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Protective Effects of Olive Oil on Liver Tissue in Swiss Rats Treated with Cyclophosphamide: A Histopathological Study.

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Original Research Article

Abstract

Background: Cyclophosphamide (CP) is a commonly used chemotherapy agent acknowledged to have hepatotoxic effects. Olive oil, which is high in antioxidants, may offer protective benefits against damage caused by such drugs.

Aims: This study aims to search the potential protective effects of olive oil on liver toxicity induced by cyclophosphamide in a rat model.

Materials and Methods: A total of nine male albino rats were allocated into three distinct groups: A Control group, a CP group receiving 150 mg/kg, and a CP group receiving both 150 mg/kg of CP and 200 mg/kg of olive oil. The doses were administered on days one, three and five. On day seven, liver tissues were harvested for histopathological evaluation.

Results: Histopathological analysis showed that CP treatment resulted in extensive liver damage, especially affecting the portal tracts and central veins. The addition of olive oil appeared to reduce some of the toxic effects detected with CP, mainly in the portal tract and sinusoidal regions. Nonetheless, some degree of liver injury persisted in the group receiving both CP and olive oil. These results imply that olive oil may offer a protective benefit against CP induced liver toxicity in rats.

Conclusion: The administration of CP led to significant histopathological alterations in the liver tissues of rats. The concurrent use of olive oil seemed to alleviate some of these detrimental effects, likely attributable to its antioxidant properties. These findings suggest that incorporating olive oil could be beneficial as a protective measure during CP chemotherapy.

Keywords: Olive oil, Cyclophosphamide, Histopathological changes, Protective effect.

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Introduction:

Cyclophosphamide (CP) is part of the oxazaphosphorine family which are alkylating agents. It is a common chemotherapeutic medication used to treat various neoplastic diseases and was approved for use in the US in 1959 (1). It is commonly used to treat a variety of malignancies, including breast, lung, ovarian, endometrial, neuroblastoma, leukemia, and neuroblastoma in a combination with other chemotherapy drugs. CP is also usually used as an immunosuppressant to treat chronic autoimmune diseases such as multiple sclerosis, systemic vasculitides, rheumatoid arthritis, autoimmune skin diseases, and systemic lupus erythematosus (2). The administration of CP is typically intravenous, depending on the condition being treated. CP is a prodrug whose therapeutic effects depend on the liver's metabolic activities for activation and inactivation (3,4). CP introduces an alkyl-group into DNA when it is activated, it works by attaching an alkyl-group to the guanine base of the DNA at the imidazole ring's seventh nitrogen atom. This leads to permanent cross--linkages in the DNA strands at the phases G2 and S of the cell cycle, which ultimately ends cell death (5). However, side-chain oxidation which results in neurotoxic metabolites inactivates CP (3,4).

In severe conditions of aplastic anemia and other immune conditions, high doses of CP have shown successful results (6). Conversely, CP can induce a range of side effects due to its cytotoxic effects on rapidly proliferating cells. Adverse effects of CP include nausea, alopecia, sickness, thrombocytopenia, pulmonary fibrosis, facial abrasions, leukopenia, hematuria, increased skin

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pigmentation, diarrhea, hemorrhagic cystitis and others (3). With CP, numerous adverse medication responses are possible. Additionally, a tiny percentage of people have severe reactions that can be fatal or cause congenital defects, birth defects, or diseases that require prolonged hospitalization (7). To prevent drug-induced liver injury, it is essential to understand the pathological processes of liver damage, patient-related risk factors and drug-related risk factors.

Hepatotoxicity is one of the major side effects that can be caused by the application of CP. Several kinds of cytotoxic metabolites could be formed as a result of the metabolic conversion of CP (8). Phosphoramide mustard and acrolein are the two primary active metabolites that result in oxidative stress and harm cellular macromolecules such proteins, lipids and nucleic acid (9). When glutathione S-transferase is present, Acrolein is a highly reactive metabolite of CP with a short biological half-life, can easily interact with glutathione. Glutathione, a protein with thiol, plays numerous vital roles, including detoxifying electrophiles and reducing oxidative stress (10). Conversely, when glutathione levels are reduced, the reactive α, β unsaturated aldehyde acrolein increases the ability to interact with cellular nucleophiles, as the thiol-groups in cysteine within proteins, and the nitrogen atoms found in histidine and lysine. This interaction can lead to a loss of protein functionality and may induce oxidative stress, potentially resulting in significant damage to hepatocytes (11). Currently, various therapeutic strategies have been developed to mitigate the side effects associated with cyclophosphamide. These include combining multiple che-

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motherapeutic agents at reduced doses and utilizing alternative analogues of cyclophosphamide (12). However, the clinical outcomes have not been encouraging, as a significant portion of patients receiving these treatments still experience liver dysfunction (13, 14). Components of olive oil have been shown to possess anticancer properties by reducing DNA oxidation, halting the cell cycle, and inducing apoptosis in tumor cells (15,16). Incorporating olive oil into the diet has been proposed as a factor in protecting DNA and lowering cancer incidence.

The aim of study:

To examine the protective effects of olive oil against cyclophosphamide-induced histopathological changes in liver tissue of Swiss albino rats.

Materials and Methods:

Nine male albino rats were divided into three groups (n=9): a control group receiving saline, a cyclophosphamide group receiving 150 mg/kg cyclophosphamide only (ip), and a cyclophosphamide +Olive Oil group receiving 150 mg/kg cyclophosphamide (ip) followed by oral gavage 200 mg/kg olive oil. The doses were on day 1, 3 and 5. On day 7, rats were humanly sacrificed, and liver tissues were collected, fixed in formalin, processed using customary histological techniques, and stained with Hematoxylin and Eosin (H&E). Histopathological changes were assessed by a blinded pathologist using light microscope. Student t-test was done on the histopathological parameters by Excel Microsoft office professional plus 2016.

Results:

The liver sections from the control group:

Demonstrated a normal lobular architecture typical

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of healthy liver tissue. The lobule, the functional unit of the liver, displays a well-organized structure that is critical for proper liver function. Within the lobules, the hepatocytes are arranged radiating from the central-vein, developing anastomosing plates of hepatocytes. The hepatocytes displayed several notable characteristics: They appeared polyhedral, which is a typical morphology for liver cells. The cytoplasm was acidophilic, indicating a high presence of proteins and organelles. Each hepatocyte contained a round central nucleus, consistent with normal nuclear morphology. The portal tracts, or triads, observed in the sections contained several normal structures which is crucial for normal liver function (Figure 1).

The liver sections from the group treated with cyclophosphamide only:

Histopathological analysis of liver tissue of the rats treated with the CP only were characterized by the alteration of the normal liver structure with hepatic necrosis of the cells and degeneration adjacent to the central-veins of the liver. Furthermore, presented were eosinophilic cytoplasm of the hepatocytes with pyknotic nucleus. Inflammatory cell infiltration was also present (Figure 2 A). Figure (2) B showed, a region of congested hepatic cords, occupied with erythrocytes called red venous congestion and a region of congested hepatic cords, a large dilated central vein also packed with erythrocytes. However, presented was the portal-triad and surrounding tissue with dilated congested portal tract packed with RBCs and inflammatory cells, and a thicker than normal wall

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of portal vein with inflammatory cells and surrounded by fibrotic area and periportal early fibrotic changes and mild inflammatory cellular cuffing. Furthermore, the liver tissue showed with dilated sinosoids with cytolysis and pyknotic nuclei of hepatocytes adjacent to a congested portal tract show focal necrosis and dilated sinusoids, with megakaryocytic effect of hepatocytes was observed (Figure 3).

The liver sections of the group treated with Cyclophosphamide and Olive Oil:

Histological changes in the tissue sections showed an area of mild deteriorated liver cells (hepatocytes), and a slightly congested central-vein, mild lymphocytic infiltration. The loss of hepatic architecture is demonstrated at the portal tract and a mild portal vessels congestion with less fibrotic and inflammatory changes. Also found are the normal structure of the bile duct, with normal hepatic nucleus structure (figure 4). Also shown in (figure 5). solitary in the center focal necrosis, with cytolysis and pyknotic nuclei of hepatocytes, eosinophilic hepatocytic granules are noticed, with monotonous nuclei with fine chromatin distribution.

Table .(1). shows the histopathological parameters of livers of rats administrated by cyclophosphamide vs cyclophosphamide with olive oil. The control group showed no significant histopathological modifications. The group treated with cyclophosphamide only higher pathological change but in the group treated with the cyclophosphamide and olive oil there is a less effect on the portal tract area and the sinusoids region. Student t-test showed a significant difference between the parameters of the control group vs the cyclo-

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phosphamide group and between the control group vs the cyclophosphamide with olive oil group. But no difference was shown between the cyclophosphamide vs cyclophosphamide with olive oil group, $p<0.05$.

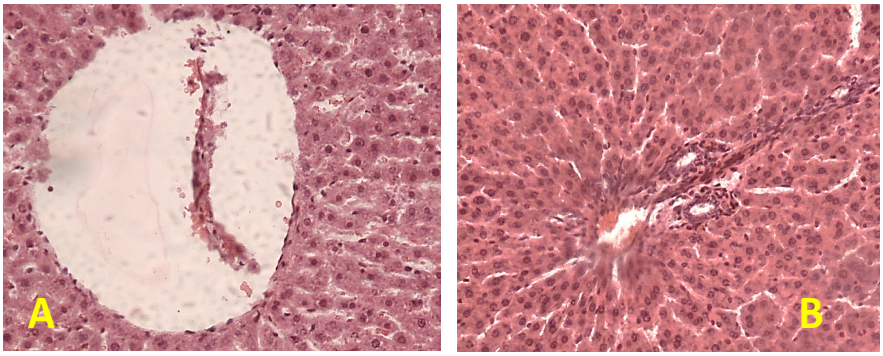


Figure .(1): Micrograph of control hepatic tissue. H and E stain. (A): Shows hepatocytes with normal central vein structures. (X200). (B): Shows normal portal-spaces, and normal structured hepatocytes. (X400).

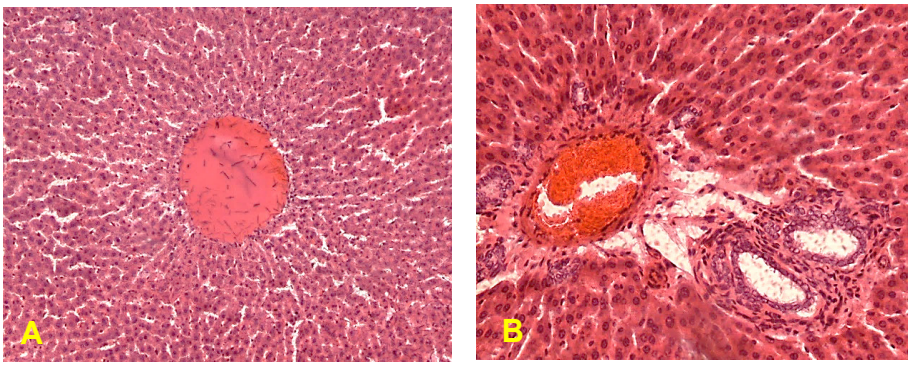


Figure. (2): Micrograph of hepatic tissue treated with Cyclophosphamide. H and E stain. (A): Displays a congested central vein and adjacent tissue with an area packed with erythrocytes (X100) (B): Demonstrates the portal triad and neighboring tissue with dilated congested portal tract packed

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with RBCs, with a thickening wall of portal-vein and periportal early fibrotic alterations and mild inflammatory cellular cuffing. (X200).

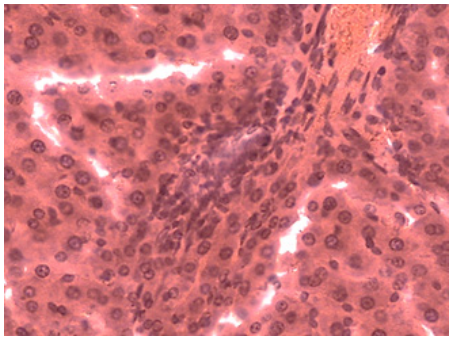


Figure .(3): Micrograph of hepatic tissue treated with Cyclophosphamide. H and E stain. (X400) Shows a congested portal tract at the upper right

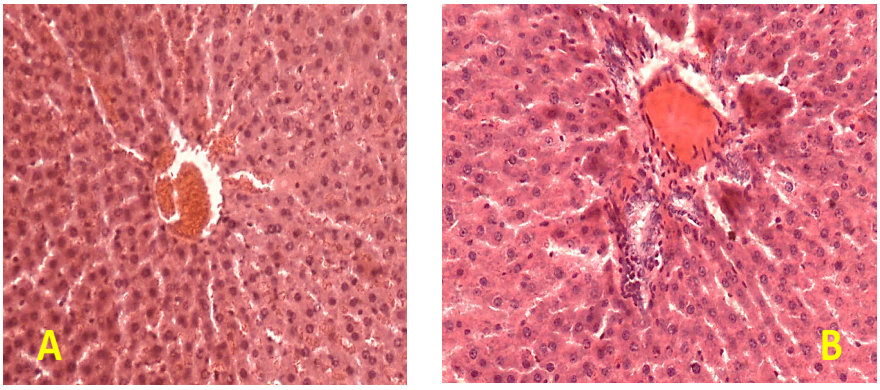


Figure .(4): Micrograph of hepatic tissue treated with both the Cyclophosphamide and Olive Oil. H and E stain. (A): Displayed, an area of slightly congested central vein. (X200) (B): Portal tract with a mild portal vessels congestion with normal bile duct structure and normal hepatic nucleus structure. (X200)

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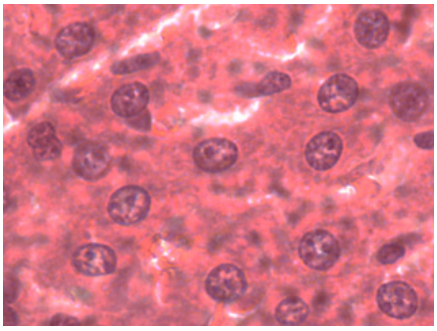


Figure.(5): Micrograph of hepatic tissue treated with both the Cyclophos-phamide and Olive Oil. H and E stain. Eosinophilic hepatocytic granules are noticed, with monotonous nuclei with fine chromatin distribution. (X1000)

Table .(1): Histopathological parameters of livers of rats administrated by cyclophosphamide vs cyclophosphamide with olive oil

Groups		Control	CPA	CPA & OO
Hepatocytes cellular changes	Hepatic vacuoles (steatosis)	-	-	-
	Cytolysis Pyknotic changes	-	+++	+++
Portal tract region	Congestion	++	++++++	++++
	Inflammatory changes	-	++	+
	Fibrotic changes	-	+ / ++	+ / +/-
Sinusoids and/or ducts	Inflammatory changes	-	-	-
	Dilatation	----	+++	---+++
	Necrosis	-	++/(FN)	+/(FN)

(+/++) Mild to moderate fibrotic changes

(+ / +/-) Mild to focal fibrotic changes

++/(FN) Mild to focal necrosis detected

++/(FN) Moderate to focal necrosis detected.

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Discussion:

This study was designed to assess the histopathological effects of CP on the hepatic tissue of albino rats and to estimate the potential protective effects of olive oil against the damage induced by CP. CP is known to effect different tissues especially when taken in large doses, the most histological studied tissues are the liver, kidney and testis. the studies showed large histopathological hepatic and nephrotoxic effects (17,18, 19). Also, when the olive oil was administered to the group with CP and olive oil it showed that the olive oil has a defensive effect against the toxic effects of the CP hepatotoxicity (20).

In this study the liver tissue from the control group displayed normal lobular architecture with well-organized hepatocytes, central veins, and portal tracts. In contrast, the liver sections from the CP-treated group showed significant alterations, including hepatocyte necrosis, congestion of hepatic cords, and inflammatory cell infiltration. CP treatment has been associated with disturbances in hepatic blood flow and cellular integrity, leading to the observed necrosis and degeneration of hepatocytes. According to a study by Talebpour et al. (2018), cyclophosphamide can induce oxidative stress and inflammation, contributing to hepatocyte injury and death (21). The presence of pyknotic nuclei within the hepatocytes further indicates cell death, a hallmark of necrosis (22). The infiltration of inflammatory cells within the liver tissue is indicative of an immune response to the damage inflicted by CP. The accumulation of inflammatory cells can aggravate liver injury through the release of proinflammatory cytokines and reactive oxygen

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species, which further exacerbate hepatocyte damage (3). This aligns with findings from various studies that highlight the role of inflammation in drug-induced liver injury (17).

The histopathological analysis revealed areas of red venous congestion characterized by dilated hepatic cords filled with erythrocytes. This occurrence is frequently observed in situations where hepatic blood flow is compromised, leading to increased pressure within the central veins (23). The observed red venous congestion and thickening of the portal vein walls are consistent with reports of CP-induced hepatic injury, further underlining the drug's potential to cause systemic toxicity (24). Additionally, the dilated portal tracts occupied with erthrocytes and inflammatory cells suggest portal hypertension or impaired venous drainage, which can occur as a consequence of hepatocyte damage and inflammation (25). Furthermore, the presence of periportal inflammatory cellular cuffing suggests constant inflammation that can lead to fibrosis if the noxious stimulus persists (26). The progression from inflammation to fibrosis is a well-documented pathway in liver pathology, emphasizing the significance of early intervention to prevent irreversible damage. Moreover, the dilated sinusoids with cytolysis and pyknotic nuclei adjacent to congested portal tracts reflects severe hepatic injury. This finding is consistent with studies indicating that sinusoidal dilation often accompanies liver injury and can lead to impaired hepatic function (27, 28). The megakaryocytic effect noted in some hepatocytes may suggest an adaptive response to stress or injury, potentially indicating altered hematopoiesis or

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thrombopoiesis in the context of liver dysfunction (29). The solitary focal necrosis observed, along with cytolysis and pyknotic nuclei in hepatocytes, indicates localized areas of cell death. Focal necrosis can be a common feature in drug-induced liver injury and is often associated with areas of significant oxidative stress or metabolic disturbance (30). The presence of eosinophilic hepatocytic granules suggests alterations in protein synthesis or storage within hepatocytes, potentially linked to the liver's response to injury (30).

In the group treated with both CP and olive oil, the histopathological changes in the liver were less prominent, the tissues displayed only mild degeneration of hepatocytes, slight congestion of the central vein, and limited lymphocytic infiltration. Moreover, the preservation of bile duct structure and normal hepatic nuclei suggests that olive oil provided some level of hepatoprotection.

This protective effect could be accredited to the anti-inflammatory and antioxidant properties of olive oil, which may help to neutralize ROS and reduce inflammation, thereby protecting hepatic cells from severe damage (31) this protective effect is also shown in other tissues (20). The existence of mildly degenerated hepatocytes suggests that while CP exerts hepatotoxic effects, the degree of damage is relatively moderate compared to the group treated with the CP only. Degeneration may manifest as cellular swelling, fatty change, or necrosis, which can be attributed to oxidative stress induced by CP (21). The protective effects of olive oil, rich in antioxidants such as oleic acid and polyphenols, may alleviate some of this damage, as suggested

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by studies indicating that dietary antioxidants can reduce oxidative stress in liver tissues (32,33,34). The beginning of slight congestion in the central vein and mild portal vessel congestion may indicate early vascular changes due to impaired hepatic blood flow. This can be a consequence of inflammation or cellular injury leading to increased pressure within the hepatic vasculature (23). The relatively mild nature of these changes suggests that the combination of CP with olive oil may have a protective effect that limits the extent of vascular compromise. Mild lymphocytic infiltration is indicative of an immune response to hepatocyte injury. While CP is known to induce inflammation and immune-mediated damage, the presence of olive oil may help modulate this response. Studies have shown that certain dietary fats can influence inflammatory pathways and reduce the severity of inflammation in liver injury (3). The reduced fibrotic modifications detected in this group could also point to a lower chronic inflammatory response, which is crucial for preventing long-term liver damage. These findings underscore the importance of dietary components in modulating drug-induced liver injury and suggest potential avenues for further research into protective strategies against hepatotoxicity.

Conclusion:

The results of this study indicate that CP causes considerable histopathological damage to the hepatic tissue of albino rats by demonstrating significant hepatocellular injury, inflammation, and alterations in vascular architecture. On the other hand, the histopathological changes observed in the liver sections from the CP and olive oil-treated group indicate a

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moderate degree of hepatotoxicity characterized by mild degeneration, vascular congestion, and localized necrosis. The protective effects of olive oil appear to mitigate some of these changes, preserving bile duct structure and reducing inflammation and fibrosis.

Recommendations:

These findings emphasize the need for careful monitoring of liver function in patients undergoing CP therapy and suggest potential pathways for therapeutic intervention to mitigate liver damage.

Ethical approval: All procedures were done with high ethical standards minimizing pain and distress and ensure humane treatment. All protocols are reviewed by the Faculty of Biomedical Sciences at the University of Benghazi scientific committee for compliance.

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