Combined effect of hydrogen sulfide and mesenchymal stem cells on mitigating liver fibrosis induced by bile duct ligation: Role of anti-inflammatory, anti-oxidant, anti-apoptotic, and anti-fibrotic biomarkers

Rehab Ahmed Mohammed [1] , Heba Mohamed Shawky [2] , Laila Ahmed Rashed [3] , Hala Mohamed Elhanbuli [4] , Dalia Nabil Abdelhafez [4] , Eman Sayed Said [5, 6,] Ramadan Mostafa Shamardan [7] , Rania Hosny Mahmoud [8]

١ Department of Physiology, Faculty of Medicine, Fayoum University, Egypt
2 Department of Physiology, Faculty of Medicine, Cairo University, Egypt
3 Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Cairo University, Egypt
4Departments of Pathology, Faculty of Medicine, Fayoum University, Egypt
5 Departments of Pharmacology, Faculty of Medicine, Fayoum University, Egypt
6Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Buraydah 52571, Saudi Arabia
7 Departments of Anatomy, Faculty of Medicine, Fayoum University, Egypt
8Departments of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Fayoum University, Egypt

Objective(s): Liver fibrosis eventually develops into cirrhosis and hepatic failure, which can only be treated with liver transplantation. We aimed to assess the potential role of hydrogen sulfide (H2 S) alone and combined with bone marrow-derived mesenchymal stem cells (BM-MSCs) on hepatic fibrosis induced by bile-duct ligation (BDL) and to compare their effects to silymarin. **Materials and Methods:** Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), and alkaline phosphatase (ALP) were investigated in serum. Gene expression levels of CBS (cystathionine β-synthase), CSE (cystathionine γ-lyase), and alpha-smooth muscle actin (α- SMA) were measured in liver tissues using RT-PCR. Hepatic protein kinase (Akt) was assessed by Western blot assay. Liver oxidative stress markers, malondialdehyde (MDA), and reduced glutathione (GSH) were analyzed by the colorimetric method. Lipocalin-2 (LCN2) and transforming growth factor-β (TGF-β) were measured using ELIZA. Liver tissues were examined by H&E and Masson trichome staining for detection of liver necrosis or fibrosis. Caspase 3 expression was evaluated by immunohistochemistry. **Results:** H2 S and BM-MSCs ameliorated liver function and inhibited inflammation and

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oxidative stress detected by significantly decreased serum ALT, AST, ALP, TB, and hepatic MDA, Akt, TGF-β, LCN2, and α-SMA expression and significantly increased CBS and CSE gene expression levels. They attenuated hepatic apoptosis evidenced by decreased hepatic caspase expression. **Conclusion:** Combined treatment with H2 S and BM-MSCs could attenuate liver fibrosis induced by BDL through mechanisms such as anti-inflammation, anti-oxidation, anti-apoptosis, anti-fibrosis, and regenerative properties indicating that using H2 S and MSCs may represent a promising approach for management of cholestatic liver fibrosis.
Key words: Bile duct ligation, Hydrogen sulfide, Liver fibrosis, Mesenchymal stem cells

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أ.د/ حنان عبدالمنعم	أ.د/ عاصم العيسوي