;

Atg5, Autophagy-related gene 5; NAFL, Non-alcoholic fatty liver; NASH, Non-alcoholic steatohepatitis; MCD, Methionine choline-deficient; HFD, High-fat diet; MPST, 3-mercaptopyruvate sulfurtransferase; Bcl-2, B-cell lymphoma-2; Bax, Bcl-2 associated X protein.

Acknowledgments

NSFC No. 81300346

Disclosure

The authors report no conflicts of interest in this work.

References

1. Teng ML, Ng CH, Huang DQ, et al. Global incidence and prevalence of nonalcoholic fatty liver disease. *Clin Mol Hepatol*. 2023;29(Suppl):S32–S42. doi:10.3350/cmh.2022.0365
2. Munteanu C, Munteanu D, Onose G. Hydrogen sulfide (H_2S) - therapeutic relevance in rehabilitation and balneotherapy Systematic literature review and meta-analysis based on the PRISMA paradigm. *Balneo PRM Res J*. 2021;12(3):176–195. doi:10.12680/balneo.2021.438
3. Ruan X, Chen Y. Metabolic inflammation and the development of non-alcoholic fatty liver disease. *Chin J Digestion*. 2020;40(9):581–584. doi:10.3760/cma.j.cn311367-20200518-00328
4. Utzschneider KM, Kahn SE. Review: the role of insulin resistance in nonalcoholic fatty liver disease. *J Clin Endocrinol Metab*. 2006;91(12):4753–4761. doi:10.1210/jc.2006-0587
5. Gao Z, Xie J. Research progress on the pathogenesis and treatment of nonalcoholic fatty liver disease. *Adv Clin Med*. 2024;14(4):1192–1198. doi:10.12677/acm.2024.1441142
6. Shi J. Zhejiang da xue xue bao. *Yi Xue Ban*. 2016;45(1):98–101. doi:10.3785/j.issn.1008-9292.2016.01.16
7. Huapeng L, Xinrong Z, Guanlin L, et al. Epidemiology and clinical outcomes of metabolic (dysfunction)-associated fatty liver disease. *J Clin Transl Hepatol*. 2021;9(6):972–982. doi:10.14218/JCTH.2021.00201
8. Yang BQ, Yin JY, Wang Q. The mechanism of action of mitochondrial dysfunction in the development of non-alcoholic fatty liver disease. *J Clin Hepatol*. 2024;40(1):147–150. doi:10.12449/JCH240124
9. Xu W, Cui C, Cui C, et al. Hepatocellular cystathionine γ lyase/hydrogen sulfide attenuates nonalcoholic fatty liver disease by activating farnesoid X receptor. *Hepatology*. 2022;76(6):1794–1810. doi:10.1002/hep.32577
10. Shibuya N, Koike S, Tanaka M, et al. A novel pathway for the production of hydrogen sulfide from D-cysteine in mammalian cells. *Nat Commun*. 2013;4(1):1366. doi:10.1038/ncomms2371
11. Hieu BT, Ying Y, Lingling C, et al. A novel liposomal S-propargyl-cysteine: a sustained release of hydrogen sulfide reducing myocardial fibrosis via TGF-β1/smad pathway. *Int J Nanomed*. 2019;14:10061–10077. doi:10.2147/IJN.S216667
12. Dongdong W, Zheng N, Kunqing Q, et al. Exogenous hydrogen sulfide mitigates the fatty liver in obese mice through improving lipid metabolism and antioxidant potential. *Med Gas Res*. 2015;5(1):1. doi:10.1186/s13618-015-0030-2
13. Cui X, Li C, He S, et al. Exogenous H_2S reduces oxidative stress induced by lipid mixture in HepG2 cells through USP22/SIRT1 axis. *Sci Rep*. 2025;15(1):23129. doi:10.1038/s41598-025-04924-2
14. Jin QY, Yuan H, Liu FY, et al. Role of hydrogen sulfide in health and disease. *MedComm*. 2024;5(9):e661. doi:10.1002/mco2.661
15. Sandesh P, Hyung-Joo C, Junyang J, et al. Physiological importance of hydrogen sulfide: emerging potent neuroprotector and neuromodulator. *Oxid Med Cell Longev*. 2016; 2016:9049782.
16. Wenjing X. Endogenous hydrogen sulfide metabolism and function in liver. *Chemistry Life*. 2020;40(08):1289–1297. doi:10.13488/j.smhx.20200230
17. Sun J, Jin X, Li Y. Current strategies for nonalcoholic fatty liver disease treatment (Review). *IntJ Mol Med*. 2024;54(4). doi:10.3892/ijmm.2024.5412
18. Pala L, Barbaro V, Dicembrini I, et al. The therapy of insulin resistance in other diseases besides type 2 diabetes. *Eating Weight Disord*. 2014;19(3):275–283. doi:10.1007/s40519-014-0139-y
19. ShinHae L, ShiYoung P, Soo CC. Insulin resistance: from mechanisms to therapeutic strategies. *Diabet Metabol J*. 2022;46(1):15–37. doi:10.4093/dmj.2021.0280
20. Ying M, Dai K. The effect of metformin combined with pioglitazone therapy on glucose-lipid metabolism and pancreatic islet function in patients with type 2 diabetes mellitus. *Guizhou Med J*. 2025;49(03):374–375.
21. Nowak K, Łupina K, Romac A, et al. Therapeutic potential of GLP-1 receptor agonists in metabolic associated steatotic liver disease. *Ann Pharmacother*. 2025;10600280251322002.
22. Khaliq A, Badshah H, Shah Y. Combination therapy with vitamin E and ertugliflozin in patients with non-alcoholic fatty liver disease and type 2 diabetes mellitus: a randomized clinical trial. *Irish J Med Sci*. 2025;(prepublish):1–10.
23. Jana B, Monika M, Martina B, et al. Pharmaceutical drugs and natural therapeutic products for the treatment of type 2 diabetes mellitus. *Pharmaceuticals*. 2021;14(8):806. doi:10.3390/ph14080806
24. Mengyao L, Wu X, Xu Q, et al. Current research status of the relationship between non-alcoholic fatty liver disease and gut microbiota metabolites. *J Med Inform*. 2025;38(04):171–175+181.
25. Yao J, Xiaobo H, Zhang X. Analysis of application effect of gut microbiota regulation in patients with non-alcoholic fatty liver disease. *Chin Community Doctors*. 2024;40(35):65–67.
26. Gao M, Zhao B, Zhou L. Effects of intestinal flora regulation therapy on liver function and blood lipid metabolism in patients with non-alcoholic fatty liver. *J North Sichuan Med College*. 2021;36(12):1597–1599+1608.

27. Sun J, Jin X, Li Y, et al. Current strategies for nonalcoholic fatty liver disease treatment (Review). *IntJ Mol Med*. 2024;54(4):88. doi:10.3892/ijmm.2024.5412
28. Wan X, Ma J, Bai H, et al. Drug advances in NAFLD: individual and combination treatment strategies of natural products and small-synthetic-molecule drugs. *Biomolecules*. 2025;15(1):140. doi:10.3390/biom15010140
29. Rong L, Zou J, Ran W, et al. Advancements in the treatment of non-alcoholic fatty liver disease (NAFLD). *Front Endocrinol*. 2023;13:1087260. doi:10.3389/fendo.2022.1087260
30. Zhao Y, Tong J, Dahong L, et al. Research progress in pathophysiological functions, determination and donor drugs of hydrogen sulfide. *Central South Pharm*. 2022;20(10):2336–2342.
31. Xianghui L, Kaixin J, Yantian R, et al. Hydrogen sulfide and its donors: keys to unlock the chains of nonalcoholic fatty liver disease. *Int J Mol Sci*. 2022;23(20):12202. doi:10.3390/ijms232012202
32. Fu X, Zhang Q, Chen Y, et al. Exogenous hydrogen sulfide improves non-alcoholic fatty liver disease by inhibiting endoplasmic reticulum stress/NLRP3 inflammasome pathway. *Mol Cell Biochem*. 2025;480(6):3813–3839. doi:10.1007/s11010-025-05220-3
33. Lee J-H, Seung-Soon I. Function of gaseous hydrogen sulfide in liver fibrosis. *BMB Reports*. 2022;55(10):481–487. doi:10.5483/BMBRep.2022.55.10.124
34. Tang S-P, Mao X-L, Chen Y-H, et al. Reactive oxygen species induce fatty liver and ischemia-reperfusion injury by promoting inflammation and cell death. *Front Immunol*. 2022;13:870239. doi:10.3389/fimmu.2022.870239
35. Jinghui L, Gui C, Fei L, et al. Research progress on hydrogen sulfide and non-alcoholic fatty liver disease. *Chin J Liver Dis*. 2024;12(02):62–66. doi:10.3969/j.issn.1674-7380.2024.02.014
36. Hong X, Qingrong X, Jia J, et al. Hydrogen sulfide protects against myocardial ischemia and reperfusion injury by activating AMP-activated protein kinase to restore autophagic flux. *Biochem Biophys Res Commun*. 2015;458(3). doi:10.1016/j.bbrc.2015.01.155
37. Shi-Wei Z, Man Z, Min Z. Liraglutide reduces lipid accumulation in steatotic L-02 cells by enhancing autophagy. *Mol Med Reports*. 2014;10(5):2351–2357. doi:10.3892/mmr.2014.2514
38. Xiaodi F. The improvement effect and mechanism of exogenous hydrogen sulfide on non-alcoholic fatty liver disease by regulating endoplasmic reticulum stress/ NLRP3 inflammasome. Henan University; 2025.
39. Yang R, Qu C, Zhou Y, et al. Hydrogen sulfide promotes Tet1- and Tet2-mediated Foxp3 demethylation to drive regulatory T cell differentiation and maintain immune homeostasis. *Immunity*. 2015;43(2):251–263. doi:10.1016/j.immuni.2015.07.017
40. Rose P, Dymock BW, Moore PK. GYY4137, a novel water-soluble, H_2S-releasing molecule. *Methods Enzymol*. 2015. doi:10.1016/bs.mie.2014.11.014
41. Comas F, Moreno-Navarrete JM. The impact of H_2S on obesity-associated metabolic disturbances. *Antioxidants*. 2021;10(5):633. doi:10.3390/antiox10050633
42. Geng B, Cai B, Liao F, et al. Increase or decrease hydrogen sulfide exert opposite lipolysis, but reduce global insulin resistance in high fatty diet induced obese mice. *PLoS One*. 2013;8(9):e73892. doi:10.1371/journal.pone.0073892
43. Yang G, Ju Y, Fu M, et al. Cystathionine gamma-lyase/hydrogen sulfide system is essential for adipogenesis and fat mass accumulation in mice. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2018;1863(2):165–176. doi:10.1016/j.bbalip.2017.11.008
44. Xu LH, Wan RS, An Y, et al. Targeting cell death in NAFLD: mechanisms and targeted therapies. *Cell Death Discovery*. 2024;10(1):399. doi:10.1038/s41420-024-02168-z
45. Al Sayegh R, Wan J, Caër C, et al. Defective autophagy in CD4 T cells drives liver fibrosis via type 3 inflammation. *Nat Commun*. 2025;16(1):3860. doi:10.1038/s41467-025-59218-y
46. Palma R, Pronio A, Romeo M, et al. The role of insulin resistance in fueling NAFLD pathogenesis: from molecular mechanisms to clinical implications. *J Clin Med*. 2022;11(13):3649. doi:10.3390/jcm11133649
47. Sun Y, Jia Y. Hydrogen sulfide alleviates insulin resistance by reducing apoptosis of adipose cells in diabetic mice. *China J Modern Med*. 2017;27(09):13–18.