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# Oxidative stress in viral hepatitis

Huseyin Erdal[1], Hacer Ozlem Kalayci[2]

[1]Aksaray University, Faculty of Medicine, Department of Medical Genetics, Aksaray, Türkiye
[2]Ordu University, Faculty of Medicine, Department of Medical Microbiology, Ordu, Türkiye

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**Abstract**

Viral hepatitis, primarily caused by hepatitis B virus (HBV) and hepatitis C virus (HCV), is a leading cause of chronic liver disease worldwide. Accumulating evidence suggests that oxidative stress (OS) plays a pivotal role in the pathogenesis and progression of viral hepatitis. OS occurs due to a disproportion between reactive oxygen species (ROS) generation and antioxidant protection, resulting in damage to cells and tissues. In viral hepatitis, viral proteins and immune-mediated inflammatory responses contribute to excessive ROS generation, resulting in oxidative damage to hepatocytes. This damage manifests as lipid peroxidation, DNA damage, and protein oxidation, which in turn promote hepatic inflammation, fibrosis, and hepatocellular carcinoma. Furthermore, OS has been implicated in the resistance to antiviral therapy observed in some patients. This review highlights the molecular mechanisms underlying OS in viral hepatitis, its contribution to liver disease progression, and its impact on treatment outcomes. Understanding these mechanisms may open new avenues for therapeutic strategies targeting OS, thereby improving the management of viral hepatitis and associated liver diseases.

**Keywords:** Oxidative stress, viral hepatitis, hepatitis C

## Introduction

Viral hepatitis (VH) is a major global health concern, affecting millions of individuals worldwide [1]. VH describes liver inflammation resulting from infection by hepatotropic viruses, such as hepatitis A, B, C, D, and E [2]. These infections can lead to acute and chronic liver diseases, including cirrhosis and hepatocellular carcinoma (HCC). Despite advances in antiviral therapy, hepatitis caused by viruses continues to be a major contributor to liver disease and death. Oxidative stress (OS) occurs as a result of the disruption of the balance between free radicals and antioxidants [3,4]. It has been implicated in the pathogenesis of various liver diseases, including those caused by viral infections. In the context of VH, OS plays a crucial role in liver injury, influencing disease progression and response to treatment [5]. OS has emerged as a critical factor in the advancement of liver disease in VH [6]. By exploring the molecular mechanisms linking viral infections to OS, this review seeks to shed light on potential therapeutic targets for mitigating liver damage and improving patient outcomes.

VH represents a significant global health burden, affecting hundreds of millions of individuals worldwide. Each of these viruses belongs to a distinct family, with unique epidemiological characteristics, transmission routes, and clinical outcomes [7]. Despite their differences, these viruses share a common target: the liver, an organ vital to numerous metabolic processes, including detoxification, bile production, and the regulation of blood sugar and cholesterol levels [8]. Hepatitis B and C are particularly concerning due to their propensity to cause chronic infections, induce severe liver-related complications such as cirrhosis and hepatocellular carcinoma (HCC) [9,10]. According to the World Health Organization (WHO), approximately 296 million people were living with chronic hepatitis B, and 58 million with chronic hepatitis C as of 2019, with these conditions contributing to nearly 1.4 million deaths annually [11]. In contrast, hepatitis A and E typically cause acute, self-limiting infections, while hepatitis D, a satellite virus requiring co-infection with hepatitis B, can exacerbate the severity of hepatitis B-related disease [2]. The pathogenesis of VH involves a complex interplay between

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**Corresponding Author:** Huseyin Erdal, Aksaray University, Faculty of Medicine, Department of Medical Genetics, Aksaray, Türkiye
Email: herdalyfa@gmail.com

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viral replication and the host immune response. The immune system's attempt to eradicate the virus often results in liver inflammation and damage [12]. Over time, chronic inflammation can lead to progressive liver fibrosis, cirrhosis, and eventually liver failure or even cancer. Understanding the mechanisms underlying this liver injury is crucial for developing effective strategies to prevent, diagnose, and treat VH [13]. This review intends to present an in-depth analysis of VH, highlighting the significance of OS in the development of liver injury.

## 1. Viral Hepatitis and Oxidative Stress

### Pathogenesis of Viral Hepatitis

The hepatitis viruses exhibit distinct modes of transmission and pathogenesis, but they share a common target: the liver [8]. Hepatitis B and C viruses (HBV and HCV) are of particular concern due to their potential to cause chronic infections [6]. Following infection, these viruses replicate within hepatocytes, eliciting an immune response that can lead to liver inflammation and damage [14]. Liver injury in VH is mainly facilitated by the host's immune response to viral antigens. Cytotoxic T lymphocytes (CTLs) serve a crucial function in recognizing and destroying infected hepatocytes [15]. However, this immune response can also result in collateral damage to the liver. The interaction between viral elements and the host's immune system creates a complex environment that promotes OS, further exacerbating liver injury. OS arises when the generation of ROS exceeds the body's capacity to neutralize them or fix the harm they inflict [16]. ROS are highly reactive molecules capable of causing damage to cellular components such as lipids, proteins, and DNA [3].

In the context of VH, ROS can be generated through several mechanisms. Hepatocytes produce ROS as a byproduct of viral replication and the host immune response [17]. The inflammation and immune response triggered by the infection can further exacerbate ROS production.

## 2. Mechanisms Linking Viral Hepatitis to Oxidative Stress

HBV infection is associated with the production of ROS through the activity of the viral X protein (HBx). HBx can modulate various cellular processes, including mitochondrial function, leading to increased ROS production [18]. This OS contributes to liver cell injury and has been implicated in the development of liver fibrosis and HCC [19]. HCV is particularly known for its strong association with OS. The HCV core protein, as well as the viral-induced activation of NADPH oxidases and mitochondria, contributes to the production of ROS in infected hepatocytes [20]. The resulting OS is a key factor in the progression of liver fibrosis and the increased risk of HCC in chronic HCV infection. The host immune response to hepatitis viruses involves the activation of immune cells, such as cytotoxic T lymphocytes and macrophages, which can produce ROS as part of their antiviral activity [21]. While this helps control the infection, the excessive production of ROS can also cause collateral damage to liver tissue, contributing to inflammation and fibrosis.

## 3. Impact of Oxidative Stress on Liver Pathology in Viral Hepatitis

OS is a key driver of liver injury in VH. ROS can damage hepatocyte membranes through lipid peroxidation, alter protein function, and induce DNA mutations [22]. These effects contribute to cell death, inflammation, and the stimulation of liver stellate cells, which play a key role in generating extracellular matrix elements that contribute to the development of fibrosis. Chronic OS in the liver can promote the progression from fibrosis to cirrhosis and eventually to HCC. The continuous oxidative damage to DNA can lead to mutations that drive the transformation of normal hepatocytes into cancerous cells [23]. Additionally, OS can promote angiogenesis and disrupt normal cellular signaling pathways, further contributing to cancer development.

## 4. Therapeutic Implications

Given the role of OS in the pathogenesis of VH, antioxidants have been explored as potential therapeutic agents. Compounds such as N-acetylcysteine (NAC), vitamin E, and other antioxidants aim to reduce ROS levels and mitigate liver damage. However, the clinical efficacy of these treatments remains under investigation, and further research is needed to determine the most effective strategies for targeting OS in hepatitis patients [24]. Antiviral therapies that reduce viral load, combined with antioxidant treatments, may provide a dual approach to managing VH. By reducing both the viral burden and the OS associated with infection, these combined therapies could potentially improve patient outcomes [25].

## 5. Mechanisms of Resistance via Oxidative Stress

### Induction of Viral Mutations

OS increases the mutation rate of viral genomes through the oxidation of nucleic acids. High mutation rates can give rise to antiviral-resistant variants. For instance, RNA viruses, like hepatitis C virus (HCV) and HIV, which already have high mutation rates, may become more resistant when oxidative damage is induced. OS can interfere with the metabolism of antiviral drugs, particularly in the liver, leading to the diminished efficacy of treatments. Increased ROS can alter the function of drug-metabolizing enzymes, impacting how antivirals are processed and decreasing their bioavailability or effectiveness.

# Conclusion

The relationship between VH and OS is complex and multifaceted, with OS playing a central role in the liver damage seen in chronic hepatitis B and C infections. Understanding this relationship is critical for developing effective therapeutic strategies to prevent and treat the long-term complications of VH, including liver fibrosis, cirrhosis, and HCC.

**Conflict of Interests**
*The authors declare that there is no conflict of interest in the study.*

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## References


1. Lanini S, Ustianowski A, Pisapia R, et al. Viral hepatitis: etiology, epidemiology, transmission, diagnostics, treatment, and prevention. Infect Dis Clin North Am. 2019;33:1045-62.
2. Castaneda D, Gonzalez AJ, Alomari M, et al. From hepatitis A to E: a critical review of viral hepatitis. World J Gastroenterol. 2021;27:1691-715.
3. Özcan O, Erdal H, Çakırca G, Yönden Z. Oxidative stress and its impacts on intracellular lipids, proteins and DNA. J Clin Exp Invest. 2015;6:331-6.
4. Ozcan O, Erdal H, Yonden Z. Biochemical aspect of oxidative stress related to ischemia-reperfusion damage. mkutfd. 2015;6:27-33.
5. Stehbens WE. Oxidative stress in viral hepatitis and AIDS. Exp Mol Pathol. 2004;77:121-32.
6. Sevastianos VA, Voulgaris TA, Dourakis SP. Hepatitis C, systemic inflammation and oxidative stress: correlations with metabolic diseases. Expert Rev Gastroenterol Hepatol. 2020;14:27-37.
7. Odenwald MA, Paul S. Viral hepatitis: past, present, and future. World J Gastroenterol. 2022;28:1405-29.
8. Pisano MB, Giadans CG, Flichman DM, et al. Viral hepatitis update: Progress and perspectives. World J Gastroenterol. 2021;27:4018-44.
9. Jeng WJ, Papatheodoridis GV, Lok ASF. Hepatitis B. Lancet. 2023;401:1039-52.
10. Preciado MV, Valva P, Escobar-Gutierrez A, et al. Hepatitis C virus molecular evolution: transmission, disease progression and antiviral therapy. World J Gastroenterol. 2014;20:15992-6013.
11. Cortesi PA, Fornari C, Conti S, et al. Hepatitis B and C in Europe: an update from the Global Burden of Disease Study 2019. Lancet Public Health. 2023;8:e701-16.
12. Koziel MJ. Immunology of viral hepatitis. Am J Med. 1996;100:98-109.
13. Muratori L, Lohse AW, Lenzi M. Diagnosis and management of autoimmune hepatitis. BMJ. 2023;380:e070201.
14. Kanda T, Sasaki R, Masuzaki R, et al. Co-occurrence of hepatitis A infection and chronic liver disease. Int J Mol Sci. 2020;21:6384.
15. Ganesan M, Wang W, Mathews S, et al. Ethanol attenuates presentation of cytotoxic T-lymphocyte epitopes on hepatocytes of HBV-infected humanized mice. Alcohol Clin Exp Res. 2022;46:40-51.
16. Erdal H, Günaydın F, Karaoğlanoğlu S. Oxidative stress in asthma. Journal of Sport and Health Researches.2023; 4:62-70.
17. Guillin OM, Vindry C, Ohlmann T, Chavatte L. Selenium, selenoproteins and viral infection. Nutrients. 2019;11:2101..
18. Liu GZ, Xu XW, Tao SH, et al. HBx facilitates ferroptosis in acute liver failure via EZH2 mediated SLC7A11 suppression. J Biomed Sci. 2021;28:67.
19. Roehlen N, Crouchet E, Baumert TF. Liver fibrosis: mechanistic concepts and therapeutic perspectives. Cells. 2020;9:875.
20. Anticoli S, Amatore D, Matarrese P, et al. Counteraction of HCV-induced oxidative stress concurs to establish chronic infection in liver cell cultures. Oxid Med Cell Longev. 2019;2019:6452390. Erratum in: Oxid Med Cell Longev. 2019;2019:3712969.
21. Park SH, Rehermann B. Immune responses to HCV and other hepatitis viruses. Immunity. 2014;40(1):13-24.
22. Czaja MJ. Cell signaling in oxidative stress-induced liver injury. Semin Liver Dis. 2007;27(4):378-89.
23. Gabbia D, Cannella L, De Martin S. The role of oxidative stress in NAFLD-NASH-HCC transition-focus on NADPH oxidases. Biomedicines. 2021;9:687.
24. Day BJ. Antioxidant therapeutics: Pandora's box. Free Radic Biol Med. 2014;66:58-64.
25. Sodano F, Gazzano E, Fruttero R, Lazzarato L. NO in viral infections: role and development of antiviral therapies. Molecules. 2022;27:2337.