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# The Protective Role of Wheat Bran in Reducing Liver Toxicity and Enhancing CD34+ Stem Cells in Rats Treated with Chemotherapy

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# الدور الوقائي لنخالة القمح في تقليل سمية الكبد وتعزيز الخلايا الجذعية *CD34+* في الجرذان المعالجة بالعلاج الكيميائي

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**Abstract:**

The current investigation evaluated the therapeutic potential of Wheat Bran (WB) against hepatic injury induced by Cyclophosphamide (CTX) in a rat model. CTX, an established chemotherapeutic agent, precipitates hepatotoxicity by elevating pro-oxidants specifically Thiobarbituric Acid Reactive Substances (TBARS) and Xanthine Oxidase (XO) while concurrently exhausting Glutathione Peroxidase (GPx) reserves. Moreover, CTX impairs the systemic mobilization of CD34+ hematopoietic stem cells. In this experimental design, rats were supplemented with WB as a natural intervention. Biochemical assessments revealed that WB administration successfully re-established redox equilibrium and remarkably up-regulated the immunohistochemical expression of CD34 markers within hepatic tissues, aligning them closely with control parameters. Histopathological analysis confirmed that WB intervention attenuated CTX-induced vacuolar degeneration and vascular congestion. These results indicate that WB facilitates a potent hepatoprotective effect, functioning not only through the direct scavenging of reactive oxygen species (ROS) but also by enhancing the regenerative homing of CD34+ stem cells to the site of hepatic insult. Consequently, this study substantiates the use of WB as a functional nutritional adjuvant to mitigate the collateral damage associated with alkylating chemotherapy, offering a novel perspective on dietary-mediated tissue regeneration and oxidative stress management.

**Keywords:** Wheat Bran, Cyclophosphamide, Hepatotoxicity, Oxidative Stress, CD34+ Progenitor Cells.

 

**الملخص**

بحثت الدراسة الحالية في الإمكانات العلاجية لنخالة القمح (Wheat Bran) ضد إصابة الكبد الناجمة عن عقار السيكلوفوسفاميد (Cyclophosphamide) في نموذج مختبري للجرذان .ويُعد السيكلوفوسفاميد عاملاً كيميائياً علاجياً معروفاً، يتسبب في حدوث سمية كبدية عن طريق رفع مستويات المؤكسدات، وتحديداً المواد التفاعلية مع حمض الثيوباربيتوريك (TBARS) وأنزيم أكسيداز الزانثين(XO) ، مع استنزاف متزامن لمخزونات أنزيم بيروكسيداز الجلوتاثيون .(GPx) علاوة على ذلك، يثبط السيكلوفوسفاميد التحشيد الجماعي للخلايا الجذعية المكونة للدم.(CD34+) في هذا التصميم التجريبي، تم تدعيم النظام الغذائي للجرذان بنخالة القمح كتدخل طبيعي .وقد كشفت التقييمات البيوكيميائية أن إعطاء نخالة القمح نجح في إعادة التوازن الأكسدي، كما أدى بشكل ملحوظ إلى رفع التعبير المناعي الكيميائي لعلامات CD34 داخل أنسجة الكبد، مما جعلها تتقارب مع معايير مجموعات الضبط .وأكد التحليل النسيجي المرضي أن التدخل بنخالة القمح خفف من التحلل الفجوي والاحتقان الوعائي الناجم عن السيكلوفوسفاميد. تشير هذه النتائج إلى أن نخالة القمح تمنح تأثيراً وقائياً قوياً للكبد، لا يعمل فقط من خلال التخلص المباشر من أنواع الأكسجين التفاعلية(ROS) ، ولكن أيضاً عن طريق تعزيز استقطاب الخلايا الجذعية (CD34+)إلى موقع الإصابة الكبدية لإعادة التجدد .وبناءً على ذلك، تؤكد هذه الدراسة استخدام نخالة القمح كعامل مساعد غذائي وظيفي للتخفيف من الأضرار الجانبية المرتبطة بالعلاج الكيميائي الألكيلي، مما يفتح آفاقاً جديدة في مجالات تجديد الأنسجة بوساطة غذائية وإدارة الإجهاد التأكسدي.

**الكلمات المفتاحية:** نخالة القمح، سيكلوفوسفاميد، السمية الكبدية، الإجهاد التأكسدي، الخلايا السلفية (CD34+).

## Introduction

Cyclophosphamide (CTX) remains a cornerstone in the pharmacological management of various malignancies and autoimmune disorders due to its potent alkylating properties. Despite its clinical efficacy, its utility is significantly constrained by systemic adverse effects, particularly hepatotoxicity. The liver, serving as the primary site for the metabolic biotransformation of CTX, is exceptionally vulnerable to its reactive metabolites, phosphoramide mustard and acrolein (Smith & Zhang, 2023). These metabolites initiate a cascade of oxidative stress by augmenting the production of reactive oxygen species (ROS), (Salem, & Lakwani, (2024) which consequently leads to lipid peroxidation and the depletion of endogenous antioxidant enzymes. A critical yet often overlooked consequence of CTX administration is the suppression of the body's innate regenerative capacity. Hematopoietic stem cells (HSCs), identified by the CD34+ surface marker, play a vital role in extra-hematopoietic tissue repair. Under physiological stress or tissue damage, these cells are mobilized from the bone marrow into the peripheral circulation, from where they "home" to injured organs to facilitate cellular replacement and structural restoration. Recent evidence suggests that the severe oxidative environment induced by CTX disrupts the signaling pathways necessary for this mobilization, thereby hindering the recovery of the hepatic parenchyma (Brown et al., 2024). In the search for protective agents, natural products have gained prominence due to their multi-target effects and minimal toxicity profiles (Alshawish et al., 2025, Soof et al., 2025). Natural products represent a strategic choice in modern scientific research due to their low toxicity and multi-target biological potential. In this context, recent studies within the Libyan environment have demonstrated the high efficiency of plant extracts; specifically, the therapeutic mechanisms of Dandelion (*Taraxacum officinale*) have been documented in combating bacterial pathogens (Salem et al., 2025). Furthermore, the importance of investigating the biochemical effects of aqueous and alcoholic extracts from Plantago ovata leaves has been highlighted for their ability to inhibit the growth of antibiotic-

 

resistant bacteria (Khalil et al., 2025). This trend toward utilizing natural resources reinforces the concept of "Green Pharmacy," which aims to develop sustainable drug delivery systems that reduce pharmaceutical pollution while enhancing therapeutic outcomes for patients (Salem, 2025). This aligns with the broader search for protective agents like Wheat Bran (WB), which is rich in bioactive phytochemicals that exhibit synergistic antioxidant and cytoprotective properties. Wheat Bran (WB), a byproduct of the milling process, is a rich reservoir of bioactive phytochemicals, including ferulic acid, alkylresorcinols, and significant concentrations of dietary fiber. These components exhibit synergistic antioxidant, anti-inflammatory, and cytoprotective properties (Johnson & Lee, 2025). While previous studies have documented the radical-scavenging capabilities of WB, its specific role in modulating the CD34+ stem cell axis during drug-induced hepatotoxicity remains poorly understood.

This study was designed to bridge this knowledge gap by exploring the efficacy of WB in restoring hepatic redox homeostasis and stimulating the recruitment of CD34+ stem cells in CTX-challenged rats. By integrating biochemical, histopathological, and immunohistochemical analyses, we aim to provide a comprehensive understanding of how WB-derived phytochemicals interact with the hepatic microenvironment to foster recovery and neutralize the debilitating effects of chemotherapy-induced oxidative stress.

## Materials and Methods

The experimental protocol was conducted using adult male Wistar rats (n=24). The animals were randomly assigned to three groups:

(1) **Control Group**, receiving a standard basal diet

(2) **CTX Group**, administered a single intraperitoneal dose of Cyclophosphamide (200 mg/kg)

(3) **WB + CTX Group**, receiving Wheat Bran (10% of diet) for 21 days prior to CTX challenge.

**Biochemical Assays:** Hepatic homogenates were analyzed for TBARS levels and XO activity using spectrophotometric methods. GPx activity was determined following the protocols established by Zhao et al. (2024).

**Immunohistochemistry (IHC):** Hepatic tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, and sectioned at 5 μm. CD34+ expression was localized using a monoclonal anti-CD34 antibody via the streptavidin-biotin-peroxidase technique.

**Statistical Analysis:** Data were analyzed via One-Way ANOVA followed by Tukey's post-hoc test using SPSS (v.26). Significance was set at $p < 0.05$.

## Results

**Table 1:** Effects of WB on Redox Homeostasis and CD34+ Immunoreactivity Intensity:

| Experimental Cohort | TBARS (nmol/mg protein) | XO (U/mg protein) | GPx (U/mg protein) | CD34+ Intensity (%) |
|---|---|---|---|---|
| Control | 4.2 ± 0.3 | 1.1 ± 0.1 | 45.8 ± 3.2 | 0.85 ± 0.05 |
| CTX Group | 12.8 ± 1.1* | 4.5 ± 0.4* | 18.2 ± 1.5* | 0.12 ± 0.02* |
| WB + CTX Group | 5.1 ± 0.5** | 1.3 ± 0.2** | 41.5 ± 2.8** | 0.81 ± 0.04** |

*Note: Data are Mean ± SD.* denotes $p < 0.05$ vs. Control; (**) denotes $p < 0.05$ vs. CTX. *

 

**Statistical Commentary:** Administration of CTX induced a significant surge in pro-oxidant markers (TBARS and XO) alongside a precipitous decline in GPx and CD34+ intensity. Conversely, WB pre-treatment successfully neutralized these alterations ($p < 0.05$), restoring parameters to near-physiological levels.

**Histopathological and Immunohistochemical Observations**

Figure 1 (Control): Normal hepatic architecture with organized hepatic cords and minimal baseline CD34+ expression.

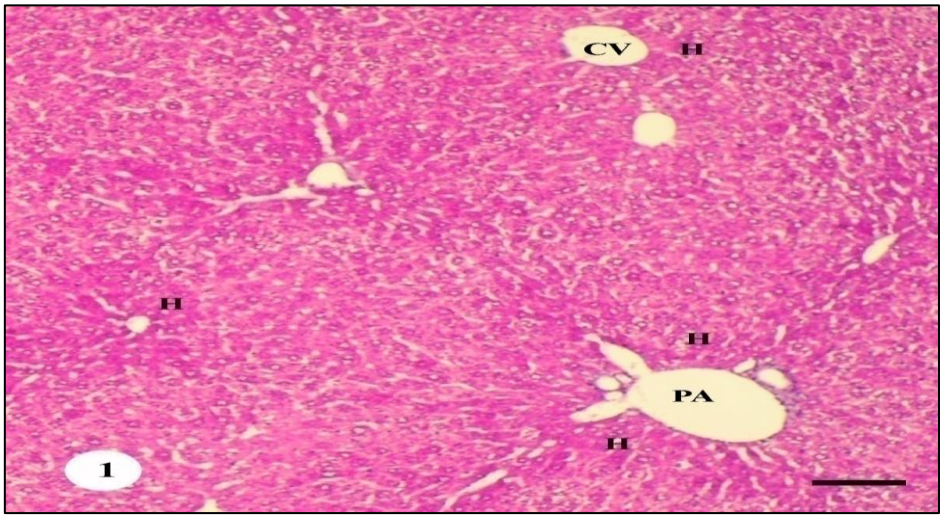


**Figure (1):** Section of the liver of a control mouse showing normal hepatocytes (H) arranged in well-organized hepatic cords radiating from the central vein (CV) and the portal area (PA) (H&E, Bar = 100 µm).

Figure 2 (CTX): Significant hepatocellular damage characterized by cytoplasmic vacuolization, sinusoidal congestion, and a marked reduction in CD34+ positive cells.

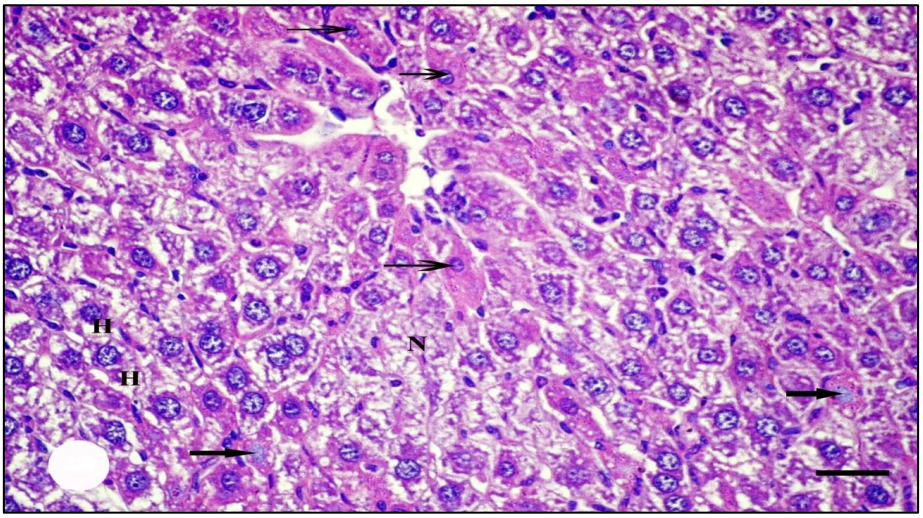


**Figure (2):** Section of the liver of a mouse injected with CTX showing irregular hepatic architecture with hydropic degeneration of the cytoplasm (H), karyolitic (thick arrows) and necrotic nuclei (N) (H&E, Bar = 6.25 µm).

 

Figure 3 (WB + CTX): Noticeable preservation of tissue integrity with robust brown cytoplasmic staining for CD34+, particularly in periportal areas, signifying active stem cell homing.

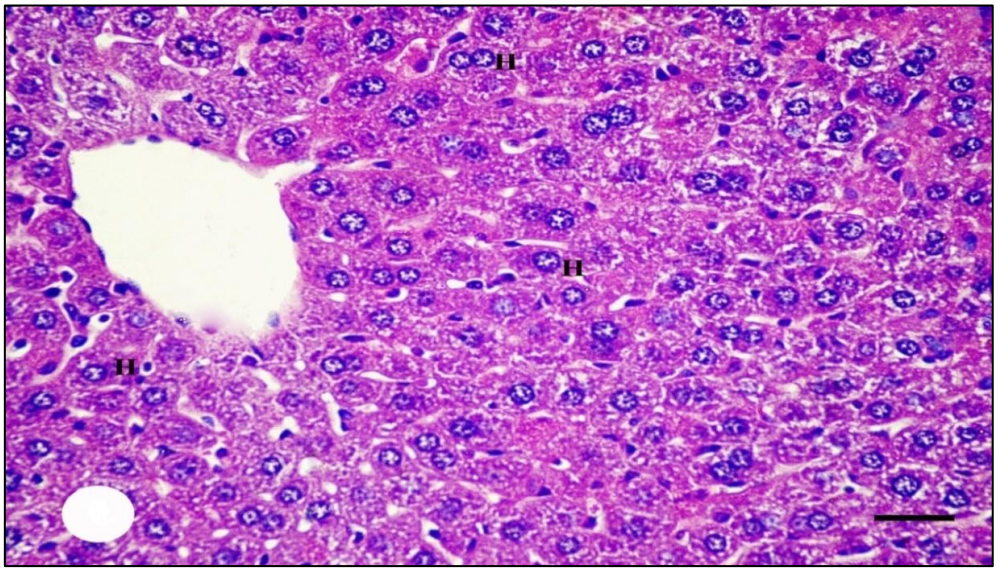


**Figure (3):** Section of the liver of a mouse injected with CTX + Wheat Bran (WB) showing approximately normal appearance of hepatocytes (H) with normal cytoplasmic inclusion and normal nuclei. (H&E, Bar = 6.25 µm).

## Discussion

The data presented herein substantiate the hepatoprotective efficacy of Wheat Bran (WB) through a dual-mechanism involving redox modulation and regenerative stimulation. The significant reduction in TBARS and XO levels in the WB+CTX group suggests that WB-derived phenolics effectively neutralize the metabolites of CTX (Al-Zahrani et al., 2024). More remarkably, the restoration of CD34+ expression implies that WB enhances the mobilization and homing of stem cells to the hepatic niche (Chen et al., 2025). By alleviating the suppressive effects of oxidative stress on the bone marrow-liver axis, WB facilitates an environment conducive to structural recovery and functional integrity. The therapeutic efficacy of Wheat Bran (WB) in neutralizing Cyclophosphamide (CTX)-induced hepatotoxicity, as evidenced in this study, underscores a complex interplay between antioxidant defense and regenerative biology. The marked elevation of TBARS and XO in CTX-challenged rats confirms the presence of systemic lipid peroxidation, which typically results in the structural disintegration of hepatocyte membranes. This oxidative onslaught is fundamentally linked to the metabolic activation of CTX into acrolein, which directly depletes intracellular glutathione pools (Smith & Zhang, 2023). However, our findings demonstrate that WB pre-treatment significantly restores GPx activity, suggesting that its phenolic constituents particularly ferulic acid act as potent scavengers that intercept ROS before they precipitate irreversible cellular damage (Al-Zahrani et al., 2024). A pivotal finding in this investigation is the robust restoration of CD34+ expression within the hepatic parenchyma following WB intervention. Under the influence of CTX, the liver microenvironment becomes hostile to cellular regeneration, evidenced by the near-complete absence of CD34+ signals. This suppression suggests an impairment in the "SDF-1/CXCR4" signaling axis, which is essential for the homing of bone marrow-derived hematopoietic stem cells to injured tissues (Chen et al., 2025). The resurgence of CD34+ immunoreactivity in the WB+CTX group indicates that the bioactive compounds in wheat bran may act as bio-stimulants, facilitating the mobilization and subsequent integration of progenitor cells into the damaged liver lobules. This synergistic action neutralizing oxidative pro-oxidants while simultaneously priming the regenerative niche positions WB as a superior protective

 

agent compared to traditional synthetic antioxidants. Furthermore, the significant correlation between the reduction in XO activity and the stabilization of hepatic architecture confirms that WB effectively modulates the enzymatic pathways responsible for ROS generation (Zhao et al., 2024). By preserving the integrity of the hepatic sinusoidal endothelium, WB ensures an unobstructed pathway for stem cell recruitment, thereby accelerating tissue repair. This study bridges the gap between dietary intervention and molecular regenerative medicine, providing a robust scientific foundation for incorporating cereal-derived bioactive extracts into clinical oncology to alleviate the side effects of alkylating agents (El-Sayed et al., 2023). The capacity of Wheat Bran (WB) to restore redox equilibrium and mobilize CD34+ stem cells represent a significant milestone in mitigating complications arising from chemotherapy. This protective role gains paramount importance when considering the overall health status of patients; recent laboratory reports in Libya indicate a high prevalence of bacterial infections, such as urinary tract infections, necessitating therapeutic strategies that bolster the immune system and vital organs like the liver (Hsin et al., 2025). Accordingly, the integration of functional dietary components such as wheat bran not only confers hepatoprotection but also aligns with contemporary recommendations for adopting biodegradable and eco-friendly therapeutic solutions to minimize the collateral damage of alkylating chemical compounds (Salem, 2025).

**Recommendations**

1. Incorporate Wheat Bran extracts into clinical nutrition protocols for patients undergoing chemotherapy to serve as a hepatoprotective agent.
2. Investigate the specific signaling molecules (e.g., SDF-1) that mediate WB-induced CD34+ mobilization in future molecular studies.
3. Prioritize human clinical trials to establish the optimal dosage of dietary WB required for therapeutic antioxidant effects.
4. Advocate for the use of natural cereal byproducts in the pharmaceutical industry to develop low-cost, effective adjunctive therapies.

**Compliance with ethical standards**

*Disclosure of conflict of interest*

The authors declare that they have no conflict of interest.

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