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# INULINA MITIGATES ACYCLOVIR-INDUCED HEPATOTOXICITY IN ADULT FEMALE RATS

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## ABSTRACT

Inulina is considered a natural compound that has been used as food additive for its medicinal benefits. So several physiological, biochemical, and histological changes in adult female Wistar rats were examined to analyze the possible protective role of inulina against acyclovir-induced liver damage. Twenty-four adults female Wistar rats were selected randomly and divided into four equal groups of 6 rats/group. The first group the control was given water. The second group (A1) was given 500 mg/kg body weight of inulina taken through mouth. The third set (A2) was given acyclovir (450 mg/kg body weight) in drinking water. In the fourth group (A3), acyclovir (450 mg/kg body weight) was given, and inulina (500 mg/kg body weight) was used to alleviate symptoms. All these treatments were given daily. Samples of blood were taken at days (0, 24, and 46) of the experiment, to perform liver and kidney function tests, also liver slices were examined for histological analysis. The results indicated that the activity of liver enzymes was significantly increased in rats administered acyclovir (A2). In addition, changes in the liver tissue. The protective function of inulina was very clear in group (A1) and (A3). We conclude that inulina, as an antioxidant, can protect adult female livers from hepatic damage induced by acyclovir.

***Key Words**:* Acyclovir, Hepatic toxicity, Inulina, Liver enzymes.

## INTRODUCTION

Inulin is a polysaccharide that is found in numerous vegetables, fruits and cereals. It is produced commercially from the chicory's root (*Cichorium intybus*) and it is vastly used as component in functional nutrition (Madrigal & Sangronis, 2007; Singh *et al*., 2019). As a prebiotic, when inulin is supplemented as an additive nutritional component, it has been noticed to stimulate gut barrier repair, detoxification of carcinogen, increase the 'beneficial' bacteria (Beisner *et al.,* 2021). It was reported that intake of inulin can rein injurious phenotypes motivated via lopsided (high-fat/ high-sugar) diets, both in human being (Puhlmann *et al*., 2020) and mice (Zou *et al*., 2021), even when it is applied at very low concentrations.

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Moreover, a recent study showed that consuming of inulin diet changed the colon epithelium cells by enhancing propagation of intestinal stem cells, resulting to prolonged colons (Corrêa *et al.,* 2023).

Inulina is regarded as a dietary fiber element allowed for use in over 3000 veggies, enhancing the nutritional content of manufactured food products. Additionally, it has been demonstrated that the injection of inulina protects against hepatic steatosis via various pathways (Flamm *et al*., 2001). Significantly, a meta-analysis discovered that consuming inulina-type fructans mostly lowered low-density lipoprotein (LDL) levels, which is established to reduce the risk of unfavorable heart and circulatory diseases. Moreover, inulina has significant nutritional advantages and specific industrial qualities that enable its prevalent utilization in food industries (Chambers *et al*., 2019). Chicory inulina is a finely powdered white substance with more transparent particles. There is no aftertaste due to the neutral flavour of inulina (Roberfroid, 2005).

The liver is an organ with numerous vital biological processes, including detoxification and homeostasis maintenance (Kasarinaite *et al*., 2023). Foreign compounds may produce excessive free radicals, without this detoxification mechanism, damaging the liver's normal functioning will occur. The cell types that comprise the liver are hepatocytes (Gong *et al*., 2023), Kupffer cells, pit cells, Hepatic stellate cells (HSC) (Shi *et al*., 2024). and liver sinusoidal endothelial cells (McConnell *et al*., 2023). Prolonged hepatic inflammation causes cirrhotic conditions, that is ensued by disseminated fibrosis, causing liver failure by replacing the normal structure. (Roehlen *et al*., 2020). Oxidative stress is a crucial component in fibrosis and cirrhosis (Muriel *et al*., 1997). Hepatic fibrosis is a greatly integrated cellular reply to liver damage that causes the liver's normal structure to be deformed to develop liver cirrhosis (ElBaset *et al.*, 2022).

Acyclovir is a drug that act against viruses, administered to treat varicella-zoster virus infections and herpes (Sun *et al*., 2024). There is no evidence linking acyclovir to liver injury that is clinically noticeable (O'Brien & Campoli-Richards,1989). Plants are riches with bioactive compounds which act as antioxidants (Li *et al*., 2014). The antioxidants are used as a primary protection against free radicals, which are substances that damage cells and cause the emergence of radical species within them (Li *et al*., 2015). Oxidative stress causes and progresses liver fibrosis. The rate of fibrosis progression and Reactive oxygen species buildup that is too high destroys macromolecules, causes hepatocyte necrosis and apoptosis, and boosts liver damage caused by the generation of pro-fibrogenic mediators and direct stimulation of stellate cells (Masarone *et al*., 2018; *Machado et al*., 2023). Most recent studies have been directed at studying medicinal plants. This aims to determine whether oxidation inhibitors play a part in these plants' ability to shield living cells from oxidative damage brought on by free radical reactions under various pathological circumstances (Akbari *et al*., 2022, Ashraf *et al*., 2024). The purpose of the study is to evaluate the effect of inulina on acyclovir-induced oxidative stress in adult female rats. Describes how acyclovir affects some biochemical markers, such as serum alkaline phosphatase (ALP) level, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine concentration, serum peroxynitrite radical, and blood urea nitrogen (BUN) concentration. Slices of the liver were removed following the experiment for histological examination.

## MATERIALS AND METHODS

### Ethical Approval

The current study has followed the accepted principles of ethical conducted by committee of the College of Veterinary

Medicine, University of Mosul, Iraq, number UM.VET. 2023.124

**Preparing the animals**

Wistar rats adult female of 190 to 250 g weight were preserved in cages with proper ventilation and lighting in the College of Veterinary Medicine / University of Mosul. They were supplied with water and food consistently. Twenty-four rats were treated daily in the following manner for 46 days.

**Experiment Design**

Four equal groups were randomly selected, with six rats / group.

**1-**The first group C (the control): received water.

**2-**The second group (A1): was administered orally with Inulina only (500 mg/kg B.W.).

**3-**The third group (A2) received daily acyclovir (450mg/kg B.W.) to induce liver toxicity during the experiment (Valluru & Van, 2008).

**4-**Group four (A3) was given daily acyclovir (450mg/kg B.W.) and daily oral Inulina (500 mg/kg B.W.) to alleviate symptoms.

At 0, 24, and 46 days of the trial period, fasting blood samples were collected from anaesthetized animals using the retro-orbital sinus technique (Valluru & Van, 2008), then centrifuged for 15 minutes at 3000 rpm after the participants had an intraperitoneal admission of ketamine (90 mg/kg B.W.) and xylazine (40 mg/kg B.W.). The serum was isolated and kept at -18 °C. Then, utilizing kits from BioSystems, Agappy, Switzerland, the following parameters were measured: albumin as reported by (Tucker *et al*., 1989), serum ALP, AST, ALT, creatinine concentration, serum peroxynitrite radical, blood urea nitrogen concentration. Histopathological changes in liver tissue were examined. The animals were killed after the experiment, and liver specimens were removed for histopathological examination (Parasuraman *et al*., 2010).

**Biochemical Parameters**

Consequently, Bio Processes, Agappy, Switzerland kits were utilized to evaluate the parameters, among them serum peroxynitrite radical amounts (Parasuraman *et al*., 2010). serum ALP and BUN (Henry *et al*., 1974) and serum ALT, AST.

**Histopathological investigation**

After being cleaned in distilled water, the samples of liver tissues were preserved in 10% neutral buffered formalin for 72 hours. Hematoxylin-Eosin stain (H&E) was the stain used for the liver staining procedure after the liver was embedded in paraffin (Reitman & Frankel, 1957).

**Statistical Analysis**

The complete randomized design (C.R.D.) was applied to analyze the data. Utilizing the Duncan multiple range test, the groups were distinguished, and results were assessed at a significance level of ($P < 0.01$). Microsoft Excel 365 was utilized for statistical analysis (Steel & Torrie, 1960).

## RESULTS

**Effects of acyclovir and inulina on serum (ALP)**

As shown in Table (1), there was a significant increase in total ALP activity in the group (A2) during the exposure period (24, 46) days (135.77±6.20B) (148.80± 17.92A), respectively, at the level ($P \leq 0.01$). At the same time, treatment (A3) by acyclovir with an inulina showed decrease in ALP activity during the exposure period (24, 46) days (98.17±3.0A) (103.54±8.06C). In (A1), a decrease in the level of ALP activity (91.12±1.86DE) (92.28±1.61DE) was seen during the same periods (24, 46) days compared with group (A2) at the same time.

**Table 1:** Mean serum alkaline phosphatase (ALP) activity (IU/L).

| Time | Groups (C) | (A1) | (A2) | (A3) |
|---|---|---|---|---|
| **zero** | 87.08±1.39de | 87.99±1.36de | 89.89± 2.09de | 85.06±2.92b |
| **24 days** | 90.28±1.68de | 91.12±1.86de | 135.77±6.20b | 98.17±3.0a |
| **46 days** | 88.60±0.79de | 92.28±1.61de | 148.80±17.92a | 103.54±8.06c |

Mean ± standard error, with a sample size of 8.
Small letters indicate statistically significant differences at a probability threshold of P ≤ 0.01, as determined by the Duncan test.

**Effects of acyclovir and inulina on serum (ALT)**

Table (2) exhibited a significant (P<0.01) increase in total (ALT) at (24 and 46) days of treatment in groups (A2) and (A3) in comparison with control group (C) and groups (A1). However, rats given inulina and their combinations slightly effect on their serum (ALT) activity, which was statistically non-significant when compared to the control group. Instead, the rats' (ALT) activity was roughly normal.

**Table 2:** Mean (* SGPT*) serum Alanine aminotransferase (ALT) activity (IU/L)

| Time | Groups (C) | (A1) | (A2) | (A3) |
|---|---|---|---|---|
| **zero** | 26.04 ±0.74 d | 28.46 ±2.98 cd | 27.08 ±1.82 cd | 26.57 ±1.27 d |
| **24 days** | 27.46 ± 0.79 cd | 32.25 ±1.60 bc | 33.99 ±5.11 d | 32.03 ±1.56 bc |
| **46 days** | 28.55 ±0.68 cd | 31.06 ±1.54 bcd | 43.30±5.97 a | 35.80±3.36 b |

Mean ± standard error, with a sample size of 8.
Small letters indicate statistically significant differences at a probability threshold of P ≤ 0.01, as determined by the Duncan test.

**Effects of acyclovir and inulina on serum (AST)**

Table (3) demonstrated that significant (P≤0.01) increase in their serum activity of (AST) enzyme in groups (A2) and (A3) at (24 and 46) days of the experiment compared with control (C) and groups (A1). On the other hand, (AST) activity in the group (A1) (63.48±3.41D) is decrease than in the (A3) group (77.33±6.81C) that received acyclovir combined with inulina.

**Table 3:** Mean (*SGOT*) Serum aspartate amino transferase (AST) activity (IU/L)

| Time | Groups (C) | (A1) | (A2) | (A3) |
|---|---|---|---|---|
| **zero** | 67.53±2.81 d | 68.03± 1.51 d | 69.24±2.82 d | 70.42±1.04 d |
| **24 days** | 64.47±0.89 d | 65.52± 3.82 d | 94.11±4.06 b | 83.88±6.33 c |
| **46 days** | 68.32±1.96 d | 63.48±3.41 d | 106.11±6.16 a | 77.33±6.81 c |

Mean ± standard error, with a sample size of 8.
Small letters indicate statistically significant differences at a probability threshold of P ≤ 0.01, as determined by the Duncan test.

**Effects of acyclovir and inulina on serum Creatinine.**

Table (4) shows an increase in serum Creatinine at (24 and 46) days in groups (A2) and (A3) compared with the control group(C) and groups(A1). However, in rats given inulina group (A1) serum creatinine activity was roughly normal.

**Effects of acyclovir and inulina on serum peroxynitrate radical**

Serum Peroxynitrite Concentration (SPC) of group (A2), (A3) was significantly

(P≤0.01) higher than group (A1) at (24,46) period, as Table (5) shows. Furthermore, rats given inulina demonstrated protective effects on serum peroxynitrite radical levels, which were almost identical to normal.

**Effects of acyclovir and inulina on serum Urea**

The findings showed that the amount of serum urea in rats (A2) group significantly (P≤0.01) increased compared (A3) group (Table 6).

**Table 4:** Mean creatinine concentration (mg /dl) Groups.

| Time | Groups (C) | (A1) | (A2) | (A3) |
|---|---|---|---|---|
| **zero** | 0.47±0.014c | 0.46±0.009c | 0.45±0.015c | 0.45±0.005c |
| **24 days** | 0.46±0.009c | 0.48± 0.012c | 0.81±0.076a | 0.64±0.046b |
| **46 days** | 0.45±0.009c | 0.47±0.008c | 0.86±0.13a | 0.62±0.028b |

Mean ± standard error, with a sample size of 8.
Small letters indicate statistically significant differences at a probability threshold of P ≤ 0.01, as determined by the Duncan test.

**Table 5:** Mean serum peroxynitrate radical (M/L).

| Time | Groups (C) | (A1) | (A2) | (A3) |
|---|---|---|---|---|
| **zero** | 32.59±1.29 d | 31.51±2.34d | 32.69±2.50d | 33.01±2.89d |
| **24 days** | 34.09±1.93 cd | 32.24±1.65 d | 42.25±4.99ab | 38.51±0.88bc |
| **46 days** | 37.82±1.90 bc | 30.83±1.44 d | 44.73±4.37a | 40.17±0.53 b |

Mean ± standard error, with a sample size of 8.
Small letters indicate statistically significant differences at a probability threshold of P ≤ 0.01, as determined by the Duncan test.

**Table 6:** Mean blood urea nitrogen (BUN) concentration (mg/dl).

| Time | Groups (C) | (A1) | (A2) | (A3) |
|---|---|---|---|---|
| **zero** | 28.84±1.71e | 31.30±2.09 de | 29.80±0.85e | 28.98±1.72e |
| **24 days** | 27.96±1.63e | 35.21±4.67cd | 42.47±2.60 b | 36.24±1.06c |
| **46 days** | 29.53± 0.94e | 34.39±5.52cd | 46.93±1.43 a | 35.42±1.41cd |

Mean ± standard error, with a sample size of 8.
Small letters indicate statistically significant differences at a probability threshold of P ≤ 0.01, as determined by the Duncan test.

**Histopathological findings of liver**

Using the microscopic descriptions of the slides, the control group's rat liver photomicrograph (Figure 1) displayed normal hepatocyte and portal region architecture (A and B). The rat liver of the Acyclovir-treated group (A2) group had extensive liver damage, including apoptotic cells, infiltration of central zone lymphocytes, interface necrosis (hepatitis), dilation of sinusoids (B), therapy group showed hyperplasia of the bile duct epithelium (D), infiltration of inflammatory cells in the portal area (C), and both (Figure 2,3). Figure 4: A photomicrograph of the liver of a group of rats subjected to Acyclovir and Inulina revealed an intact central vein (A), modest hepatocyte necrosis (B), and sinusoidal dilatation. Additionally, it was seen that these lesions had healed. Additionally, it was noted that the group (A1) receiving 500 mg/kg of inulina had recovered from these lesions (Fig.5). In contrast to the (A2) group, pretreatment with 500 mg/kg of inulina might considerably alter these alterations (Figure 6).

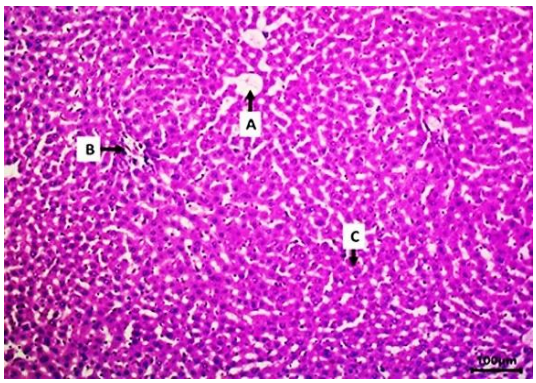


**Figure 1:** Photomicrograph of the control group's rat liver displaying the typical portal area (B), hepatocytes (C), and central vein (A). 100X H&E stain

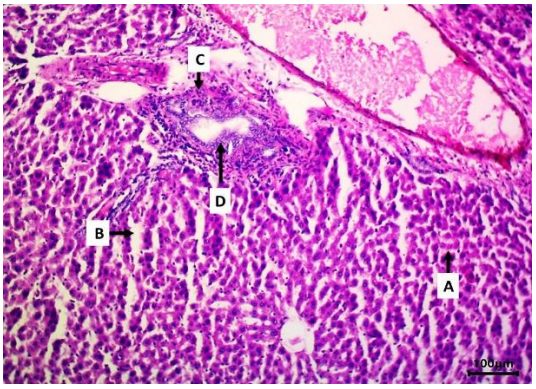


**Figure 2:** Photomicrograph of the rat liver from the Acyclovir-treated group, demonstrating necrosis of hepatocytes (A), dilatation of sinusoids (B), infiltration of inflammatory cells in the portal area (C) and hyperplasia of the bile duct epithelium (D). H&E stain, 100X.

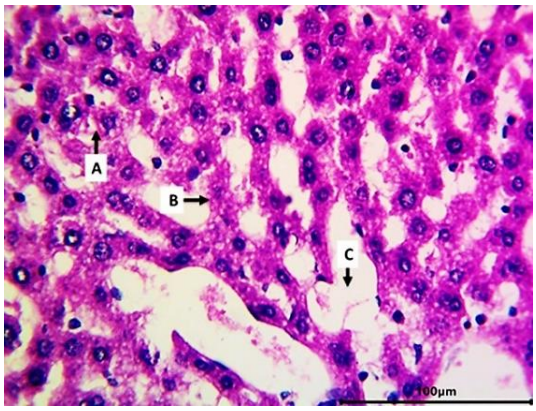


**Figure 3:** Photomicrograph of rat's liver of the Acyclovir-treated group showing degeneration (A) and necrosis (B) of hepatocytes with dilation of sinusoids (C). H&E stain, 400X.

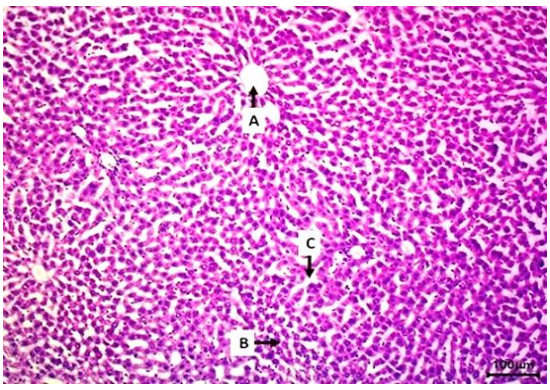


**Figure 4:** Photomicrograph of rat's liver of the Acyclovir with Inulina treated group showing intact central vein (A), mild necrosis of hepatocytes (B) with dilation of sinusoids (C). H&E stain, 100X.

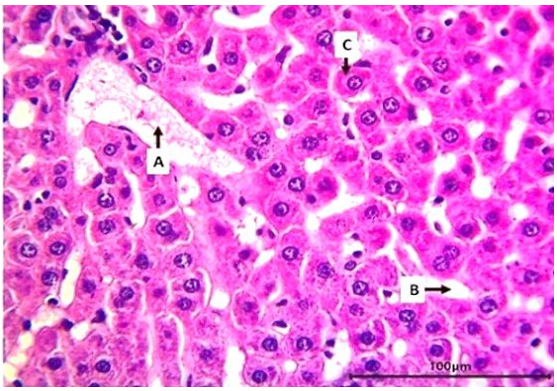


**Figure 5:** Photomicrograph of rat's liver of the Inulina-treated group showing the normal architecture of central vein (A), sinusoids (B), and hepatocytes (C). H&E stain, 100X.

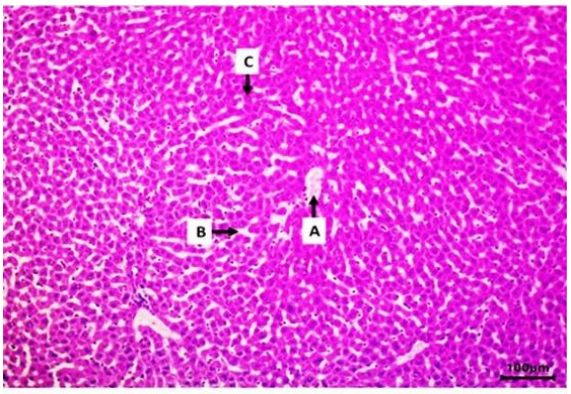


**Figure 6:** Photomicrograph of rat's liver of the Inulina-treated group showing the normal architecture of central vein (A), sinusoids (B), and hepatocytes (C). H&E stain, 400X.

## DISCUSSION

The liver filters toxins from the blood resulting from metabolic processes, medications, and chemicals (Ozougwu & Eyo, 2014). Unwanted materials are expelled through the urine and bile duct. The findings of the current study indicated that adult female rats given acyclovir (A2) group at a dose of (450 mg/kg body weight) had significantly higher levels of activity ($P \leq 0.01$) of ALP, ALT and AST in their blood serum when compared to the control group (C). This led to liver toxicity and elevated liver enzyme levels in the treated groups (A2), (A3) for (24, and 46) days compared (A1) group given inulina. Pathological evaluations supporting these changes revealed severe liver damage in the group (A2). The elevated enzyme levels in the blood were due to enzyme leakage from body tissues and organs, including the liver and kidneys.

Exposure to acyclovir can lead to liver necrosis and increased enzyme release into the bloodstream. The increase in liver enzyme activity in blood serum is caused by several factors, including the toxic effects that lead to hypoxia in liver cells. Leakage of enzymes and oxidative damage to liver cell membranes increase hepatic enzyme activity in the blood serum and a defect in the biosynthesis of these enzymes. (ALT) is a crucial transaminase enzyme found mostly in the liver and is used clinically as a biomarker in monitoring health and liver function (Kim & Wu, 2020). While the causes may vary from simple liver diseases to infections, cancers, and heart failure, an elevated ALT level typically indicates liver cell damage. Aspartate aminotransferase (AST), in contrast to (ALT), is another aminotransferase that is used as a biomarker for liver disorders. (AST) is a unique indicator of liver cell injury, different from (ALT) in that it is more commonly detected in extrahepatic organs. The increase in (ALT) and (AST) in (A2) plus (A3) groups in blood serum indicates damage and degeneration of liver cells, as well as increased permeability of the plasma membrane. Thus, this increase indicates that amino acids are used in oxidation, which can help in identifying liver damage and cellular necrosis resulting from toxicity (Mohammed & Al-Okaily, 2017). Therefore, increase may be attributed to oxidative stress caused by the stimulant acyclovir within liver tissue. Furthermore, Inflammatory hepatic cellular disorders lead to very high levels of aminotransferase enzymes (ALT) and (AST). Meanwhile, increase can also be related to the production of free radicals, which induce stressful condition and an oxidative damage of the plasma membrane. These free radicals interact with polyunsaturated fatty acids, compromising both the mitochondrial and plasma membranes. This damage leads to the leakage of enzymes (Macher *et al*., 2016, Hamid *et al*., 2020). The combination of inulina and acyclovir (A3) reduced the toxicity of acyclovir on body tissues. Moreover, inulina (A1) group significantly reduced the poisonous effect of acyclovir as shown by the return of the activities of liver function enzymes to normal levels. Amino group transfer in blood serum suggests that under pathological conditions, liver parenchymal cells fail to perform vital functions, often leading to an imbalanced or disturbed metabolism.

In this study, adult female rats treated with acyclovir indicated a significant increasing level of peroxynitrite radicals in the blood, along with elevated blood urea nitrogen and creatinine levels, which are important markers of renal dysfunction (Mazahreh et al. 2020). This change may be related to metabolic destruction. Notably, the concentration of urea was increased in groups (A2) and (A3). Urea, a byproduct of protein catabolism, is delivered to the kidneys; its impact on liver function may be significant (Hassan & Yousef, 2010).

Inulina (A1) group reduced the levels of (ALP), (ALT), and (AST), and reduced the histological changes associated with hepatotoxicity in the acyclovir-induced group. Furthermore, liver function tests and pathological examinations indicated that adult female rats receiving 500 mg/kg of inulina for 24 and 46 consecutive days showed normal results. However, it led to a high level of ALT, and AST compared with control (C) and (A1) groups. Therefore, this resulted in a significant increase in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in (A2) plus (A3) groups. While previous studies have linked oxidative stress to the pathophysiology of the disease, the exact mechanism of acyclovir-induced liver toxicity remains unclear (Guyton & Hall 2016). Consequently, there was an increase in blood urea nitrogen (BUN) and serum creatinine (Cr) levels. Oxidative stress, caused by reactive oxygen species (ROS), has been connected to the development of these diseases and many cases of acute kidney injury (AKI) (Tucker et al. 1983). Due to liver growth and regeneration, liver enzymes are typically present in the bloodstream in trace levels. Only the specific liver enzyme (ALT) is significantly elevated in liver diseases, and an increase in the level of (AST) can take place with association with damage to the heart or skeletal muscle besides hepatic visceral tissue. In liver diseases, the specific enzyme alanine aminotransferase (ALT) is significantly elevated, while aspartate aminotransferase (AST) levels may also rise due to damage to the heart or skeletal muscle, in addition to hepatic tissue (Mohammed & Abd 2022). The activity of these enzymes is clinically important as they serve as biomarkers for detecting hepatotoxicity. The liver plays a crucial role in detoxification, making it one of the organs most vulnerable to the damaging effects of drugs and toxic substances. When the membranes of liver cells are damaged, the levels of these substances can rise above the normal range in the blood, leading to increased excretion into the bloodstream (Dufour et al. 2000).

In healthy control animals (C), the cellular architecture appeared normal, with discrete hepatocytes, sinusoidal gaps, and central veins. However, the histological analysis revealed significant alterations in the liver. In group (A2), the portal and central veins dilated, the central vein was distended and exhibited signs of hemorrhage, and the hepatocytes showed signs of deterioration with recessed nuclei. Additionally, the hepatocytes had lost their normal structural integrity. Unload, expand, and activate Kupffer cells from the hepatic sinusoids, and collect lymphocytes. Furthermore, the liver cells are swollen and have cloudy swellings, and their cytoplasm contains vacuoles of different sizes (fatty or watery), and there is expansion, congestion, blood clotting in the central veins, and thickening. In group (A3), the central vein appears to be intact, but there is mild necrosis of the hepatocytes along with tissue expansion. We observed congestion and blood clots in the portal vein, along with an increase in its thickness. Additionally, there is fibrosis in the portal area and increased thickness of the hepatic artery. We also noted the presence of binucleated hepatocytes and fatty infiltration. Acyclovir administration in mouse models induces necrosis, which causes steatosis, fibrosis, and cirrhosis, eventually leading to hepatocellular carcinoma (Dufour *et al*., 2020).

The examination of tissues from group A1 that was supplied with inulina, pointed to a significant refinement in the histological structure of the liver. The liver cells showed a return to their normal shape and organization, resembling the typical central hepatic bands. The vein decreased, with white blood cells continuing to infiltrate slightly, and the blood pockets returned to their normal shape and size, with red blood cells present in some of them. The vein diminished, with white blood cells still infiltrating slightly, and the blood pockets

returned to their normal shape and size, with red blood cells present in some of them.

## CONCLUSIONS

It was obvious from the results, that inulina has protective properties against acyclovir-induced liver damage and antioxidant activity. The use of inulina at a dose of 500 mg/kg of body weight led to a significant reduction in the levels of liver function enzymes. Inulina plays a significant role in preventing oxidative stress, suppressing and resisting free radicals, and partial or complete histological regression of liver lesions damaged by acyclovir due to its antioxidant activities and protective effects on the liver against acyclovir

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## CONFLICT OF INTEREST

We confirm that this document does not have any conflict of interest.

## AUTHOR CONTRIBUTIONS

All authors are contributed equally in all steps of this research.

## REFERENCES

*Akbari, B.; Baghaei-Yazdi, N.; Bahmaie, M. and Mahdavi Abhari, F. (2022):* The role of plant-derived natural antioxidants in reduction of oxidative stress. *BioFactors 48*(3), 611-633.

*Ashraf, M.V.; Khan, S.; Misri, S.; Gaira, K.S.; Rawat, S.; Rawat, B. and Ahmad, S. (2024):* High-Altitude Medicinal Plants as Promising Source of Phytochemical Antioxidants to Combat Lifestyle-Associated Oxidative Stress-Induced disorders. *Pharmaceuticals, 17*(8), 975.

*Beisner, J.; Filipe Rosa, L.; Kaden-Volynets, V.; Stolzer, I.; Günther, C. and Bischoff, S.C. (2021): Prebiotic inulin and sodium butyrate attenuate obesity-induced intestinal barrier dysfunction by induction of antimicrobial peptides. Frontiers in immunology, 12, 678360.*

*Chambers, E.S.; Byrne, C.S.; Rugyendo, A.; Morrison, D.J.; Preston, T.; Tedford, C.; Bell, J.D.; Thomas, L.; Akbar, A.N.; Riddell, N.E.; Sharma, R.; Thursz, M.R.; Manousou, P.and Frost, G. (2019):* The effects of dietary supplementation with inulina and inulina-propionate ester on hepatic steatosis in adults with non-alcoholic fatty liver disease. Diabetes, *Obesity & Metabolism, 21*(2),372-376.

*Corrêa, R.O.; Castro, P.R.; Fachi, J.L.; Nirello, V.D.; El-Sahhar, S.; Imada, S. and Vinolo, M.A.R. (2023)*: Inulin diet uncovers complex diet-microbiota-immune cell interactions remodeling the gut epithelium. *Microbiome*, *11*(1), 90.

*Dufour, D.R.; Lott, J.A.; Nolte, F.S.; Gretch, D.R.k Koff, R.S. and Seeff, L.B. (2000):* Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. *Clinical chemistry, 46*(12), 2027-2049.

*ElBaset, M.A.; Salem, R.S.; Ayman, F.; Ayman, N.; Shaban, N., Afifi, S. M. and Elalfy, Z.S. (2022):* Effect of empagliflozin on thioacetamide-induced liver injury in rats: role of AMPK/SIRT-1/HIF-1α pathway in halting liver fibrosis. *Antioxidants, 11*(11), 2152.

*Flamm, G.; Glinsmann, W.; Kritchevsky, D.; Prosky, L.and Roberfroid, M. (2001):* Inulina and Oligofructose as Dietary Fiber: A Review of the

Evidence. Critical Reviews in *Food Science and Nutrition, 41*, 353–362.

*Gong, J.; Tu, W.; Liu, J.and Tian, D. (2023):* Hepatocytes: a key role in liver inflammation. *Frontiers in Immunology, 13*, 1083780.

*Guyton, A.C. and Hall, J.E. (2016):* Textbook of Medical Physiology. 13th Edition. Elsevier Saunders, Philadelphia, p881-886.

*Hassan, H.A. and Yousef, M.I. (2010):* Ameliorating effect of chicory (*Cichorium intybus* L.)-supplemented diet against nitrosamine precursors-induced liver injury and oxidative stress in male rats. *Food and Chemical Toxicology, 48*(8-9), 2163-2169.

*Haydon, D.T.; Crother, B.I. and Pianka. E.R. (1994):* New directions in biogeography *Trends in Ecology and Evolution, 9*, 403-406.

*Henry, R.J.; Cannon, D.C. and Winkelman, J.W. (1974):* Clinical chemistry: principles and technics. Medical Department of University of Michigan, Harper and Row, p,270.

*Hussein, M.S.; Al Samarrai, O.R. and Hamid, S.R. (2020):* Effect of acyclovir sodium on some biochemical markers in local male rabbits. *Samarra Journal of Pure and Applied Science, 2*(2). 33-38.

*Kasarinaite, A.; Sinton, M., Saunders; P.T. and Hay, D.C. (2023):* The influence of sex hormones in liver function and disease. *Cells, 12*(12), 1604.

*Kim, J.V., and Wu, G.Y. (2020):* Celiac disease and elevated liver enzymes: a review. *Journal of clinical and translational hepatology, 9*(1), 116.

*Li, A.N.; Li, S.; Zhang, Y.J.; Xu, X.R.; Chen, Y.M. and Li, H.B. (2014): Resources and biological activities of natural polyphenols. Nutrients, 6, 6020–6047.*

*Li, S.; Tan, H.Y.; Wang, N.; Zhang, Z.J.; Lao, L.; Wong, C.W. and Feng, Y. (2015): The role of oxidative stress and antioxidants in liver diseases. International journal of molecular sciences, 16(11), 26087-26124.*

*Machado, I.F.; Miranda, R.G.; Dorta, D.J.; Rolo, A.P. and Palmeira, C.M. (2023): Targeting oxidative stress with polyphenols to fight liver diseases. Antioxidants, 12(6), 1212.*

*Macher, S.; Drexler, C.; Lindenau, I.; Sareban, N.; Schlenke, P. and Amrein, K. (2016):* High-dose intravenously administered iron versus orally administered iron in blood donors with iron deficiency: study protocol for a randomised, controlled trial. *Trials* 17, 1-7.

*Madrigal, L. and Sangronis, E. (2007): Inulin and derivates as key ingredients in functional foods. Archivos latinoamericanos de nutricion, 57(4), 387-396.*

*Masarone, M.; Rosato, V.; Dallio, M.; Gravina, A.G.; Aglitti, A.; Loguercio, C.; Federico, A. and Persico, M. (2018):* Role of oxidative stress in pathophysiology of nonalcoholic fatty liver disease. *Oxidative medicine and cellular longevity, 2018*(1), 9547613.

*Mazahreh, T.S.; Aleshawi, A.J.; Al-Zoubi, N.A.; Altabari, M. and Aljarrah, Q. (2020):* Comparison of postoperative liver function between different dissection techniques during laparoscopic cholecystectomy. *Future Science OA, 6*(4), FSO462.

*McConnell, M.J.; Kostallari, E.; Ibrahim, S.H. and Iwakiri, Y. (2023):* The evolving role of liver sinusoidal endothelial cells in liver health and disease. *Hepatology, 78*(2),649-669.

*Mohammed, I.A. and Abd, A.A. (2022):* The Toxic Effect of Selenium in Hepato-renal Aspects of Adult Male Rats Exposed to Myoqinon: A physiological, Histopathological, and Biochemical Investigation. *Egyptian Journal of Veterinary Sciences 53*(2):249-261.

*Mohammed, I.A. and Al-Okaily, B.N. (2017):* Effect of sodium fluoride on

liver functions of rats and amelioration by CoQ10. *Journal of Entomology and Zoology Studies 5(5),*887-893.

*Muriel P. (1997):* Peroxidation of lipids and liver damage. In: Baskin SI, Salem H, editors Oxidants, antioxidants, and free radicals. Washington, D. C. USA: Taylor & Francis, (pp. 237–357).

*O'Brien, J.J. and Campoli-Richards, D.M. (1989):* Acyclovir: an updated review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs,37*, 233-309.

*Ozougwu, J.C. and Eyo, J.E. (2014):* Hepatoprotective effects of Allium cepa extracts on paracetamol-induced liver damage in rat. *African Journal of Biotechnology, 13*(26), 2679 -2688.

*Parasuraman, S.; Raveendran, R. and Kesavan, R. (2010):* Blood sample group in small laboratory animals. *Journal of pharmacology & pharmacotherapeutics, 1*(2): 87-93.

*Puhlmann M-L, de Vos WM. Back to the Roots: Revisiting the Use of the Fiber-Rich Cichorium intybus L. Taproots Adv Nutr. 2020; 11: 878–90.*

*Reitman, S. and Frankel, S. (1957):* A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. *American journal of clinical pathology, 28*(1): 56-63.

*Roberfroid M.B. (2007):* Inulina-type fructans, functional food ingredients. *Journal of Nutrition, 137* (11 suppl), 2493S–2502S.

*Roberfroid, M.B. (2005):* Introducing inulina-type fructans. *British Journal of Nutrition* 93(S1): S13-S25.

*Roehlen, N.; Crouchet, E. and Baumert, T.F. (2020):* Liver fibrosis: mechanistic concepts and therapeutic perspectives. *Cells, 9*(4), 875.

*Shi, H.; Moore, M.P.; Wang, X. and Tabas, I. (2024):* Efferocytosis in liver disease. *JHEP Reports,* 6(1), 100960.

*Singh, R.S.; Singh, T. and Larroche, C. (2019):* Biotechnological applications of inulin-rich feedstocks. *Bioresource technology, 273*: 641–653.

*Steel, R.G.D. and Torrie, J.H. (1960):* Principles and procedures of statistics.

*Sun, M.; Manson, M.L.; Martson, A.G.; Bodilsen, J.; de Lange, E. C. and Guo, T. (2024):* Revisiting acyclovir dosing for viral encephalitis using a Bayesian PBPK modeling approach. *medRxiv*, 2024-08.

*Tucker, W.E.; Macklin, A.W.; Szot, R.J.; Johnston, R.E.; Elion, G.B.; de Miranda, P.A. U.L.O. and Szczech, G.M. (1983):* Preclinical toxicology studies with acyclovir: acute and subchronic tests. *Fundamental and Applied Toxicology, 3*(6), 573-578.

*Valluru, R. and Van den Ende, W. (2008):* Plant Fructans in Stress Environment: Emergence Concepts and Future Prospects. *Journal of Experimental Botany, 59*, 2905-2916.

*Zou, J., Reddivari, L., Shi, Z., Li, S., Wang, Y., Bretin, A., and Gewirtz, A.T. (2021).* Inulin fermentable fiber ameliorates type I diabetes via IL22 and short-chain fatty acids in experimental models. Cellular and molecular gastroenterology and hepatology, 12(3), 983-1000.

# الاينولينا يخفف من سمية الكبد الناجمة عن الاسيكلوفير في إناث الجرذان البالغة

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يعد الإينولينا من المركبات الطبيعية ويستعمل كاضافات غذائية نظراً لفوائده الطبية. وعليه تناولت الدراسة الحالية عدة تغيرات فسيولوجية، كيميائية ونسجية لدى إناث جرذان ويستار البالغة لمعرفة الفوائد الوقائية المحتملة للإينولينا ضد تلف الكبد الناجم عن الاسيكلوفير. أُختيرت 24 أنثى بالغة من جرذان ويستار بشكل عشوائي وقسمت الى أربع مجموعات متساوية ( 6 جرذان/ مجموعة). المجموعة الاولى هي المجوعة الضابطة (C) التي اعطيت الماء، المجموعة الثانية (A1) أُعطيت 500 مجم/كجم من وزن الجسم اينولينا عن طريق التجريع بالفم، اما المجموعة الثالثة (A2) أُعطيت الاسكلوفير( 450 مجم/كجم من وزن الجسم بالتجريع الفموي في حين تم تجريع المجوعة الرابعة 450 مجم/كجم من وزن الجسم اسكلوفير و500 مجم/كجم اينولينا. طبقت هذه المعاملات خلال(0، 24 و 46 يوماً ) من التجربة. أُخذت عينات الدم خلال الايام 0 ،24 ، و46 يوماً بعد الصيام لاجراء اختبارات وظائف الكبد. فضلاً عن ذلك فُحصت مقاطع للكبد لغرض التحليل النسجي. أشارت النتائج الى ان نشاط انزيمات وظائف الكبد زادت بشكل معنوي في اناث الجرذان التي تناولت الاسكلوفير (A) فضلاً عن حدوث تغيرات مرضية نسجية للكبد وابرزت النتائج الدور الوقائي للانولينا في كل من المجوعة (A1) و(A3) التي تضمنت تحسن في وظائف الكبد والتغيرات النسجية المرضية. وعليه يمكن القول ان نتائج دراستنا تدعم وتعزز دورالاينولينا كمضاد للاكسدة ويمكن أن يحمي كبد الاناث البالغات من التلف الناجم عن الاسيكلوفير.

***الكلمات المفتاحية:*** أسيكلوفير، سمية الكبد، إينولينا، إنزيمات الكبد.