

Hepatoprotective Effect of Sidr Honey Against X-ray-Induced Biochemical Alterations in Male Rabbits

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Abstract

The present study aimed to investigate the protective effects of Sidr honey against liver toxicity induced by X-ray irradiation. Irradiation was performed using an X-ray system operated at a tube voltage of 80 kV. The absorbed dose delivered to the target was estimated to be 5.5 Gy, with exposure settings of 8,835 mAs at a source-to-sample distance (SSD) of 98 cm by measuring glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and Alkaline phosphatase. The study included twenty adult male rabbits, with an average weight of 1.700-2.000 Kg. Rabbits were randomly divided into four groups (n=5/group), as follows: Group(1): rabbits were orally gavage with distilled water as negative control. Group(2): rabbits were given orally 1.2 g/kg body weight of honey by gavage daily for 30 days. Group(3): rabbits were exposed to X-ray once a day for seven days and consider positive control. Group(4): rabbits were treated with honey daily for 30 days and then exposed to X-ray irradiation for seven days. The results showed exposure male rabbits in G3 to X-rays led to a significant increase in the glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and a significant decrease of alkaline phosphatase when compared to the control group. While, the treated with honey (Group 4) before irradiated by X-rays led to significant improvement in the levels of the liver enzymes mentioned above when compared with the rabbits that exposed to X-rays in positive control (Group 3). The present study demonstrated that Sidr honey may have a protective effect on liver functions in male rabbits exposed to X-ray. Therefore, we recommend that those who working in the field of radiology should consume Sidr honey according to the medical doses recommended for humans.

Keywords: Hepatoprotective, Male rabbits, Physiological, Sidr honey, X-ray.

التأثير الوقائي لعسل السدر على الكبد ضد التغيرات الفسيولوجية الناجمة عن التعرض للأشعة السينية في ذكور الأرانب

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الملخص

هدفت هذه الدراسة إلى التحقق من التأثيرات الوقائية لعسل السدر ضد الآثار الضارة للتعرض للأشعة على الكبد، أُجري ذلك باستخدام نظام للأشعة السينية يعمل بجهد أنبوبي قدره 80 كيلوفولت (kV). وقُدِّرَت الجرعة الممتصة الواصلة إلى العينة المستهدفة بـ 5.5 غراي (Gy)، وذلك عند إعدادات تعريض بلغت 8,835 ملي أمبير-ثانية (mAs) ومسافة بين المصدر والعينة (SSD) قدرها 98 سم. شملت الدراسة عشرين أرنبًا بالغًا من الذكور، بمتوسط وزن يتراوح بين 1.700 و 2.000 كيلوغرام. قُسمَت الأرانب عشوائيًا إلى أربع مجموعات (خمسة أرانب في كل مجموعة)، كما يلي: المجموعة الأولى: أعطيت الأرانب ماء مقطر عن طريق التغذية القسرية الفموية كمجموعة ضابطة سلبية. المجموعة الثانية: أعطيت الأرانب 1.2 غرام/كيلوغرام من وزن



الجسم من العسل عن طريق التغذية القسرية الفموية يوميًا لمدة 30 يومًا. المجموعة الثالثة: عُرِضَت الأرانب للأشعة السينية مرة واحدة يوميًا لمدة سبعة أيام، واعتُبرت مجموعة ضابطة إيجابية. المجموعة الرابعة: عُولِجَت الأرانب بالعسل يوميًا لمدة 30 يومًا، ثم عُرِضَت للأشعة السينية لمدة سبعة أيام. أظهرت النتائج ان تعرض ذكور الأرانب في المجموعة الثالثة للأشعة السينية أدى إلى زيادة ملحوظة في إنزيمات ناقلة أمين الأوكسالوأسيتيك وناقلة أمين البيروفيك، وانخفاض ملحوظ في إنزيم الفوسفاتاز القلوي، مقارنةً بالمجموعة الضابطة. في المقابل، أدى تناول عسل السدر قبل التعرض للأشعة السينية في المجموعة الرابعة إلى تحسن ملحوظ في مستويات إنزيمات الكبد المذكورة أعلاه، مقارنةً بالأرانب التي تعرضت للأشعة السينية فقط في مجموعة الضبط الإيجابي. خلصت هذه الدراسة إلى أن عسل السدر له تأثير مفيد على وظائف الكبد لدى ذكور الأرانب المعرضة للأشعة السينية، لذا نوصي العاملين في المجال الطبي الإشعاعي وكذلك المرضى الذين يتعرضون للأشعة بتناول عسل السدر وفقًا للجرعات الطبية الموصى بها للبشر.

الكلمات المفتاحية: الوقاية الكبدية، ذكور الأرانب، فسيولوجي، عسل السدر، الأشعة السينية.

Introduction

The ionizing radiation has several advantageous usage in medicine, such as diagnostic and therapeutic procedures (Hawley, 2013). However, depending on the exposure period and dose, living cells can be somewhat sensitive to radiation. The primary impact of radiation on biological materials is the alteration of chemical characteristics within cells. These alterations could be related to the dissociation of hemolytic molecules and the formation of secondary electrons, which produce hydrogen peroxide and free radical roots in bodily fluids. As the radiation dose increases, these effects may correspondingly intensify (Hall, 2000). Radiation can kill living things, but when it is used appropriately, it can also be beneficial to human health.

Ionizing radiations are known to cause oxidative stress on target tissues, primarily by producing reactive oxygen species (ROS), which upset the balance between pro-oxidants and antioxidants in the cells (Hahn *et al.*, 1994). ROS also attack a variety of cellular macromolecules, including proteins, lipids, and DNA, ultimately leading to the death of cells (Bhosle *et al.*, 2005; Mansour and Hafez, 2012). Ionizing radiation is utilized in industrial and medical settings, and one type of it is called an X-ray (Falk, 2006). To mitigate these harmful side effects, researchers have investigated various therapeutic interventions, including natural remedies like honey that possess strong radioprotective and antioxidant properties

Honey is a complex nutritional sweetener composed mainly of carbohydrates (60–85%) and water (12–23%). It also contains small amounts of other compounds, such as organic acids, minerals, vitamins, enzymes, proteins, amino acids, Maillard reaction products, volatile compounds, and several bioactive substances (phenols and flavonoids, among others), as well as pollen grains (White, 1979; Cano *et al.*, 2001; Gomes *et al.*, 2010; Almeida-Muradian *et al.*, 2013). Honey is usually consumed in natura, and as a food ingredient. Sometimes honey has also been employed in both human and veterinary medicine (Joseph *et al.*, 2007; Nigussie *et*

al., 2012). Honey's biological and nutritional properties are decisive for the consumers' choice, as well as for the commercialization management of this food.

Because high-metabolic organs like the liver is especially vulnerable to radiation-induced damage, natural radioprotectors such as honey are being extensively evaluated for this organ-specific detoxifying and curative properties (Sharma and Goyal, 2014; Karami *et al.*, 2015). Kidney has been reported to be moderately radiosensitive and is capable of regenerating after radiation induced cytotoxic injuries (Purohit *et al.*, 2007). However, some studies have revealed that the kidneys are amongst the most radiosensitive organ of the abdominal system (Kanter *et al.*, 2011). Irradiation induced alterations in biochemical parameters revealed hepatic and renal dysfunction in mice, suggesting their vulnerability to radiation exposure (El-Shennawy *et al.*, 2016). This study was designed to evaluate the possible beneficial effect of honey on liver functions in male rabbits exposed to X-ray irradiation.

Materials and methods

Experimental Animals

The study employed twenty adult male rabbits, all native to the area, weighing between 1.700 and 2.000 kg. The rabbits were kept in groups in cages of 100 x 85 x 45 cm at the Zoology Department's facilities at Omar AL-Mukhtar University. The experiment was conducted in a climate-controlled laboratory maintained at $25 \pm 1^\circ\text{C}$ using an automated air conditioning system, and the photoperiod was maintained at a 12 hour light/ and 12 hour dark cycle over 30 days on April 2024. The rabbits were given commercial standard pellets to eat and unlimited access to water. One week before to the start of the experiment, the animals were acclimated to the laboratory environment.

Experimental groups and protocol

Rabbits were randomly distributed into four groups (five rabbits/group).

Group I: control - normal control rabbits were daily given distilled water orally.

Group II: Healthy male rabbits were given Sider honey at does 1.2 g/kg of body weight daily for a month (Mohamed, 2014).

Group III: (X- ray exposure group): Healthy male rabbits were exposed to X-ray irradiation at a dose of 5.5 Gy, from a distance of 98 cm once a day for a week (Guttman and Kahn, 1963).

Group IV: Healthy male rabbits were orally administered Sidr honey at a dose of 1.2 g/kg body weight daily for 30 consecutive days prior to X-ray exposure, after which exposed to X-ray irradiation at dose 5.5 Gy from a distance of 98 cm ones a day for a week.

All groups of rabbits were experimented on for a month and blood samples were then collected. A centrifuge was used to separate blood samples at approximately 4000 rpm for 4 minutes. This was to extract the serum, through which the levels of the following were measured:

Glutamic oxaloacetic transaminase (GOT)

The transaminase reaction between L-aspartate and oxoglutarate is catalysed by the GOT. When malate dehydrogenase (MDH) is present, the 2-Oxalactate that has been produced is converted to malate. NADH is converted to NAD as the reaction moves on. The decrease in absorbance at 340 nm is used to track the depletion of NADH per unit of time. A colour shift was observed spectrophotometrically after 100 μl of the 32 samples were combined with 800 μl of reagent 1 (80 mmol/L Tris-buffer, pH 7.8, 240 mmol/L L-Aspartate, and 1200 U/L MDH)

and 200µl of reagent 2 (15 mmol/L 2-Oxoglutarate and 0.18 mmol/L NADH). The mixture was thoroughly mixed and aspirated right away.

Glutamic pyruvic transaminase (GPT)

The GPT was measured using a ready-to-use kit from Archem Diagnostic Company. The transaminase process between alanine and 2-oxoglutarate is catalysed by the enzyme. In the presence of lactate dehydrogenase, the pyruvate produced is converted to lactate (LDH). NADH is converted to NAD as the reaction moves on. The decrease in absorbance at 340 nm is used to track the depletion of NADH per unit of time. 100µl of the sample were added to 800µl of reagent 1 (120 mM Tris buffer, pH 7.15, 500mM L-alanine, and 1700 U/L LDH) and 200µl of reagent 2 (18mM 2-oxoglutarate and 0.18mM NADH), mixed well and aspirated immediately and the color change read by a spectrophotometer (Model UV-1800, Shimadzu Corporation, Kyoto, Japan).

Alkaline phosphatase (ALP)

This enzyme was measured using an Archem Diagnostic Company ready-to-use kit. 4-NPP is hydrolyzed by ALP in an alkaline environment to produce 4-nitrophenol. Spectrophotometric detection of the 4-nitrophenol produced at 405 nm yields an alkaline phosphatase activity measurement for the sample. 200µl of reagent 2 (100 nmol/L p-nitrophenyl phosphate) and 20µl of reagent 1 (1mol/L ethanolamine pH 10.4 and 0.5mmol/L magnesium chloride). A spectrophotometer was used to measure the colour shift after the mixture had been well mixed and aspirated right away.

Statistical analysis

Data were expressed as mean $\pm$ standard error (SE). Statistical differences among experimental groups were evaluated using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons. Student's t-test was applied when comparisons were limited to two groups. Differences were considered statistically significant at $P < 0.05$. Statistical analyses were performed using Minitab statistical software (version 17).

Results

Effect of honey, X-ray, and their combination on the serum GOT

The mean values of GOT activity across the control and experimental groups are presented in Figure (1). No statistically significant difference was observed between the honey group (35.67 ± 1.4529) and the control group (33.00 ± 1.5275). Conversely, X-ray exposure caused a significant increase in GOT activity in the X-ray group (101.33 ± 2.4037) compared to the control group (33.00 ± 1.5275). However, honey administration prior to or alongside X-ray exposure (H-X group) significantly reduced GOT levels (32.33 ± 1.8559) compared to the X-ray group only ($p < 0.05$).

Effect of honey, X-ray, and their combination on the serum GPT

Figure (2) illustrate the mean activity levels of GPT across the control and experimental groups. No statistically significant difference in mean GPT activity was observed between the honey-treated group (34.67 ± 1.4529) and the control group (36.00 ± 1.1547). Conversely, exposure to X-rays induced a significant increase in mean GPT activity (114.33 ± 2.9627) compared to the control group ($P < 0.05$). However, pre/co-administration of honey in the X-ray irradiated group (H-X) significantly attenuated this effect, resulting in a marked reduction in GPT levels (43.33 ± 1.7638) compared to the X-ray group alone ($P < 0.05$).

Effect of honey, X-ray, and their combination on the serum ALP

Serum ALP activity levels for all experimental groups are summarized in Figure (3). ALP levels showed no significant alteration in the honey group (118.00 ± 1.7320) relative to the control group (120.00 ± 0.577). In contrast, a significant drop in ALP activity was recorded in the X-ray irradiated group (71.00 ± 3.2145) compared to control values ($P < 0.05$). Notably, honey pre-treatment followed by X-ray exposure (H-X group) significantly restored ALP levels (94.00 ± 2.0816) in comparison to the X-ray group ($P < 0.05$), though still exhibiting a significant decline relative to the control group ($P < 0.05$).

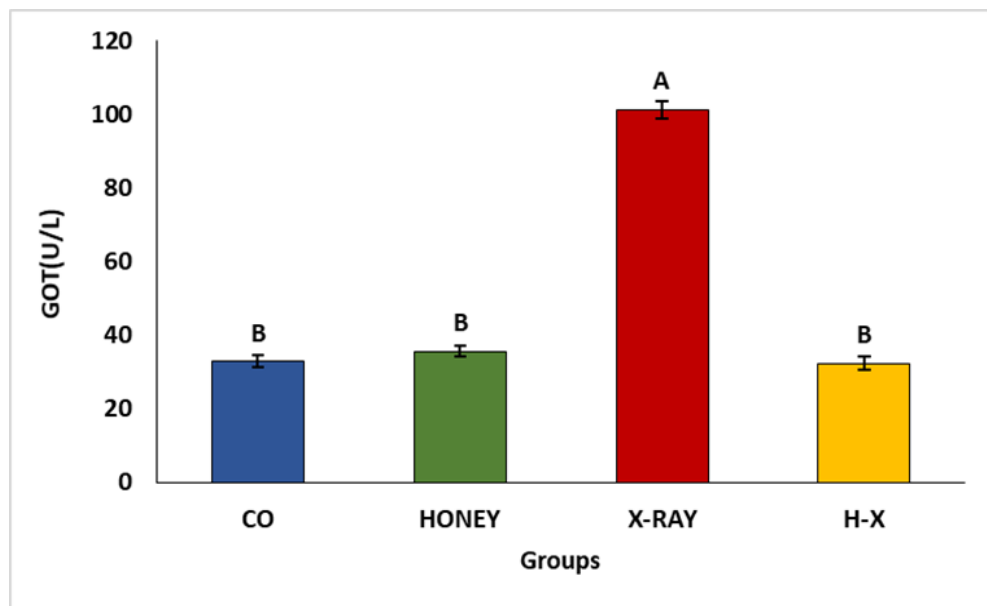


Figure 1: Changes in mean values of GOT activity (Mean ± SEM) in control and experimental groups.

Means with different superscripts (A & B) were significantly different at $P \leq 0.05$, were means superscripts with the same letters mean that there is no significant difference ($P > 0.05$).

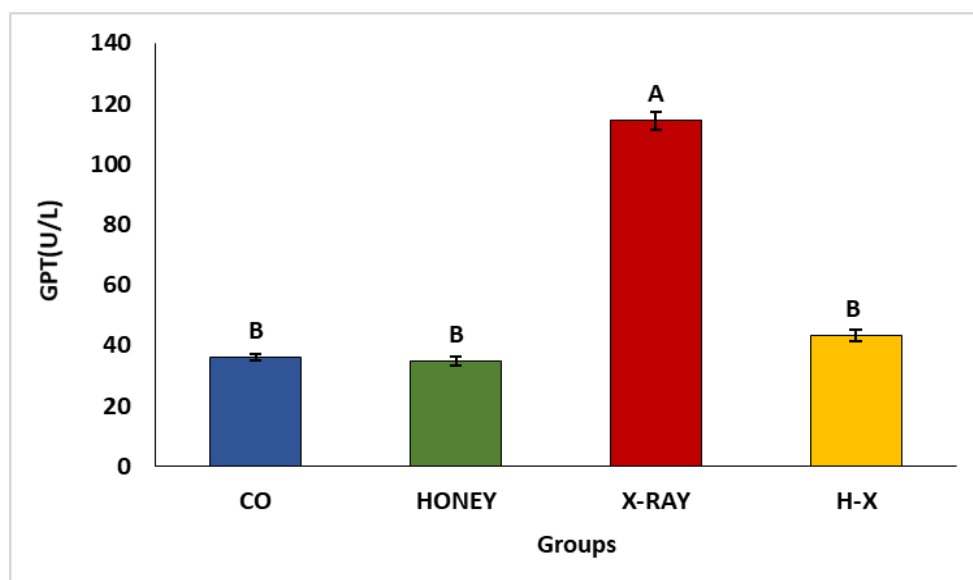


Figure 2: Changes in mean values of GPT activity (Mean ± SEM) in control and experimental groups.

Means with different superscripts (A & B) were significantly different at $P \leq 0.05$, were means superscripts with the same letters mean that there is no significant difference ($P > 0.05$).

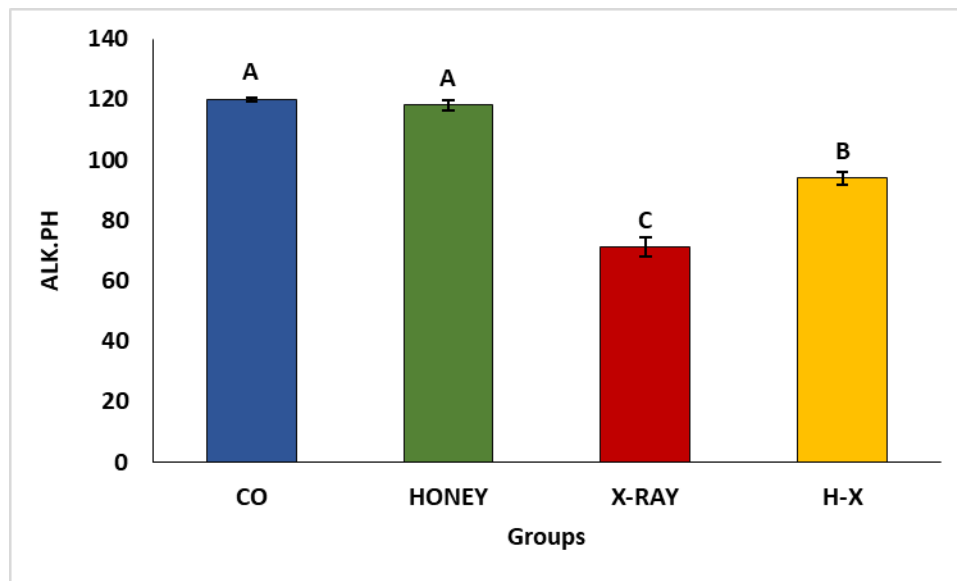


Figure-3: Changes in mean values of ALP activity (Mean $\pm$ SEM) in control and experimental groups.

Means with different superscripts (A, B & C) were significantly different at $P \leq 0.05$, were means superscripts with the same letters mean that there is no significant difference ($P > 0.05$).

Discussion

Exposure to X-rays, as a form of ionizing radiation, can induce excessive generation of reactive oxygen species (ROS), primarily through the radiolysis of cellular water, resulting in oxidative stress. These reactive species can interact with various cellular macromolecules, including membrane lipids containing polyunsaturated fatty acids, thereby initiating lipid peroxidation and causing oxidative damage to cellular structures (Azzam *et al.*, 2012; Reisz *et al.*, 2014). Lipid peroxidation represents a major consequence of radiation-induced oxidative stress and results in the formation of reactive aldehydes, including malondialdehyde (MDA), which is widely used as a biomarker of oxidative damage. Increased MDA levels have been reported in tissues and biological fluids following exposure to ionizing radiation (Reisz *et al.*, 2014; Kim and Jung, 2017). Therefore, the present study aimed to investigate the possible radioprotective effect of honey on liver function, as assessed by serum GPT, GOT, and ALP, in male rabbits exposed to X-rays.

The present study demonstrated a significant increase in serum GPT and GOT activities in the groups exposed to X-rays compared with the control and honey-treated groups. These findings indicate that exposure to X-ray radiation may induce hepatic cellular injury, resulting in increased membrane permeability and the subsequent leakage of intracellular enzymes, particularly GPT and GOT, into the circulation. The present findings are consistent with those reported by Makhoul and Makhoul (2012), who demonstrated that exposure to ionizing radiation caused significant elevations in serum GPT and GOT activities, reflecting radiation-induced hepatic damage. Similarly, Parastesh *et al.* (2025) reported a significant increase in serum GOT and GPT levels in rats exposed to whole-body X-ray radiation, supporting the view that ionizing radiation can adversely affect hepatic function.

Furthermore, similar elevations in GPT and GOT have been reported in other experimental models of radiation-induced liver injury. For example, Mansour and Hafez (2012) demonstrated significant increases in serum transaminases following irradiation, indicating hepatocellular damage. Likewise, Cheng *et al.* (2015) observed significant increases in serum

GOT and GPT following liver irradiation in rats, particularly during the later stages after radiation exposure.

Interestingly, the present study demonstrated a decrease in serum ALP activity in the X-ray-exposed groups. This result is supported by the findings of Ludewig and Chanutin (1950), who investigated the effects of X-ray irradiation on enzyme activity in rats and demonstrated that exposure to X-rays could alter alkaline phosphatase activity in plasma and tissues. Their observations support the possibility that ALP activity may decrease following irradiation under certain experimental conditions.

A recent experimental study by Li *et al.* (2020) examined the effects of X-ray irradiation in rats and found that alkaline phosphatase activity was significantly reduced by approximately 30.5% and 39.6% following exposure to 1 Gy and 5 Gy X-ray radiation, respectively, compared with the non-irradiated control group. This finding is particularly consistent with the decrease in ALP observed in the present study. Therefore, the decrease in ALP observed in the present study may be related to the radiation dose, duration of exposure, and the time interval between irradiation and biochemical assessment. Indeed, the response of ALP to ionizing radiation appears to vary depending on these factors. For example, another experimental study using therapeutic X-rays in mice reported that although GPT and GOT increased after irradiation, ALP showed a significant decrease at one specific post-irradiation time point, while it increased at another time points.

Collectively, the present findings suggest that X-ray exposure induced hepatic dysfunction, as evidenced by the elevation of GPT and GOT and the alteration of ALP activity. The observed changes in liver enzymes may be associated with radiation-induced oxidative stress and cellular damage. The improvement observed in the honey-treated group may indicate a potential radioprotective effect of honey, possibly through its antioxidant properties and its ability to reduce oxidative damage and preserve hepatocellular integrity.

Several studies have indicated that the elaboration of bone matrix is a function of ALP (Li *et al.*, 2012; Tominami *et al.*, 2017). Interestingly, according to Ma *et al.* (2021), a significant histological indication of bone damage following exposure to large doses of X-radiation is the disappearance of osteoblasts, which have long been known to be associated with the formation of osseous tissue.

In addition, Orimo (2010) also provide evidence for the theory that phosphatase is synthesized by the osteoblasts, in that there is an increased production of phosphatase in osteoblastic types of osteogenic sarcoma. These sarcomata showed a fall in plasma phosphatase after x-irradiation. This result differed from GPT, GOT that showed levels of liver enzymes (ALT and AST) increased significantly in serum of rats after gamma irradiation. Kafafy (2000) reported similar results in rats exposed to gamma radiation. The results of the current study are also consistent with those found previously which reported significant increase in liver enzyme levels in rats exposed to 8.00 Gy gamma radiation (Ramadan *et al.*, 2001). The increase in the serum levels of liver enzymes in this study could be attributed to the computed tomography radiation-induces damage of cellular membranes of hepatocytes, which leads to an increase in the permeability of cell membranes and facilitates the passage of these enzymes outside the cells. This is because increase in serum levels of liver enzymes are related to the extent of hepatocellular damage and the leakage of these intracellular enzymes into the bloodstream (Nada, 2008). The increase in the enzymatic activities (GOT, GPT) after irradiation is related

to either the release of enzymes from radio-sensitive tissues or to the extensive breakdown of liver parenchyma or due to the change in tissues permeability as a result of radiation exposure which is in agreement with Saad and El Masry (2005).

The findings of this experimental study demonstrate that honey consumption significantly modulates key biochemical parameters in healthy individuals, notably leading to a reduction in liver enzyme levels. Furthermore, honey administration elevated systemic antioxidant capacity and key nutrient concentrations, an effect likely mediated by its rich nutritional and antioxidant profile (Al-Waili, 1999, 2001, 2003). These results suggest that more pronounced physiological responses may be achieved through extended interventions exceeding two weeks.

honey lowers plasma concentrations of Thromboxane-B₂, Prostaglandin-E₂, and Prostaglandin F₂-alpha (Andersen and Markham, 2006). In healthy subjects, honey increased antioxidant agents, serum iron, blood indices, trace elements, and decreased immunoglobulin E and liver and muscle enzymes (Al-Waili, 2003). In addition, Al-waili *et al.* (2006) found that a significant reduction in AST, ALT, in rats' model exposed to total food restriction and 50% honey feeding as compared with the other animals. It was concluded that honey feeding during total food restriction has protective effects on both liver and kidney (Fihri *et al.*, 2016).

The hepatoprotective effect of Sidr honey is likely attributed to its rich content of antioxidant compounds, including flavonoids, phenolic acids, and vitamin C, which can scavenge ROS, inhibit LPO, and stabilize cellular membranes, thereby reducing enzyme leakage (Alvarez-Suarez *et al.*, 2013; Mohamed *et al.*, 2011). Supporting this interpretation, Khwaldeh *et al.* (2024) demonstrated that honey-derived polyphenols enhance antioxidant defenses and mitigate hepatic oxidative damage.

Conclusion

In the present study, it can be concluded that Sidr honey may have a protective effect on some physiological parameters in male rabbits exposed to X-ray, so we recommend the category working in the medical field of radiation to take Sidr honey.

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