Magna Scientia Advanced Research and Reviews

eISSN: 2582-9394

Cross Ref DOI: 10.30574/msarr

Journal homepage: https://magnascientiapub.com/journals/msarr/

(RESEARCH ARTICLE)

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Effect of *Curcuma longa* Extract on 8-OHdG Expression in Mice Model of Alcohol-Induced Hepatitis

Bintang Aulia Nur Ika Putri [1], Willy Sandhika [2,*] and Husin Thamrin [3]

[1] *Student of Medical Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[2] *Department of Anatomic Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[3] *Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*

Magna Scientia Advanced Research and Reviews, 2025, 15(02), 063-068

Publication history: Received 18 October 2025; revised on 25 November 2025; accepted on 27 November 2025

Article DOI: https://doi.org/10.30574/msarr.2025.15.2.0140

Abstract

Introduction: Hepatic steatosis, an early stage of fatty liver disease, can progress to more severe liver conditions such as steatohepatitis, fibrosis, and cirrhosis if left untreated. Excessive alcohol consumption is a primary cause, leading to oxidative stress in the liver, which can be detected by the biomarker 8-OHdG. *Curcuma longa*, containing curcumin, is known for its antioxidant and hepatoprotective properties, potentially mitigating liver oxidative damage.

Methods: This study investigated the effects of *Curcuma longa* extract on oxidative stress in a mouse model of alcohol-induced liver damage. Male mice were divided into four groups: normal rats as a control group (K1), alcohol-treated group (P1), *Curcuma longa* extract-treated group (P2), and alcohol plus *Curcuma longa* extract-treated group (P3). The 8-OHdG expression was assessed using immunohistochemistry (IHC) to evaluate oxidative stress in liver cells.

Results: The alcohol-treated group (P1) showed the highest 8-OHdG expression, indicating significant oxidative stress. The *Curcuma longa* extract group (P2) did not show significant differences compared to the control group, suggesting no added oxidative stress. In contrast, the combination group (P3) exhibited reduced 8-OHdG expression, highlighting the hepatoprotective effect of *Curcuma longa* extract.

Conclusion: These findings suggest that *Curcuma longa* extract can reduce oxidative stress in alcohol-induced liver damage without harming normal liver function, offering potential therapeutic benefits for preventing liver damage caused by excessive alcohol consumption.

Keywords: Healthy Life-Style; Hepatitis; *Curcuma longa*; 8-Ohdg; Oxidative Stress

1. Introduction

Hepatic steatosis, an early manifestation of fatty liver disease, is a condition that affects a significant proportion of the global population. If left untreated, it can progress to more severe liver diseases such as steatohepatitis, fibrosis, and cirrhosis [1]. Over 25% of the global population experiences varying degrees of hepatic steatosis, with alcohol consumption, obesity, diabetes mellitus, and poor dietary habits being major contributing factors [2]. In Asia, the prevalence of hepatic steatosis is notably high, with an estimated 22.6% of the population affected [3], while in Indonesia, the prevalence is even higher at 30.6%, particularly in individuals aged 40-49 years [4]. Alcohol consumption is a primary cause of hepatic steatosis [5]. This accumulation triggers oxidative stress, which is linked to liver damage, as observed in elevated levels of the oxidative stress marker, 8-Hydroxy-2-Deoxyguanosine (8-OHdG) [6].

* Corresponding author: Willy Sandhika

Current treatments for steatohepatitis focus on alcohol cessation, corticosteroids to reduce inflammation, and antifibrotic therapies to prevent further liver damage [7]. However, these treatments have limitations, including the adverse long-term effects of corticosteroids and the inability to significantly reverse liver damage [8]. An emerging alternative is *Curcuma longa*, commonly known as turmeric, which contains curcumin. Curcumin has been shown to possess antioxidant, anti-inflammatory, and hepatoprotective properties that can protect the liver from oxidative damage with fewer side effects. Several studies have highlighted curcumin's potential in reducing oxidative damage in animal models of alcohol-induced hepatitis [9], as well as its ability to enhance antioxidant defenses and prevent the occurrence of oxidative stress-related diseases [10].

Research has demonstrated that *Curcuma longa* possesses hepatoprotective, antioxidant, anti- inflammatory, and antifibrotic properties [11]. It can reduce lipid accumulation and regulate lipid metabolism in the liver, offering a promising therapeutic option for fatty liver conditions. *C. longa* extract can reduce hepatic steatosis and mitigate liver damage caused by alcohol consumption [12]. Despite these findings, there is limited research on the specific mechanisms by which *C. longa* reduces oxidative stress, particularly through the modulation of 8-OHdG expression [13].

The novelty of this research lies in the evaluation of *C. longa* extract's ability to reduce oxidative stress in an alcohol-induced mouse model by assessing the expression of 8- OHdG as a biomarker of oxidative damage. This study aims to provide new insights into the potential of *Curcuma longa* as a therapeutic or adjunctive treatment for oxidative liver damage caused by excessive alcohol consumption, addressing the gap in understanding its precise mechanisms in oxidative stress reduction.

2. Methods

2.1. Animal model

This research is an experimental laboratory research using a true experimental design with a randomized post- test only control group design. The sample used consisted of 28 male mice (*Mus musculus*) weighing 30–35 grams and aged 4–5 months. The mice selected for this study were healthy, active, and free from anatomical abnormalities. The mice were divided into four treatment groups as follows:

- Control group (K1): No alcohol or *Curcuma longa* extract administered
- Treatment group I (P1): Alcohol induced without *Curcuma longa* extract
- Treatment group II (P2): *Curcuma longa* extract administered without alcohol
- Treatment group III (P3): Alcohol induced and *Curcuma longa* extract administered

The research was conducted at the Department of Biochemistry and Department of Anatomic Pathology Laboratories, Faculty of Medicine, Universitas Airlangga, Surabaya. The study has obtained ethical clearance from the Health Research Ethics Committee, Faculty of Medicine, Airlangga University, Surabaya, with approval number 112/EC/KEPK/FKUA/2024.

2.2. *Curcuma longa* ethanol extract preparation

The *Curcuma longa* extract was prepared using the maceration method. The *Curcuma longa* rhizome powder was obtained from Materia Medika Batu. *Curcuma longa* powder were placed in a macerator and mixed with 3.5 liters of 96% ethanol solvent. The mixture was soaked for 24 hours at room temperature. After soaking, the macerate was filtered using filter paper and vacuum-pumped, then re-macerated. The resulting macerate was evaporated at 50°C using an evaporator until a thick extract was obtained.

2.3. Induction of alcohol and *C.longa* ethanol extract

The extract used was 96% ethanol extract of *Curcuma longa* at a dose of 100 mg/kgBW, administered orally using a feeding tube.

2.4. 8-OHdG Immunohistochemistry assay

Microscopic examination of the liver was performed by dissecting the liver from the treated mice. The liver was dissected a day after the induction of alcohol and *Curcuma longa* extract. The liver was fixed in 10% formalin for 24 hours, then processed using the paraffin embedding method and sectioned with a microtome. The sections were then stained with Immunohistochemistry (IHC) to assess the expression of 8-OHdG, an oxidative damage biomarker. The parameters were examined under a binocular light microscope at 400x magnification across 5 visual fields. For hydropic

degeneration, a 10x10 box graticule was used to assist with counting. Tissue preparation and observation were conducted in the Anatomical Pathology Laboratory, Faculty of Medicine, Airlangga University.

2.5. Statistical analysis

Statistical analysis was performed using SPSS version 16. The Shapiro-Wilk test was used to assess the normality of the data distribution, while Levene's test was applied to evaluate data homogeneity. As the data did not meet the assumptions for One-Way ANOVA, Welch ANOVA was employed instead. To identify significant differences between the groups, post hoc analysis was carried out using the Games-Howell test. A p-value of less than 0.05 was considered statistically significant.

3. Results

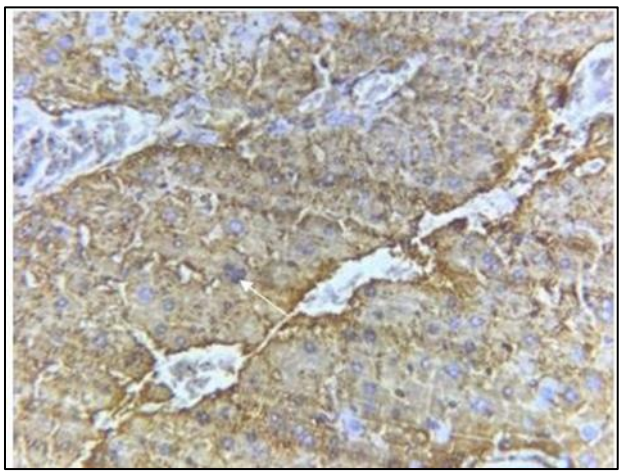
3.1. Expression of 8-OHdG

The expression of 8-OHdG was assessed in hepatocyte cytoplasm, and the data presented in Table 1 indicates notable differences in the number of 8-OHdG-positive hepatocytes across the experimental groups.

Table 1 Mean value, standard deviation, minimum value, and maximum value of 8-OhdG

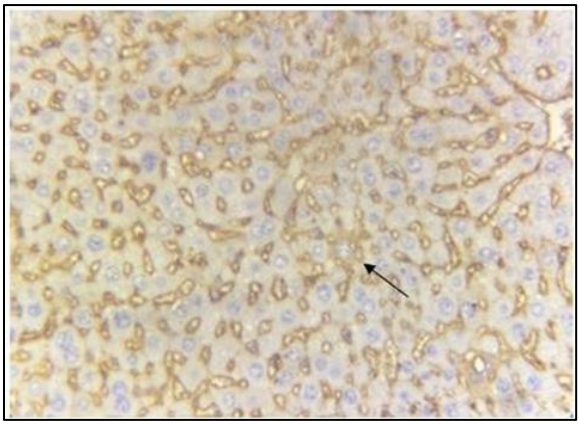
No	Groups	N	8-OHdG			
			Mean	SD	Min	Max
1	K1	6	33.88	5.74	23.33	40.00
2	P1	6	242.06	23.57	205.90	273.30
3	P2	6	31.10	4.17	23.33	35.00
4	P3	6	77.73	7.82	66.50	86.60

From Table 1 above, the data shows that the number of hepatocyte cells expressing 8-OHdG in the alcohol-induced hepatitis model group (P1) is more pronounced compared to the K1, P2, and P3 groups.



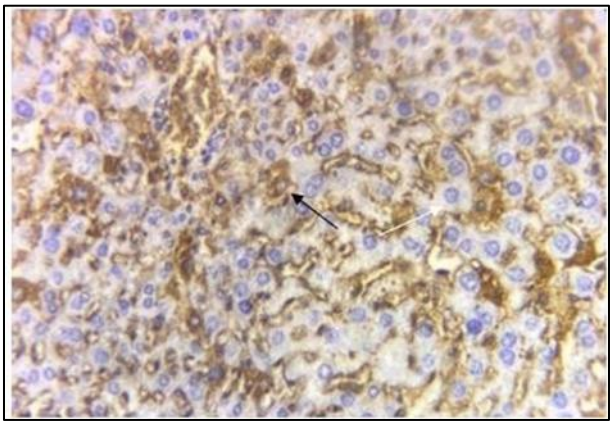
Note: White arrows = Hepatocyte cells expressing 8- OHdG

Figure 1 Histopathological image of 8-OHdG expression in the liver of the alcohol-induced hepatitis model. IHC staining at 40x magnification



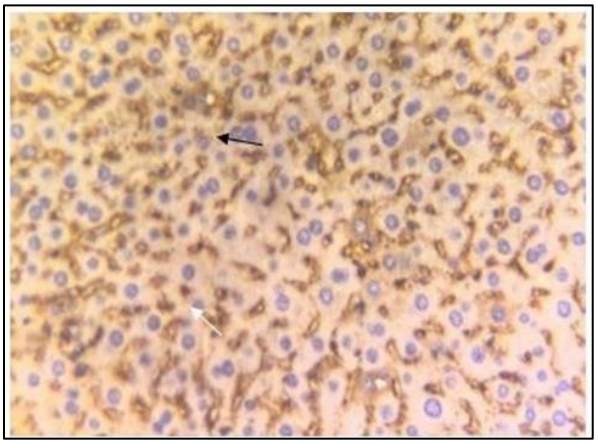
Note: Black arrows = Hepatocyte cells expressing 8-OhdG

Figure 2 Histopathological image of 8-OHdG expression in the liver of the non-hepatitis model treated with *C.longa* extract. IHC staining at 40x magnification.



Note: Black arrows = Hepatocyte cells expressing 8-OHdG Note: White arrows = Hepatocyte cells not expressing 8- OhdG

Figure 3 Histopathological image of 8-OHdG expression in the liver of the alcohol-induced hepatitis model treated with 100mg/kg body weight *C.longa* extract). IHC staining at 40x magnification.



Note: White arrows = Normal hepatocyte cells

Figure 4 Histopathological image of 8-OHdG expression in the liver of the non-hepatitis model with no treatment. IHC staining at 40x magnification. Note: Black arrows = Hepatocyte cells expressing 8- OHdG

4. Discussion

The results of this study showed that the alcohol-induced group (P1) exhibited a significant increase in 8-OHdG expression, indicating high oxidative stress in the liver. This was confirmed by a statistical significance of p = 0.000, showing that alcohol consumption induces significant oxidative DNA damage, as evidenced by elevated 8-OHdG levels. Chronic alcohol consumption increases 8-OHdG, a biomarker of DNA damage [14].

In the *Curcuma longa* extract group (P2), there was no significant difference in 8-OHdG expression compared to the control group (K1, p = 0.775). This suggests that *Curcuma longa* extract does not induce oxidative stress in normal liver conditions, demonstrating its safety and non-toxic effects on healthy hepatocytes. Curcumin, the active compound in *Curcuma longa*, neutralizes ROS and enhances antioxidant enzyme activity [10].

In the group receiving both alcohol and *Curcuma longa* extract (P3), there was a significant reduction in 8-OHdG expression compared to the alcohol-only group (P1, p = 0.000). This supports the hepatoprotective effect of *Curcuma longa*, where curcumin acts to reduce oxidative damage by suppressing ROS production. Although *Curcuma longa* was effective in reducing oxidative stress, it did not fully restore liver function to normal levels. This indicates that while the extract has therapeutic potential, further research is needed to explore its long-term efficacy.

The comparison between P1, P2, and P3 showed that *Curcuma longa* extract significantly reduced 8-OHdG expression in both the P2 (non-alcoholic) and P3 (alcoholic) groups, with a statistical significance of p = 0.000. This demonstrates that curcumin protects liver cells from oxidative stress, as confirmed by [15], who found that curcumin activates the Nrf-2 pathway, enhancing antioxidant defense.

Furthermore, the comparison between P2 and P3 revealed that P3 had a higher 8-OHdG expression than P2 due to the prior alcohol exposure, though *Curcuma longa* still significantly reduced 8-OHdG expression in P3 compared to P1. This shows that *Curcuma longa* can function both as a preventive and therapeutic agent, offering protection even after alcohol- induced damage. These findings support the research of [16], who showed that *Curcuma longa* helps reduce oxidative stress and provides protective effects against liver damage.

Furthermore, curcumin's ability to block the activation of NF-κB, a transcription factor associated with inflammation, provides additional insight into the anti-inflammatory properties of *Curcuma longa* in the liver. This mechanism contributes to faster hepatocyte regeneration, as observed by [17]. *Curcuma longa* also suppresses CYP2E1 activity, the enzyme responsible for alcohol metabolism, thereby reducing ROS production.

5. Conclusion

The expression of 8-OHdG in the control group (K1) was low, indicating that no oxidative stress occurred in normal conditions. In the alcohol-induced group (P1), there was a significant increase in 8-OHdG, confirming that alcohol causes high oxidative stress in the liver. The *Curcuma longa* extract group (P2), which did not receive alcohol, showed no significant increase in 8-OHdG, suggesting that the extract does not induce oxidative stress and is safe for normal hepatocytes. In the group treated with both alcohol and *Curcuma longa* extract (P3), 8-OHdG expression significantly decreased, demonstrating the protective antioxidant effect of *Curcuma longa* against alcohol-induced oxidative stress. The findings suggest that *Curcuma longa* has significant antioxidant and hepatoprotective properties, helping to maintain redox balance in hepatocytes, without causing additional oxidative stress in normal conditions. Future research should investigate the molecular mechanisms responsible for the hepatoprotective effects of *Curcuma longa* and explore its potential therapeutic uses in liver diseases associated with oxidative stress.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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