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Assessment of The Protective Role of Ginger Against Paracetamol-Induced Hepatotoxicity: A Comparative Study According to the Time Period

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تقييم الدور الوقائي للزنجبيل ضد سمية الكبد الناتجة عن الباراسيتامول: دراسة مقارنة وفقا للفترة الزمنية

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Abstract:
Following a previous study (2013) that demonstrated ginger,s failure to protect the liver from paracetamol toxicity and its potential to exacerbate the harmful effects. This study aimed to clarify whether the duration of the dose used in the experiment affected ginger,s protective role. Male rabbits were used to study the effects of different doses of aqueous ginger extract (100,200,400)mg administered for 15 and 30 days on paracetamol-induced hepatotoxicity. The results showed that paracetamol caused liver tissue damage, elevated ALP,AST,ALT, Bilirubin levels, and decreased Albumin, total protein levels. Pre-dose of ginger for 15 days improved the physiological and histological changes. Unfortunately, pre-dose of ginger for 30 days further reduced albumin levels.

Keywords: Ginger, Hipatotoxicity, Paracetamol

الملخص
بناءا على دراسة سابقة اجريت سنة (2013) والتي تبين فيها فشل الزنجبيل في حماية الكبد من سمية الباراسيتامول بل فاقم آثاره ضارة. هدفت هذه الدراسة الى توضيح ما اذا كانت مدة التجريع المستخدمة اثر على الدور الوقائي للزنجبيل. حيث تم استخدام ذكور الأرانب لدراسة تأثيرات الجرعات المختلفة من مستخلص الزنجبيل المائي(100,200,400)ملغ/كغ لمدة 15يوم و30يوم على السمية الكبدية التي يسببها الباراسيتامول. اظهرت النتائج أن الباراسيتامول تسبب في تلف أنسجة الكبد وارتفاع مستوى (ALP,AST,ALT) وكذلك البيليروبين الكلي، وأدى الى انخفاض مستوى الالبومين والبروتين الكلي. وتبين أن التجريع المسبق للمستخلص المائي للزنجبيل لمدة 15 يوم أدى الى تحسين التغيرات الفسيولوجية والنسيجية، في حين خفض التجريع المسبق للمستخلص المائي للزنجبيل لمدة 30 يوم من مستوى الالبومين.

الكلمات المفتاحية: الزنجبيل، السمية الكبدية، الباراسيتامول

1. Introduction

The use of medicinal plants in treating diseases is one of the most popular areas of traditional medicine worldwide, this expansion in use is attributed to a better understanding of the mechanisms by which plant products positively and effectively affect the body's health. (Panda & Naik, 2009) Numerous studies have shown the importance of plant extracts in protecting living tissues from the harmful effects of free radicals. Among these plants is ginger *Zingiber officinale*, a tropical plant belonging to the Zingiberaceae family, which has an important place in herbal medicine. (Castleman, 2001)

Ginger contains many effective chemical compounds that are used in the treatment of many diseases, especially polyphenolic compounds and flavonoids. As well 6-gingerol and shogaol which is characterized by antioxidant activity where it enhances the copying of protective genes in cells (HO-1, NQOI, GCLC) by activating the pathway Nrf 2-ARE it helps regulate GSH metabolism and maintains the balance of oxidation and reduction. (Hong *et al.*, 2020) and anti-cancer, which distinguishes ginger with its distinctive taste. (Rahmani & Aly, 2014; Prasad & Tyagi, 2015)

The liver is one of the most important organs in the metabolic process, the liver is the primary target of toxicity resulting from drugs and foreign bodies. (Sachan & Singh, 2018) liver toxicity may be caused by reactive metabolites resulting from the metabolism of the primary drug compound, and not directly from the primary compound. (Saukkonen *et al.*, 2006) which therefore depends on the concentration of the toxic substance. (Kedderis, 1996) some studies have shown that some drugs, such as fenitrothion, paracetamol, It may cause liver and kidney toxicity in experimental animals, (El-Naggar *et al.*, 2015; Rašković *et al.*, 2015) and at high doses of paracetamol it causes a great depletion of glutathione (GSH) from the liver cells, which results in the generation of free radicals, so it causes liver toxicity. (Sarkar *et al.*, 2022; Jaeschke & Ramachandran, 2024) Therefore, the aim of this study was to investigate the effects of different doses of aqueous ginger extract (100,200,400)mg administered for 15 and 30 days on paracetamol-induced hepatotoxicity.

2. Materials and Methods

2.1 Experimental animals:

In this study, 48 adult male local rabbits were used, weighing between 800 and 2000 grams approximately, which were obtained from the markets and were housed in cages and provided with all laboratory conditions of ventilation and lighting (13 hours of light: 11 hours of darkness) and a temperature of 25 + 2 C. They were provided with drinking water.

2.2 Plant sample collection:

Ginger roots were obtained from local markets, where they were cleaned, dried and ground with an electric mixer to obtain a fine powder.

2.3 Preparation of the aqueous extract of ginger:

The aqueous extract of ginger was prepared according to (Shalaby & Saifan, 2014), where one liter of distilled water was added to 200 grams of plant powder and left to boil for 10 minutes, then the solution was left to cool, next the solution was filtered. The extract concentration of 200mg/ml, half of which is (100mg) and double concentration (400mg) and the extract was kept in the refrigerator until it was used to dose rabbits through the gastric tube.

2.4 Chemicals:

Paracetamol tablets 500 mg were used from the company BRISTOL LABORATORIES LTD Which were purchased from local pharmacies and then one and a half tablets were dissolved in 5 ml of distilled water.

2.5 Experimental design:

48 male rabbits, were left for a week as an acclimatization period they were randomly divided into 8 groups, with 6 rabbits in each group, which were treated as following: **Group1**: The control group was treated with a physiological solution for 30 days. **Group2**: was given a single dose of Paracetamol 750 mg /kg of body weight. based on previous searches that used paracetamol at the same dose and duration (رمزي, 2011; Mejbel *et al.*, 2024) **Group 3**:Daily dose of ginger extract 100 mg / kg for 15 days and after 30 minutes of the last dose, a dose of 750 mg paracetamol. **Group 4:** Daily dose of ginger extract dose 200 mg /kg for 15 days and after 30 minutes of the last dose, a dose of paracetamol 750 mg /kg. was **Group 5:**Daily dose of ginger extract dose 400 mg/kg for 15 days and after 30 minutes of the last dose, a dose of 750 mg paracetamol. **Group 6**: Daily dose of ginger extract dose 100 mg /kg for 30 days and after 30 minutes of the last dose, a dose of paracetamol 750 mg /kg. **Group 7:** Daily dose of ginger extract dose 200 mg /kg for 30 days and after 30 minutes of the last dose, a dose of paracetamol 750 mg /kg. **Group 8:** Daily dose of ginger extract dose 400 mg/kg for 30 days and after 30 minutes of the last dose, a dose of paracetamol 750 mg /kg.

2.6 Biochemical analyses:

The secretion rate of some liver enzymes was measured using a spectrophotometer manufactured by the German company ROBERT, where the reagents used to measure the concentration of enzymes were used. The activity of aspartate aminotransferase (AST), Alanine aminotransferase (ALT) enzymes was measured using UV light according to the International Federation of Clinical Chemistry and laboratory medicine (IFCC) , while the activity of alkaline phosphatase (ALP) was measured using kinetic photometer according to the (IFCC) method (Thomas, 1998) using Diasys reagent kits. Serum total protein and total bilirubin concentrations were determined according to the method of (Thomas, 1998) using a spectrophotometer, while serum albumin was estimated according to the method (Doumas *et al.*, 1997) using the colorimetric method.

2.7 Histopathological study:

Samples of liver tissue were embedded in paraffin blocks, dehydrated in increasing alcohol grades, and fixed in a 10% buffered formalin solution. After cutting 4-5 µm slices from the prepared blocks and staining them with haematoxylin and eosin (H&E). the pathologist used a ligth microscope (Optika microscope) made in italy to see the preparations.(الانصاري & سلامة, 1999)

2.8 Statistical analysis:

The results were analyzed statistically using the (SPSS-25) statistical program. And were expressed as mean ± the (SEM) standard error. One-way analysis of variance (ANOVA) was used to examine the data for comparisons between various variables. Comparisons between groups were performed using the Dunnett test, and the predictive value of (P-value) was used, which indicates the statistical significance if it is less than 5%.

3. Results:

The results indicated in that, the rabbits treated with a single dose of paracetamol caused a significant increase (p-value < 0.05) in the level of liver enzymes (ALP, AST, ALT) as well as total bilirubin. Pre-treatment with ginger aqueous extract 100mg for 15days has decreased the level ALP, AST and bilirubin by 72.37%, 56.36%, 88% respectively. As well as 100mg for 30 days at 84.8%, 84.8%, 58% respectively, compared to the positive control group. At the same time, pre-dose of ginger at a concentration of 200mg for 15 days reduced the levels of ALP, AST and bilirubin by 74.7%, 48.5%, 88% respectively, and 200mg for 30days by 86.5%, 71.7%, 94% respectively, compared to the positive control. pre-dose of ginger at a concentration of 400mg for 15 days reduced the levels of ALP, ALT, AST and bilirubin by 76.6%, 46%, 36.88%, 84.5% respectively, and 400mg for 30days reduced the levels of ALP, AST and bilirubin by 81.3%, 68.8%,91.6% respectively, compared to the positive control , as shown in table (1)

Table (1) illustrate changes in liver enzymes and total bilirubin are shown in the experimental groups

Groups	ALP	ALT	AST	Total Bilirubin
Negative control	48 ± 2.75	40 ± 0.81	42 ± 1.77	0.23±0.03
Positive control (APAP)	257 ± 7.26*	71 ± 2.08*	128.33 ± 23.9*	0.84±0.04*
100mg ginger +APAP(15D)	71± 13.4#	57.5± 1.5	56± 3#	0.1±0.00#
200mg ginger +APAP(15D)	65± 17.7#	51.3± 4.3	66± 1.2#	0.1±0.00#
400mg ginger +APAP(15D)	60± 6#	38.3± 0.6#	81± 3.7*#	0.13±0.03#
100mg ginger +APAP(30D)	39± 6.3#	52± 10.3	19.5± 5.5#	0.35±0.25#
200mg ginger +APAP(30D)	34.5± 2.5#	51± 18	36.3± 9.4#	0.05±0.05#
400mg ginger +APAP(30D)	48± 5.78#	50± 6.6	40± 2#	0.07±0.02#

Samples were taken based on the mean ± standard error (SE) (*) significant change (p-value <0.05) compared to the negative control, (#) significant change (p-value <0.05) compared to the Positive control (APAP)

In contrast, paracetamol administration resulted in a significant decrease in albumin and total protein levels (Table 2). Meanwhile, pre-dose with (100,200,400)mg aqueous ginger extracts for 15 days led to an increase in albumin levels of 46.45%, 48.38%, 45.16% respectively, compared to the positive control. On the other hand, pre-dosing with ginger (100,200,400)mg for 30days reduced albumin levels by 54.8%, 51.6%, 45.16% respectively, compared to the positive control.

The results showed a significant increase in the total protein level in the groups pre-dose with aqueous ginger extract (400)mg for 15days by 58.33% compared to the positive control.

Table (2) illustrate changes in Albumin and total protein are shown in the experimental groups

Groups	Albumin	Total protein
Negative control	4.6±0.26	5.97±0.27
Positive control (APAP)	3.1±0.2*	3.6±0.67*
100mg ginger +APAP15D	4.54±0.34#	5.1±0.5
200mg ginger +APAP15D	4.6±0.36#	5.16±0.4
400mg ginger +APAP15D	4.5±0.45#	5.7±0.62#
100mg ginger +APAP30D	1.4±0.12*#	4.1±0.2*
200mg ginger +APAP30D	1.5±0.15*#	4.2±0.26
400mg ginger +APAP30D	1.7±0.17*#	4.7±0.05

Samples were taken based on the mean ± standard error (SE) (*) significant change (p-value <0.05) compared to the negative control, (#) significant change (p-value <0.05) compared to the Positive control (APAP)

3.2 Histological changes

Histological examination of liver sections from the negative control group showed normal hepatocytes with central nuclei and homogeneous cytoplasm (Figure 1). in contrast, histological examination of the positive control group showed severe dilation of the central vein, hemorrhage accompanied by necrosis and extensive inflammatory cells (Figure 2).

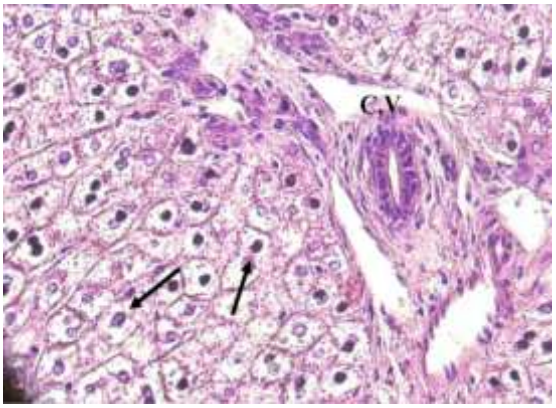

Figure (1) microscopic photos of the tissues of the liver in the negative group: hepatic cells (black arrow),central vein (C.V) (H&E; 100x)

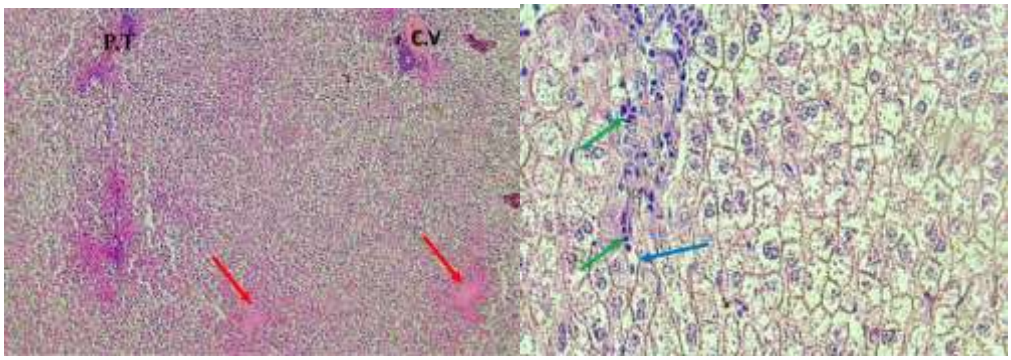

Figure (2) shows microscopic images of liver tissue sections in the group treated with a single dose of 750mg of paracetamol: A: central vein (C.V), necrosis (red arrow), portal tract (P.T) (H&E; 40x) B: inflammatory cells (green arrow), Kupffer cells within the dilated sinusoids (blue arrow) (H&E; 100x)

While the groups pre-dose with (100,200,400)mg of aqueous ginger extract for 15 days showed a marked improvement in liver tissue through the restoration of the normal diameter of the central vein and shrinkage of cytoplasmic vacuoles compared to the positive control group. Similarly, (100,200,400)mg groups for 30 days showed improvement in liver tissue compared to the positive control group, but to a lesser extent than the groups dosed for 15 days.

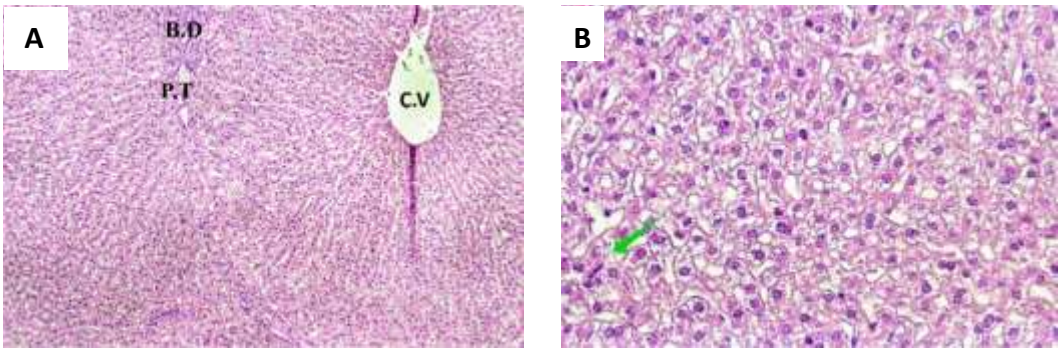

Figure (3) shows microscopic images of liver tissue sections in the group treated with ginger aqueous extract 100mg 15D and single dose of 750mg of paracetamol: A: bile ducts (B.D), portal tract (P.T), central vein (C.V) (H&E; 40x), B: inflammatory cells (green arrow) (H&E; 100x)

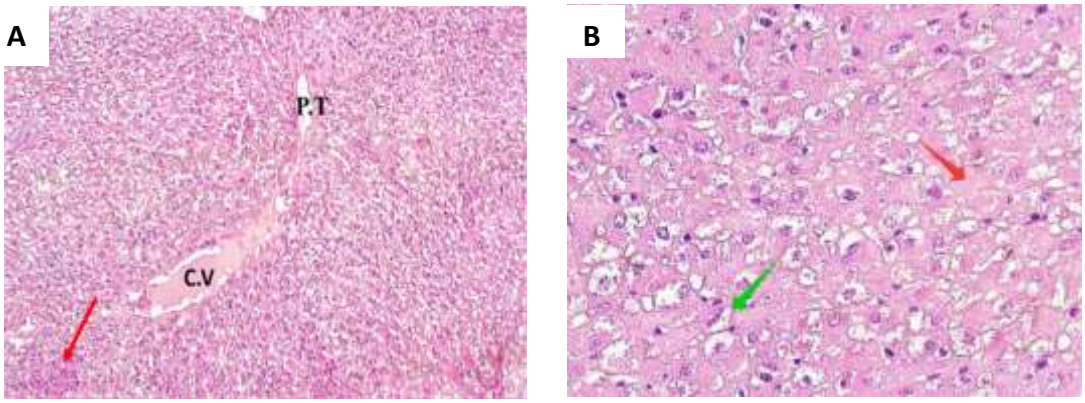

Figure (4) shows microscopic images of liver tissue sections in the group treated with ginger aqueous extract 200mg 15D and single dose of 750mg of paracetamol: A: cytoplasmic gaps (red arrow), portal tract (P.T), central vein (C.V) (H&E; 40x), B: inflammatory cells (green arrow), cytoplasmic gaps (red arrow) (H&E; 100x)

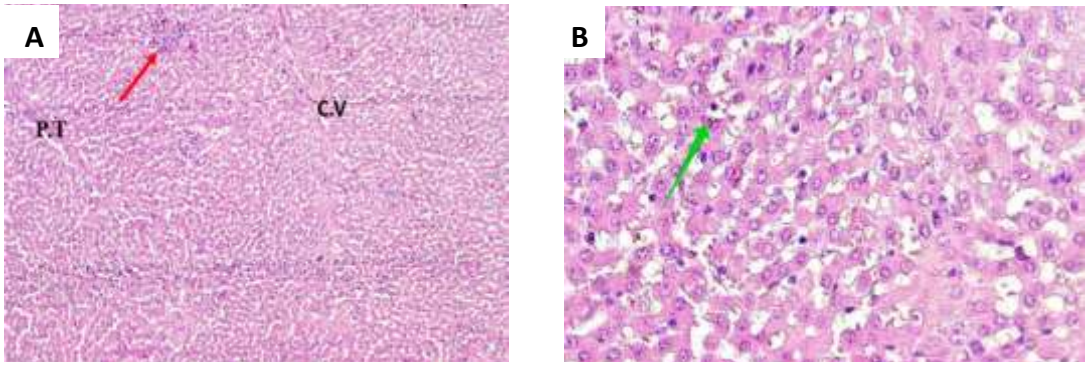

Figure (5) shows microscopic images of liver tissue sections in the group treated with ginger aqueous extract 400mg 15D and single dose of 750mg of paracetamol: A: cytoplasmic gaps (red arrow), portal tract (P.T), central vein (C.V) (H&E; 40x), B: inflammatory cells (green arrow) (H&E; 100x)

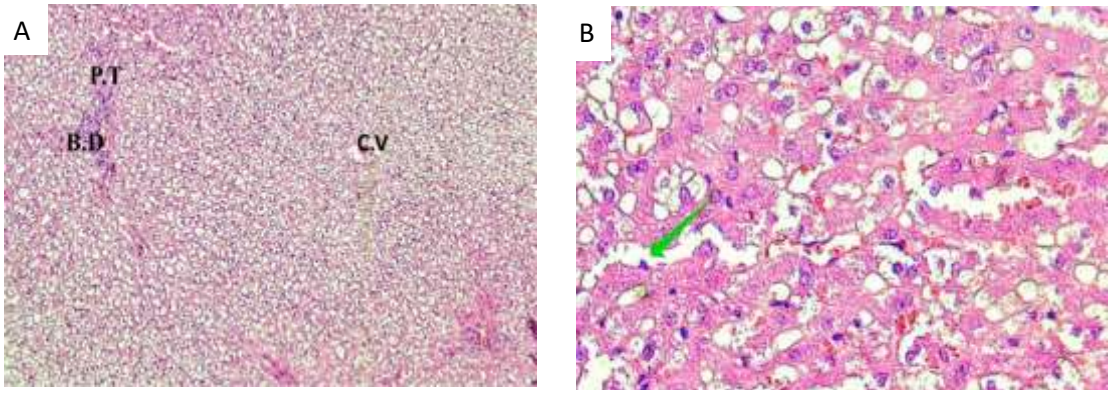

Figure (6) shows microscopic images of liver tissue sections in the group treated with ginger aqueous extract 100mg 30D and single dose of 750mg of paracetamol: A: portal tract (P.T), central vein (C.V) (H&E; 40x), B: inflammatory cells (green arrow) (H&E; 100x)

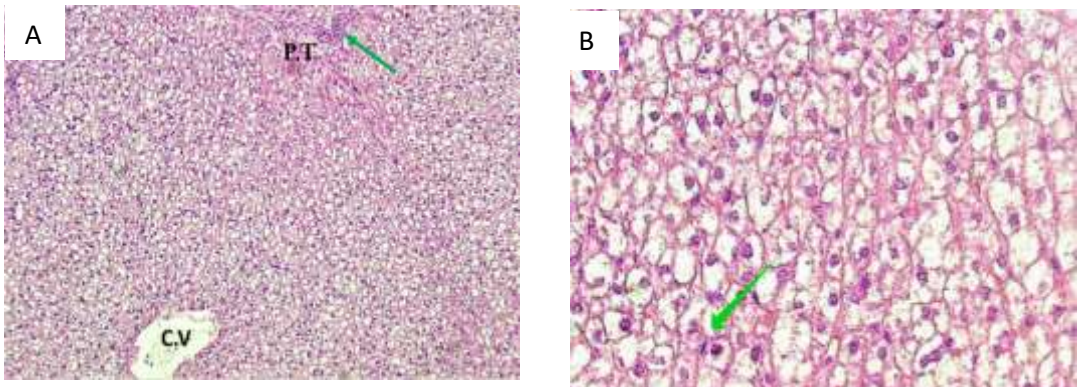

Figure (7) shows microscopic images of liver tissue sections in the group treated with ginger aqueous extract 200mg 30D and single dose of 750mg of paracetamol: A: portal tract (P.T), central vein (C.V), inflammatory cells (green arrow) (H&E; 40x), B: inflammatory cells (green arrow) (H&E; 100x)

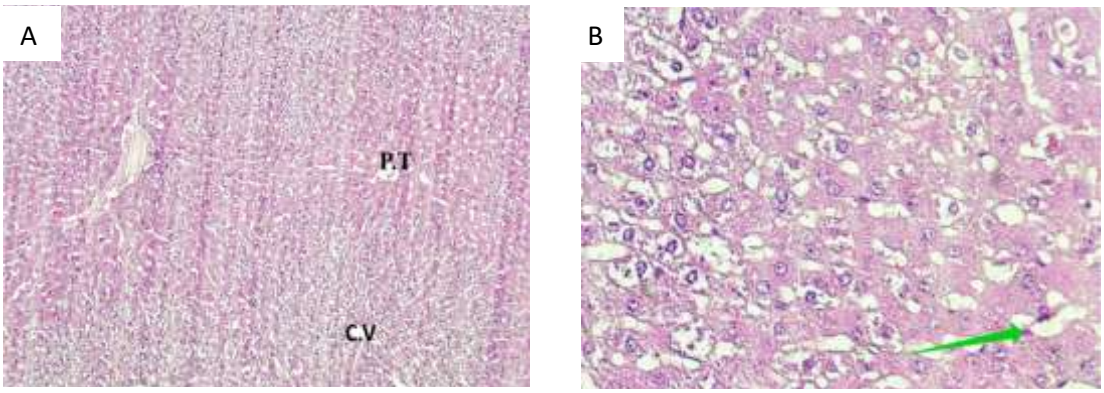

Figure (8) shows microscopic images of liver tissue sections in the group treated with ginger aqueous extract 400mg 30D and single dose of 750mg of paracetamol: A: portal tract (P.T), central vein (C.V) (H&E; 40x), B: inflammatory cells (green arrow) (H&E; 100x)

4. Discussion

This study was conducted to determine the protective role of the aqueous extract of ginger at different concentrations (100,200,400) mg/kg and for different periods 15days, 30 days on paracetamol-induced hepatotoxicity at a dose of 750 mg/kg.The results of the current study showed some changes in liver function in rabbits that were given a single dose of (750 mg/kg b.w) of paracetamol on the last day of the experiment. It included a significant increase in the level of liver enzymes (ALP, AST, ALT) and bilirubin when compared with

the negative group. These results were consistent with a number of studies conducted previously, including: (Duppa *et al.*, 2020; Elmesilhy & Nasef, 2024; الشبيلي, 2024; Abdel-Rasol *et al.*, 2025; Tratrat *et al.*, 2025)

The increase in liver enzymes in the blood serum of rabbits dosed with paracetamol can be explained by the increase in the concentration of the metabolite of paracetamol (NAPQI) and the decrease in the glutathione (GSH) store, which leading to the binding of (NAPQI) to protein molecules on the liver cell membranes by covalent bonds, resulting in tissue necrosis, nuclear disintegration, and leakage of liver enzymes (ALT, AST, ALP) into the bloodstream. (Yoon *et al.*, 2016; Ilahi *et al.*, 2019)

The study results also showed a significant decrease (p-value <0.05) in the concentration of albumin and total protein in the blood serum of rabbits dosed with Paracetamol (750mg/kg b.w) compared with the negative group. These results are consistent with the study (Parameshappa *et al.*, 2012; Abdel-Azeem *et al.*, 2013; Elmesilhy & Nasef, 2024; الشبيلي, 2024). On the other hand, the results of the study showed a significant improvement in the levels of (ALT,AST,ALP and bilirubin) in the groups previously dosed with the aqueous extract of ginger (100,200,400)mg/kg for 15 days, as well as the groups dosed for 30 days compared with the positive control group. These results were similar to previous studies, including a study (Bakr *et al.*, 2019; Abaekwume & Kagbo, 2021; Hai, 2024)

And the study results showed an improvement in the levels of albumin in the groups pre-dose with an aqueous extract of ginger (100,200,400)mg/kg for 15 days, and group pre-dose ginger (400)mg/kg increase in total protein level compared with the positive control group (dose with a single dose of paracetamol 750mg) This result was consistent with the study (Ragab *et al.*, 2024; Abdel-Rasol *et al.*, 2025)

While the groups dosed with ginger at doses of (100,200,400) mg/kg for 30days showed a decrease in albumin levels. On the other hand, total protein level no significant compared with the positive control group. This effect can be explained by the fact that ginger may increase the rate of absorption of paracetamol by the digestive system, as (Stewart *et al.*, 1991) stated that some of the active components of ginger stimulate digestion and absorption and reduce constipation by stimulating and increasing the activity of the muscles of the digestive system. It was shown that administering 150mg of ginger containing 2 mg of 6-shogaol increased intestinal blood flow. (Chrubasik *et al.*, 2005) This was agreed with the result of (Lebda *et al.*, 2013)

Histological results for the liver in the paracetamol (750mg) group showed severe central vein dilatation with severe congestion and necrosis of the liver tissue. Meanwhile, histological examination of the groups previously given an aqueous extract of ginger (100,200,400)mg/kg for 15days before administering a dose of paracetamol 750mg showed an improvement in liver histology compared to the group that took paracetamol only, the central vein showed its normal diameter, with few inflammatory cells and shrinkage of cytoplasmic vacuoles. These findings were consistent with (Abdel-Azeem *et al.*, 2013)

As for the results of the microscopic examination of the groups that were previously dosed with the aqueous extract of ginger (100,200,400)mg/kg for 30days before giving the paracetamol dose, they were less effective compared to the groups that were dosed with ginger (100,200,400)mg/kg for 15days, as they reduced the dilation of the central vein with the presence of red blood cell congestion, moderate disintegration in the portal duct, and the presence of inflammatory cells.

5. Conclusion

The results of this study showed that the duration of exposure of the experimental animals to ginger has an effect, as the albumin level improved in the groups treated for 15 days, while it decreased further in the groups treated for 30days, when compared with the positive control group. Further experimental studies are needed to understand the mechanism of action.

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