IBN SINA

Ibn Sina Journal of Medical Science, Health & Pharmacy
Vol. 4, No. 9, 2026, pp. 22-40
ISSN 3104-6428
https://ibn-sina-journal-of-medical-sciences.jo

Effects of 28-Day Sub-Lethal Glyphosate Exposure on Liver and Kidney Histopathology and Oxidative Stress in Mice: An Experimental Study in Malaysia

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DOI: https://doi.org/10.64440/IBNSINA/SINA0030

ARTICLE INFO

Article history
Received May 11, 2026
Revised May 24, 2026
Accepted Sep 02, 2026

Keywords
Glyphosate;
Fibrosis;
Liver;
Kidney;
Histopathology;
Sub-lethal exposure;
Mice.

ABSTRACT

Background: Glyphosate is a widely used herbicide, and prolonged exposure to sub-lethal concentrations may affect tissues involved in detoxification and elimination—the present study aimed to evaluate glyphosate-associated fibrotic changes in liver and kidney tissues following repeated exposure. **Methods:** Monash University's Animal Research (ARASC), based at Monash University and located at Bangunan L15, Universiti Sains Malaysia, 11800 Pulau Pinang, Malaysia, allowed the researchers to conduct this experimental study on its premises. Male Swiss albino mice were exposed to a sub-lethal dose of glyphosate (50 mg/kg body weight) by oral gavage for 28 consecutive days, while the control group received saline. At the end of the exposure period, liver and kidney tissues were collected and examined histologically. Fibrosis was assessed according to the degree of collagen and extracellular matrix deposition. **Results:** Mild fibrotic changes were detected in both liver and kidney tissues of glyphosate-exposed mice. The mean fibrosis score was 1.2 ± 0.4 in the liver and 1.0 ± 0.3 in the kidney, whereas the control group showed no detectable fibrosis. The liver exhibited a slightly greater fibrotic response than the kidney. **Conclusion:** Twenty-eight-day sub-lethal glyphosate exposure was associated with mild fibrosis in both liver and kidney tissues of mice. These findings indicate that repeated glyphosate exposure may initiate early fibrotic tissue remodeling in these organs. Further studies involving longer exposure periods and specific molecular markers of fibrosis are needed to determine the progression and underlying mechanisms of this response.

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1.Introduction

Since its introduction in the 1970s, glyphosate, a broad-spectrum herbicide, has become one of the most widely used chemicals in agriculture worldwide. The widespread use of glyphosate has raised growing concerns about its potential long-term effects on human health and the environment, as well as its repercussions for the animal kingdom [1]. Although glyphosate is generally considered safe when used according to recommended safety regulations, prolonged or sub-lethal exposure may induce biological alterations that are not immediately apparent. As illustrated in Figure 1, sub-lethal glyphosate exposure may promote oxidative stress, characterized by increased Reactive Oxygen Species (ROS), which can contribute to histopathological injury in the liver and kidneys [2]. Since glyphosate has become widely used worldwide, its possible long-term impact on humans and the environment has become a growing concern. Although glyphosate is largely considered safe when used according to safety regulations, growing evidence raises doubts about its potential health hazards, particularly with long-term or sub-lethal exposure.

Sub-lethal doses of glyphosate are especially concerning because of their cumulative effects; they may not be apparent at first but can cause severe health problems in the long term. Glyphosate is mostly applied in farming, and environmental pollution has exposed both humans and wildlife to small doses over prolonged periods. The impact of chronic, low-level exposure to glyphosate on human health is poorly investigated, unlike acute toxicity, which is well researched [3]. Although the acute impacts of glyphosate, including intoxication, are well established, sub-lethal, long-term impacts (especially at doses frequently found in the environment) remain poorly investigated [4].

This knowledge gap is a matter of concern, and even more so as sub-lethal doses could have minor but important biological effects that could be realized with time, and this could lead to long-term chronic diseases and disorders.

Some studies have proposed that glyphosate exposure can be associated with oxidative stress, a state caused by an imbalance between Reactive Oxygen Species (ROS) and antioxidant defense mechanisms that results in cellular damage [5]. Oxidative stress is also a common pathway by which environmental toxins such as glyphosate cause tissue damage and lead to organ dysfunction [6]. Glyphosate has been shown to cause oxidative stress in different organisms, negatively affecting organs involved in detoxification (liver and kidneys). The liver and kidneys are the organs most affected by oxidative stress because of their key roles in detoxifying xenobiotics (such as pesticides). Long-term exposure to low levels of glyphosate may disrupt these organs' function and induce histopathological alterations, such as inflammation, fibrosis, and necrosis [7].

Despite the growing body of literature on glyphosate's potential toxicity, gaps remain in research on its sublethal effects, especially its long-term effects on liver and renal tissues. Although some evidence suggests that glyphosate exposure can lead to histopathological changes such as liver necrosis and kidney damage, such research typically focuses on high doses, which do not reflect real-world exposure conditions [8]. Moreover, the impacts of sub-lethal doses of glyphosate on the extent of oxidative stress and resulting tissue damage in critical organs such as the liver and kidneys are not well understood, and further studies are needed to determine the scope of its influence [9].

This research gap is alarming because it prevents a complete picture of the dangers of low-level, long-term glyphosate exposure. The researcher will seek to fill this gap by evaluating the histopathologic effects of sub-lethal doses of glyphosate in liver and kidney tissues in mice. This aims to determine the extent of oxidative stress and tissue damage that could occur with long-term exposure to sub-lethal doses of glyphosate. Through histological analysis of the tissues, we will identify necrosis, inflammation, and fibrosis; these are common effects of tissue injury due to oxidative stress [10]. Further, the research will determine ROS levels in liver and kidney tissue to test the correlation between oxidative stress and histopathology. It will also help identify health hazards associated with chronic, low-level exposure to glyphosate, focusing on sub-lethal doses, to clarify the long-term health consequences of glyphosate use.

Understanding the effects of sub-lethal glyphosate exposure is crucial for evaluating the environmental and public health risks associated with its widespread use. Although glyphosate is an essential tool in agriculture, its extensive application raises significant concerns about its potential long-term effects on both human health and ecological systems [11]. The findings from this study could have important implications for revising safety guidelines for glyphosate use, especially regarding permissible exposure levels for both workers and surrounding communities. Additionally, these findings could contribute to future research efforts aimed at further elucidating the potential health risks posed by glyphosate. As the body of evidence on glyphosate's health effects grows, it is imperative to continue investigating its potential risks, particularly chronic exposure to sub-lethal doses, to better protect public health and the environment [12].

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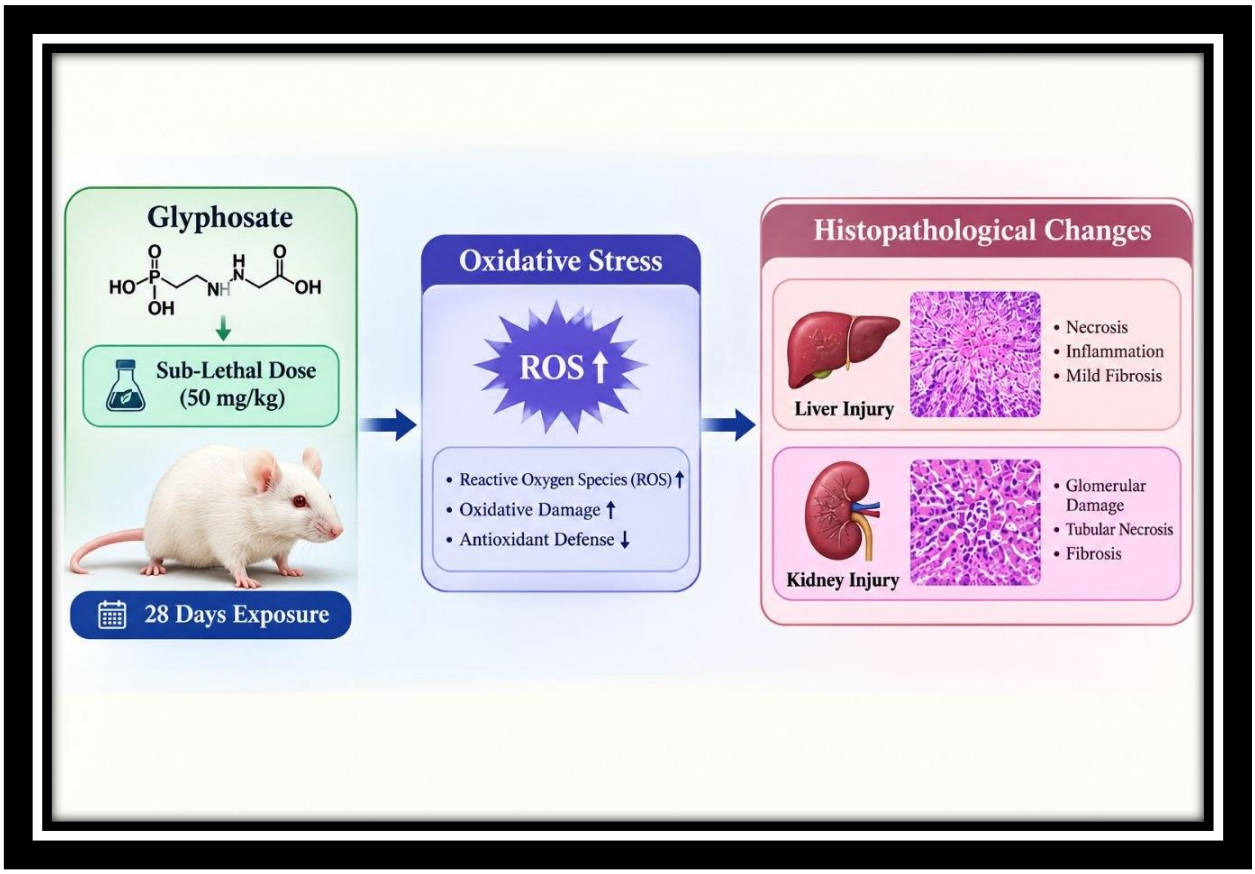

Figure 1. Schematic Representation of 28-Day Sub-Lethal Glyphosate Exposure and Its Effects on Oxidative Stress and Liver and Kidney Histopathology in Mice.

This flowchart outlines the key stages of glyphosate exposure, from its widespread use in agriculture to sub-lethal exposure that results in oxidative stress, histopathological damage in the liver and kidneys, and the implications for safety guidelines and future research [13].

2.Research Objectives

1. To investigate histopathological changes in liver and kidney tissues of mice exposed to sub-lethal glyphosate doses

2. To measure ROS levels in liver and kidney tissues following sub-lethal glyphosate exposure

3. To compare oxidative stress and tissue damage between glyphosate-exposed and control groups

3.Methodology

3.1Study Design

The experiment used male Swiss albino mice (Mus musculus) aged 8-10 weeks, obtained from a certified vendor. These mice were chosen because they are well documented in toxicological studies and respond predictably to chemical agents. Before the experiment commenced, the mice were allowed to adapt to the laboratory environment for 7 days to reduce stress and maintain stable health parameters. The animals were kept in the usual laboratory cages and subjected to a 12-hour light/dark cycle, with ad libitum access to food and water throughout the study. Monash University's Animal Research (ARASC), based at Monash University in Pulau Pinang, Malaysia, approved the study, and all procedures were carried out in accordance with animal welfare recommendations.

The animals were randomly assigned to two groups: the experimental group (n=12), which was exposed to sub-lethal doses of glyphosate, and the control group (n=12), which was exposed to a similar dose of saline solution as a vehicle control. During the research, mice were monitored daily for signs of toxicity and distress. General health and weight gain were observed, without any of the animals showing serious distress or a weight loss of more than 20 percent, which would have forced the removal of that particular animal through euthanasia. The purpose of the study was to evaluate the long-term consequences of exposure to a sub-lethal amount of glyphosate on liver and kidney tissues in terms of histopathological changes and the degree of oxidative stress.

3.2 Glyphosate Exposure

A technical grade of glyphosate (95%) was purchased from a commercial manufacturer and dissolved in saline for administration. The experimental group received a daily dose of 50mg/kg body weight of glyphosate orally via gavage. The dose was chosen according to previous research, which proved that it is enough to cause oxidative stress and tissue damage without causing instant death [14]. The control group received the same amount of saline solution (10 ml/kg body weight) to account for possible vehicle effects. The glyphosate exposure period was 28 consecutive days, representing a chronic, low-level exposure scenario more relevant to environmental and occupational exposure than acute dosing.

3.3 Tissue Collection

At the conclusion of the 28 days, all mice were euthanized in accordance with approved guidelines for humane euthanasia by an overdose of isoflurane. Right after the euthanasia, liver and kidneys were removed as part of the operative process, and the health conditions of the liver and kidneys

were observed visually. Phosphate-buffered saline (PBS) was used to wash the organs to remove excess blood and any other chemicals that might have remained in the tissue samples.

The excised organs were treated in two ways: half of the liver and kidney tissues were fixed in 10% formalin for microscopic analysis, and the other half was kept at -80 C for analysis of oxidative stress biomarkers. This two-fold strategy allowed us to combine molecular and histological analyses of the consequences of glyphosate exposure on organ well-being. Tissues were fixed in formalin for at least 24 hours, then embedded in paraffin blocks. The remaining tissues were placed in cryovials and stored at -80C to maintain protein integrity for future biochemical assays.

3.4 Histological Examination

Standard histological processes were used to fix the liver and kidney tissue and embed it in paraffin to assess changes occurring in the tissue. After embedding, 5 µm-thick tissue sections were cut with a microtome and placed on glass slides. These sections were stained with hematoxylin and eosin (H&E) [15], a common technique that reveals tissue morphology and enables easy identification of structural changes, including necrosis, inflammation, and fibrosis[16].

Histopathological studies focused on three major signs of tissue destruction: necrosis, inflammation, and fibrosis. Necrosis was characterized by cellular swelling, loss of membrane integrity, and tissue disintegration. Inflammation was defined by inflammatory cells penetrating the tissue, including neutrophils, macrophages, and lymphocytes. The grade of inflammation was assigned based on the extent and severity of the infiltrates, where 0 represented no inflammation, 1 represented mild inflammation (limited number of inflammatory cells), 2 represented moderate inflammation (a few inflammatory cells), and 3 represented extensive inflammation (large areas of inflammatory tissue). Fibrosis, the build-up of extracellular materials like collagen, was measured by determining the degree of collagen deposition in the tissue. These three parameters played a significant role in determining the level of destruction of liver and kidney tissues after glyphosate exposure.

3.5 Oxidative Stress Measurement

The level of oxidative stress caused by glyphosate exposure was also assessed by measuring ROS levels using the dichlorofluorescein diacetate (DCFH-DA) assay. ROS are highly reactive molecules that can damage cell components such as lipids, proteins, and DNA. The DCFH-DA assay is a credible technique for identifying ROS in biological tissues [17].

In this article, liver and kidney tissues were homogenized in ice-cold phosphate-buffered saline (PBS). To remove cell debris, the homogenates were centrifuged (10,000 rpm) at 4°C, and the supernatants were then used to perform the assay. DCFH-DA (10 µM) was incubated with the supernatants at 37°C for 30 minutes. Upon contact with ROS, DCFH-DA is oxidized to form the Fluorescent Compound Dichlorofluorescein (DCF) [18], which was measured using a fluorescence microplate reader. Fluorescence intensity was quantified at excitation/emission wavelengths of 485/535 nm. These results were adjusted to protein content, determined by the Bradford assay, and expressed as fluorescence units per milligram of protein. Analysis of ROS levels in liver and kidney tissues provided clues about glyphosate-induced oxidative damage and helped correlate oxidative stress with histopathological changes.

3.6 Statistical Analysis

All data were analyzed using GraphPad Prism software. An unpaired Student t-test was used to compare scores for histopathological variables and ROS between the glyphosate-exposed group and the control group. Results were presented as the mean ± standard deviation (SD). A p-value below 0.05 was termed statistically significant. The Pearson correlation coefficient was also used to determine the relationship between histopathological alterations and oxidative stress [19]. This indicated the strength and direction of the relationship between oxidative stress markers and the degree of tissue damage, providing more comprehensive insight into the effects of glyphosate exposure on liver and kidney health [20].

4. Results

4.1 Histopathological Assessment of Fibrosis

Histopathological examination revealed fibrotic alterations in both liver and kidney tissues of mice exposed to sub-lethal glyphosate for 28 days. The observed fibrosis was characterized by collagen deposition and tissue remodeling, with more evident changes in the liver than in the kidney [21].

4.1.1 Fibrosis in Liver Tissue

Figure 1 indicates fibrosis in the liver tissue of mice exposed to glyphosate, with mild collagen deposition and tissue remodeling. The liver fibrosis score in the glyphosate-exposed group was 1.2 + 0.4, indicating mild fibrosis. The control group had no fibrosis (score of 0), as shown in Table 1.

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Group	Fibrosis Score
Glyphosate-Exposed	1.2 ± 0.4
Control	0

Table 1: Fibrosis Scoring in Liver Tissues of Glyphosate-Exposed Mice

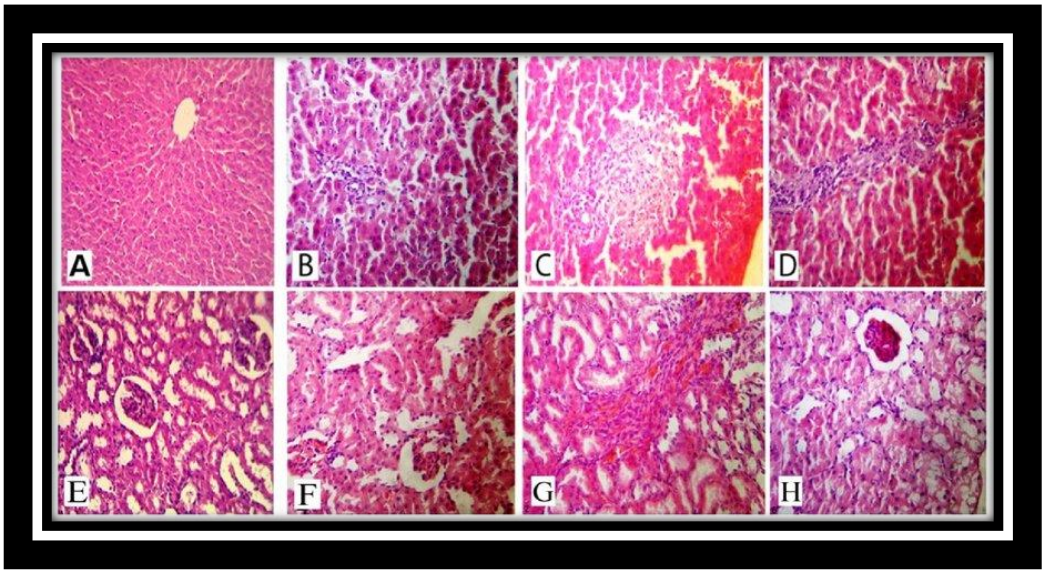

Figure 1: This photomicrograph shows portal inflammation and periportal fibrosis in the liver, indicative of chronic liver injury

The image depicts histopathological changes in liver and kidney tissues from experimental mice stained with hematoxylin and eosin. (A) show normal liver structure, while panels (B),(C), and (D) exhibit varying degrees of necrosis, inflammation, and fibrosis. (E) through (H) illustrate renal tissue with glomerular and tubular damage, highlighting necrosis, inflammation, and fibrosis. These alterations reflect the toxic effects of glyphosate exposure, leading to significant tissue damage in both organs [22].

4.1.2 Fibrosis in Kidney Tissue

Figure 2 shows mild fibrosis in the kidney tissue of mice exposed to glyphosate, with collagen deposition in the interstitial spaces between the tubules and glomeruli. The glyphosate-exposed group had a kidney fibrosis score of 1.0 + 0.3, indicating mild fibrosis. No fibrosis was evident in the control group, and the score was 0, as indicated in Table 2.

Group	Fibrosis Score
Glyphosate-Exposed	1.0 ± 0.3
Control	0

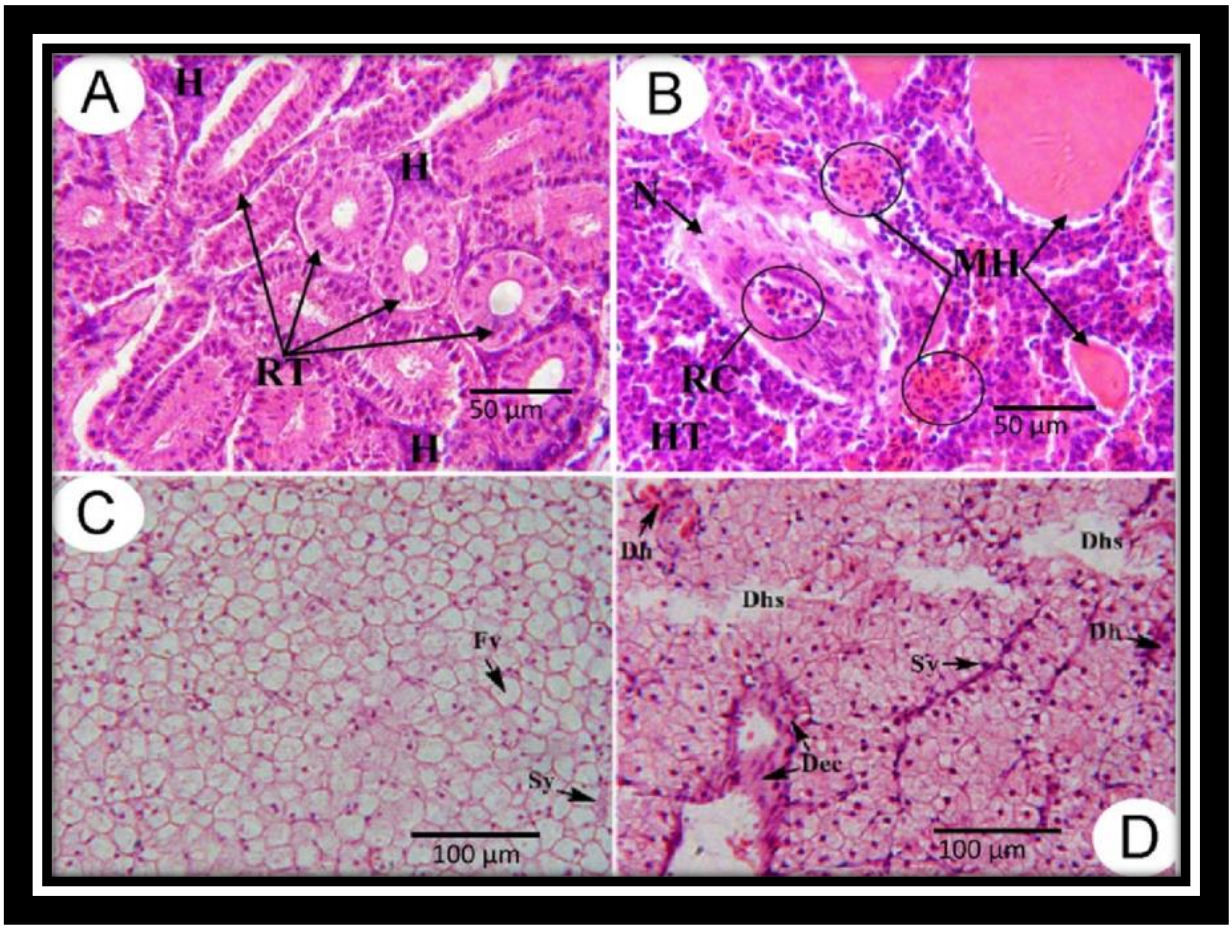

Table 2: Fibrosis Scoring in Kidney Tissues of Glyphosate-Exposed Mice

Figure 2: Histopathological Changes in Liver and Kidney Tissues Following Toxic Exposure

The image displays histological alterations in liver and kidney tissues stained with Hematoxylin and Eosin (H&E). (A) shows normal liver architecture, while (B) illustrates necrosis and inflammation. (C) highlights fatty infiltration in liver tissue, and (D) shows fibrosis in kidney tissue, reflecting the toxic effects of exposure [23].

4.2 Oxidative Stress Findings

Measurement of Reactive Oxygen Species (ROS) in liver and kidney tissues from glyphosate-exposed mice showed oxidative stress [24].

4.2.1 ROS Levels in Liver Tissue

The liver had high ROS levels, with the glyphosate-exposed group at 2.0 ± 0.5 fluorescence units/mg protein and the control group at 0.0 ± 0.1 fluorescence units/mg protein. These findings show that glyphosate exposure causes oxidative stress in the liver, leading to a significant rise in ROS production, as indicated in Table 3.

Group	ROS Levels (Fluorescence Units/mg Protein)
Glyphosate-Exposed	2.0 ± 0.5
Control	0.0 ± 0.1

Table 3: ROS Levels in Liver Tissue from Glyphosate-Exposed Mice

4.2.2 ROS Levels in Kidney Tissue

Similarly, ROS content differed significantly in kidney tissue: 1.8 ± 0.6 fluorescence units/mg protein in the glyphosate-exposed group and 0.0 ± 0.1 fluorescence units/mg protein in the control group. The findings suggest that glyphosate exposure causes critical oxidative stress in kidney tissues, as shown in Table 4.

Group	ROS Levels (Fluorescence Units/mg Protein)
Glyphosate-Exposed	1.8 ± 0.6
Control	0.0 ± 0.1

Table 4: ROS Levels in Kidney Tissue from Glyphosate-Exposed Mice

4.3 Correlation Between ROS and Histopathological Changes

Pearson correlation analysis showed a positive correlation between ROS levels and histopathological changes, especially inflammation and fibrosis in liver (r = 0.78) and kidney (r =

0.72) tissues. This relationship indicates that oxidative stress plays an important role in liver and kidney tissue damage following glyphosate exposure, as shown in Table 5.

Organ	Pearson's Correlation (ROS vs Histopathology)
Liver	0.78
Kidney	0.72

Table 5: Statistical Analysis of Histopathological and ROS Data in Glyphosate-Exposed Mice

5.Discussion

The present study demonstrated mild fibrotic changes in both liver and kidney tissues following 28 days of sub-lethal glyphosate exposure. The fibrosis score was higher in the liver (1.2 ± 0.4) than in the kidney (1.0 ± 0.3), whereas no fibrosis was observed in the control group. These findings suggest that repeated exposure to glyphosate may induce early tissue remodeling in organs involved in xenobiotic metabolism and elimination [25].

The slightly higher hepatic fibrosis score may relate to the liver's central role in metabolizing and detoxifying foreign compounds. Continuous exposure to chemical stressors can promote cellular stress and extracellular matrix deposition, potentially initiating an early fibrotic response. Previous research has reported that glyphosate exposure can produce pathological alterations in hepatic and renal tissues, supporting the possibility that repeated exposure may contribute to progressive tissue injury and remodeling [26]. Mild renal fibrosis may similarly reflect the kidney's susceptibility to prolonged chemical exposure. The kidneys are continuously exposed to circulating metabolites and participate in xenobiotic elimination, making them particularly vulnerable to toxin-induced tissue alterations. Previous studies have emphasized the association between oxidative stress and organ injury, particularly in tissues involved in detoxification and waste elimination [27]. An important finding of the present study was elevated ROS in both liver and kidney tissues. ROS levels reached 2.0 ± 0.5 fluorescence units/mg protein in the liver and 1.8 ± 0.6 fluorescence units/mg protein in the kidney. Furthermore, we observed positive correlations between ROS levels and histopathological changes in the liver (r = 0.78) and kidney (r = 0.72). These findings suggest

that oxidative stress may contribute to the observed fibrotic changes. Previous experimental work has demonstrated that sub-lethal glyphosate exposure can alter antioxidant defenses and increase lipid peroxidation in liver and kidney tissues, providing biological support for an oxidative mechanism of tissue injury [28].

The relationship between oxidative stress and fibrosis is biologically plausible because persistent oxidative imbalance can promote cellular injury and tissue remodeling. Excessive ROS may affect cellular components and activate pathways involved in extracellular matrix accumulation and repair. Reviews of glyphosate toxicity have similarly identified oxidative stress as an important mechanism potentially underlying organ damage following glyphosate-based herbicide exposure [29].

The present findings should, however, be interpreted as evidence of an association rather than definitive proof that glyphosate-induced oxidative stress directly caused fibrosis [30]. The current study measured ROS and histopathological fibrosis but did not evaluate specific molecular markers of fibrogenesis, such as collagen expression or transforming growth factor-β signaling [31]. Therefore, further studies incorporating molecular and biochemical markers of fibrosis are required to clarify the mechanisms underlying the observed tissue remodeling [32].

Overall, detecting mild fibrosis in both liver and kidney tissues after 28 days of sub-lethal glyphosate exposure indicates that repeated exposure may initiate early structural changes in these organs. The combination of fibrotic alterations and increased ROS levels supports the potential involvement of oxidative stress in this response. Nevertheless, the relatively short exposure period emphasizes the need for longer-term experimental studies to determine whether the observed mild fibrosis progresses with continued glyphosate exposure [33].

6.Conclusion

The present study demonstrated that repeated sub-lethal exposure to glyphosate for 28 days occurred in Malaysian tropical conditions of Pulau Pinang. Temperatures were extraordinarily high, with high heat and moisture, and humidity was relatively high at 90%. This experiment was associated with mild fibrotic changes in both liver and kidney tissues. The hepatic fibrosis score was slightly higher than the renal fibrosis score. In contrast, no fibrosis was observed in the control group, suggesting that repeated glyphosate exposure may induce early structural remodeling in organs involved in xenobiotic metabolism and elimination.

The observed increase in reactive oxygen species (ROS) levels in both liver and kidney tissues, together with the strong positive correlations between ROS levels and histopathological fibrosis, supports a potential role of oxidative stress in the development of these early fibrotic alterations.

However, the findings indicate an association rather than definitive evidence of a direct causal pathway between glyphosate-induced oxidative stress and fibrosis.

Overall, the findings suggest that prolonged exposure to sub-lethal concentrations of glyphosate may initiate early fibrotic responses in hepatic and renal tissues. Further long-term studies incorporating specific molecular and biochemical markers of fibrogenesis, including collagen deposition and transforming growth factor-β signaling, are recommended to clarify the mechanisms involved and determine whether these early changes progress with continued exposure.

Ethical Considerations

This study was reviewed and approved by Monash University's Animal Research and Animal Ethics Committee (ARASC), Malaysia, under ethical approval number **U.S.M2026-MY-14D-188-FF-ARASC176.** All procedures involving animals were conducted in accordance with the approved experimental protocol and applicable institutional guidelines for the humane care and use of laboratory animals.

A total of 24 male Swiss albino mice were used in the study. The animals were acclimatized for seven days before experimentation and maintained under standard laboratory conditions with free access to food and water. The animals were monitored daily throughout the 28-day experimental period for signs of toxicity, behavioral abnormalities, distress, and changes in body weight. Humane endpoints were established, including substantial deterioration in health or body-weight loss exceeding 20%, at which point the affected animal would have been humanely euthanized. No animal reached these predefined humane endpoints during the study.

The study followed the principles of the **3Rs—Replacement, Reduction, and Refinement** to minimize the number of animals used and reduce potential pain, distress, and suffering while maintaining the scientific validity of the experiment. At the completion of the 28-day exposure period, all animals were humanely euthanized using an overdose of isoflurane in accordance with the approved animal-welfare protocol. Tissue collection was performed immediately after euthanasia to minimize unnecessary manipulation and distress.

The researchers confirm that all animal-use procedures were conducted under the approved ethical protocol and that animal welfare was maintained throughout the study.

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List of Abbrevations:

(ROS): reactive oxygen species; **(H&E):** hematoxylin and eosin; **(PBS):** Phosphate-buffered saline **; (SD):** standard deviation;

Acknowledgment:

The authors would like to express their sincere gratitude to Monash University's Animal Research and Animal Ethics Committee (ARASC), Malaysia, for reviewing and approving the animal experimentation protocol under ethical approval number **U.S.M2026-MY-14D-188-FF-ARASC176**. The authors also acknowledge the support and facilities provided for conducting the animal experiments and subsequent tissue analyses.

The authors gratefully acknowledge the research grant provided by the university to support the experimental procedures, animal exposure, tissue collection, histopathological examinations, and related laboratory analyses under grant number **U.S.M-AKK26-H.D.S-MY-2026.**

In addition, **Noor Al-Ilm for Publishing and Distribution** provided the authors with a small partial research-support grant under grant number **SINA-MY-89A-66D-NN-2026.**

The authors further acknowledge the Editorial Office of the ****Ibn Sina Journal of Medical Science, Health & Pharmacy**** and ****Noor Al-Ilm for Publishing and Distribution**** for providing editorial and publication support and for granting a ****full waiver of the article processing charges (APCs)****, thereby enabling the present work to be published without publication fees to the authors.

The authors gratefully acknowledge all individuals and institutions whose assistance, cooperation, and support contributed to the successful completion of this study.

Author Contribution:

All authors contributed equally to the main contributor to this paper. All authors read and approved the final paper.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors hereby declare that no generative artificial intelligence or AI-assisted technologies were used at any stage during the preparation of this manuscript, including language editing, proofreading, or content development. The authors take full responsibility for the originality and integrity of the work presented in this publication.

Funding:

This study was supported by a research grant awarded by the university to the authors to conduct the experimental procedures, animal exposure, tissue collection, histopathological examinations, and related laboratory analyses. The university research grant was issued under grant number ****U.S.M-AKK26-H.D.S-MY-2026**.**

In addition, **Noor Al-Ilm for Publishing and Distribution** provided the authors with a small partial research-support grant under grant number ****SINA-MY-89A-66D-NN-2026****, in addition to a **full waiver of the article publication charges (APCs)**. This partial financial support and publication-fee waiver were provided solely to facilitate the research and publication process and had **no influence whatsoever** on the experimental design, animal procedures, data collection, data analysis, interpretation of the findings, manuscript preparation, peer-review or editorial process, editorial decisions, or the final decision to publish the manuscript.

The funding institutions and supporting organization had no role in determining the scientific outcomes or conclusions of the study. The authors retain full responsibility for the scientific content and conclusions presented in this manuscript.

Conflicts of Interest:

"The authors declare no conflict of interest."

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