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Histopathological Changes of Heart, Liver, and Duodenum in Iron Overload: Comparing the Role of Quercetin with Deferoxamine

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A B S T R A C T

The aim of this study was to perform a comparison between quercetin and deferoxamine (DFO) on the heart, liver, and duodenum in iron overloaded rabbits. Four groups of adult rabbits (each of seven) used in the current study were treated as follows for 28 days: control (C): were injected intraperitoneally (IP) normal saline every 72 hours + normal saline orally daily. T1, T2, and T3 groups were IP injected with iron dextran 100 mg/kg every 72 hours, T1 was left without treatment, group T2 was administrated with quercetin 350 mg/kg orally daily, and group T3 was injected with DFO 125 mg/kg intramuscularly (IM) daily. At the end of experiment, all animals were sacrificed, and tissue specimens were collected from the heart, liver, and duodenum for histopathological study. The results of T1 group showed edema, and iron deposition between the myocardial cells. The T2 group showed slight edema between the myocardium. T3 group showed edema, thickening, and congestion of blood vessels, all groups showed a positive result of the Prussian blue stain (PBS) compared to the control. The liver sections for the T1 group revealed iron overload, fibrosis, and hepatocyte necrosis. T2 and T3 groups showed mild vacuolation of hepatocytes, a decrease in iron overload, and these groups showed a positive result of the PBS compared to the control. Duodenum sections for T1 group showed hemochromatosis. while T2 group showed mild iron deposition. Positive result of PBS in T1 and T3 compared to the T2 and control were observed. Conclusion: Quercetin mitigates histological changes in iron overloaded rabbits due to its properties as an iron chelating agent compared to DFO.

Keywords: quercetin, deferoxamine, iron overload, heart, liver, duodenum

INTRODUCTION

Iron is one of the important elements in the body that maintains physiological functions such as DNA synthesis, oxygen and electron transport, and enzymes reactions (1). Iron absorbed from the intestines does not have any physiological route of excretion (2). When iron storge proteins become saturated with iron, free iron accumulates in the tissues and plasma, this includes labile plasma iron and non-transferable bound iron, also cells take free iron to form labile iron pools (3). Iron overload produces reactive oxygen species (ROS) and contributes to oxidative stress (OS) (4). Due to increased amount of non-heme iron that is not bound to transferrin that responsible for free radicals' formation (5). In the biological systems, iron is a catalytic reaction that is mediated by free radicals, and oxidative damage to nucleic acids, lipids, and proteins, can result in cell organelles being damage (6). In the animals that treated with iron over dose, there was a related dose accumulation of iron within hepatocytes or intra sinusoidal cells (7). Since iron overload can cause the dysfunction of many organs such as heart, liver and endocrine glands (8).

Iron chelation treatment is a life-saving for disorders caused by an iron overload (9). Due to its extensive clinical history and inexpensive cost, the iron chelator deferoxamine (DFO) remains a first-line treatment choice for reducing iron load in patients with transfusion dependent thalassemia (10). DFO binds with free iron in the plasma within cells at a 1:1 ratio (11). The iron that is bound with DFO and excreted through the urine or bile can be removed from the tissue by directly binding with it, DFO does not bind with iron that is bound with transferrin., hemoglobin., or cytochrome molecules, therefore, only a little amount of chelating iron is needed at any given time (12).

Flavonoids may have high antioxidant activities and be less toxic due to their unique structures. (13-15).

Quercetin is an example of naturally flavonoids under a category named flavonols, it is found in different fruits and vegetables such as apple, green tea, onion, cauliflower, nuts, berries, broccoli, and cabbage (16). Also, quercetin, considered a potent antioxidant, can mitigate cell damage caused by OS via chelating metals, scavenging ROS, and protecting against LPO (17). The mechanism by which quercetin treated the iron overload depends on its antioxidant properties and iron chelation (18).

Therefore, the aim of this study was to perform a comparison between quercetin in alleviating the effect of iron overload on the heart, liver, and duodenum and compare it with deferoxamine (DFO).

MATERIALS AND METHODS

Ethics

All procedures used in this study were reviewed and approved by The Scientific Committee of the Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Baghdad, Iraq, and the Ethics Committee of the College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq in compliance with the ethical principles of animal welfare.

Animals and Experimental Design

Twenty-eight adult male rabbits were used in the current study; about six months old and weighed between 1.7-2 kg. They were obtained from the animal's house at the Veterinary Medicine College, University of Baghdad. The animals were reared under controlled conditions at 22–25 °C. Animals were divided randomly into four groups and treated for 28 days as follows: Group C: Animals were intraperitoneally (I.P.) injected with normal saline every 72 h + normal saline orally each day (negative control), while T1, T2, and T3 groups were I.P. injected with iron dextran (100 mg/kg) every 72 h (14). Furthermore, rabbits in the T2 group, were treated with quercetin (350 mg/kg, purity of 95%, Brightol Company, China) orally daily, and in the T3 group, were injected with DFO (125 mg/kg, Novartis Company, Switzerland) I.M. daily (19). Through the experiment, the animals were weighed weekly because quercetin and DFO were given according to weight. Quercetin was dissolved in the solution containing 1 ml of dimethyl sulfoxide (DMSO) and 99 mL of distal water. At the end of experiment, animals were sacrificed, and tissue specimens were collected from the heart, liver and duodenum and put in 10% formalin for histopathological study according to the method described by (20). The Iron Prussian Blue Reaction (Mallory's method) that was used in the current study was done according to the method described by (21).

RESULTS

Histopathological Changes of Heart

Heart sections of iron overload rabbits (T1) show edema between the myocardial muscles with inflammatory cells infiltration, fibrosis among the myocardial muscles with fibroblast proliferation and iron particles deposition with a positive result of the Prussian blue stain (increase in iron overload) (Figures 2, 3). was observed as compare to the control group (Figure 1). Histopathological sections of rabbit's heart in the T2 group show slight edema between the myocardial fibers and a positive result of the Prussian blue stain (low iron overload) are shown in (Figures 4, 5). Whereas group T3 show edema between the myocardial fibers, and arterial hyperemia surrounded by edematous fluid and few inflammatory cells with a positive result of the Prussian blue stain (moderate iron overload) (Figures 6-8).

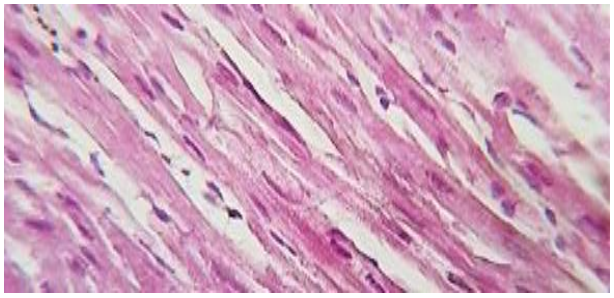

Figure 1. Histological section of a rabbit heart for the control group shows normal histological structures. H&E, 400×.

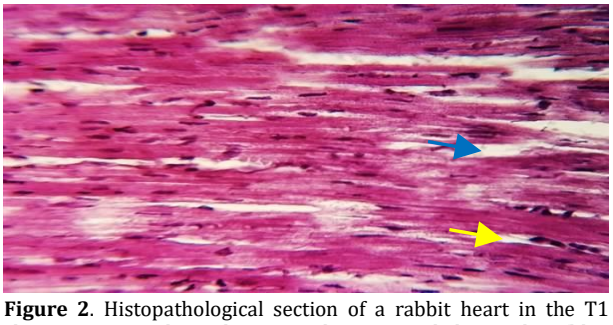

Figure 2. Histopathological section of a rabbit heart in the T1 shows severe edema between the myocardial muscles (blue arrow), with inflammatory cells infiltration (yellow arrow). H&E, 400×.

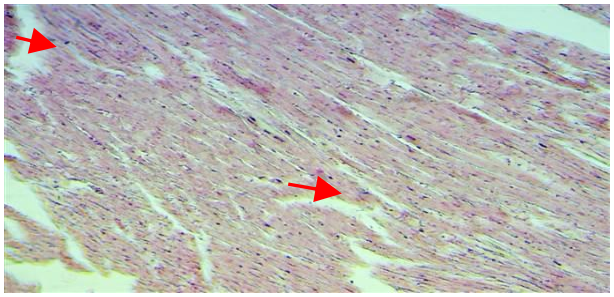

Figure 3. Histopathological section of a rabbit heart in theT1 shows positive result (increase in iron overload appear as blue color) (red arrows). Prussian bleu stain,100×

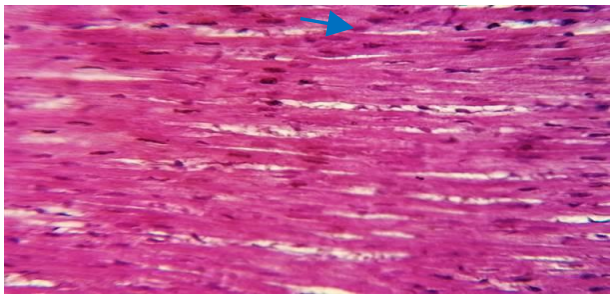

Figure 4. Histopathological section of a rabbit heart in the T2 group shows slight edema between the myocardial fibers (blue arrow). H&E, 400×

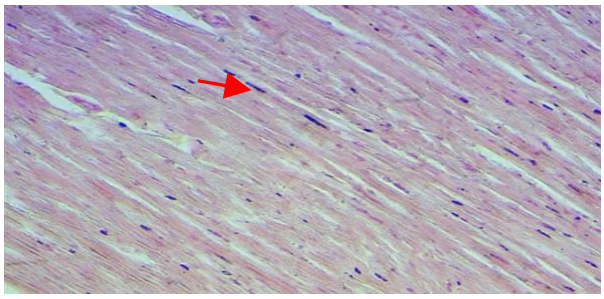

Figure 5. Histopathological section of a rabbit heart in the T2 group shows positive result (low iron overload appear as blue color. Prussian bleu stain,100×

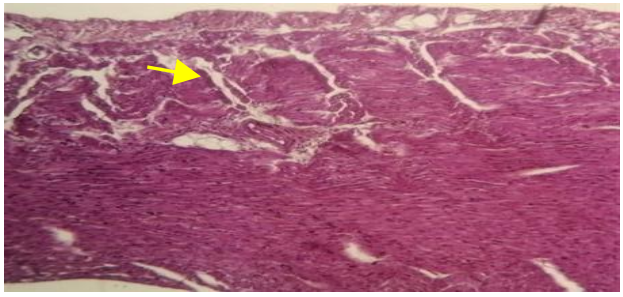

Figure 6. Histopathological section of a rabbit heart for the T3 group shows severe edema between the myocardial fibers (yellow arrow). H&E, 100×

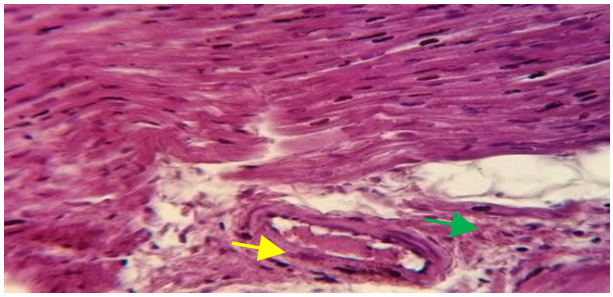

Figure 7. Histopathological section of a rabbit heart for the T3 group shows thickening and arterial hyperemia surrounded by edematous fluid (yellow arrow) with few inflammatory cells (green arrow) (H&E, stains, 400x)

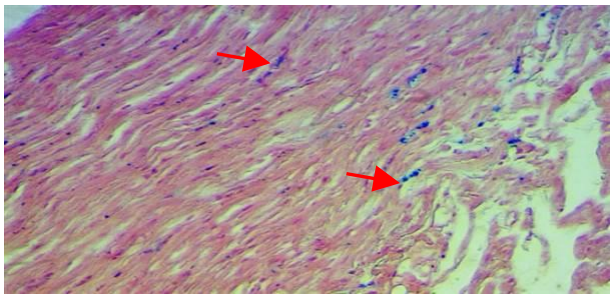

Figure 8. Histological section of a rabbit heart for theT3 group shows positive result (moderate iron overload appear as blue color) (red arrows) (Prussian bleu stain,100x).

Histopathological Changes of Liver

Histopathological sections of rabbit liver for the T1 group show iron overload in hepatocyte cytoplasm and hepatic sinusoids, with thickening of portal area, single cell necrosis, also show positive result for the Prussian blue stain (increase in iron overload) (Figures 11, 12). Compared with control group (Figures 9, 10). Iron overload rabbits treated with quercetin (T2) group show vacuolation of hepatocytes, with a decrease in iron overload and an increase in mitotic division, also showed positive result for the Prussian blue stain (moderate iron overload), (Figures 13-15) when compared with other groups. Besides histopathological sections of rabbit liver for the T3 group exhibit decrease in iron overload, fibrosis around the portal area and vacuolation of hepatocytes, fibrosis and inflammatory cells around the portal area also show a positive result for the Prussian blue stain (increased iron overload) (Figures 16-18).

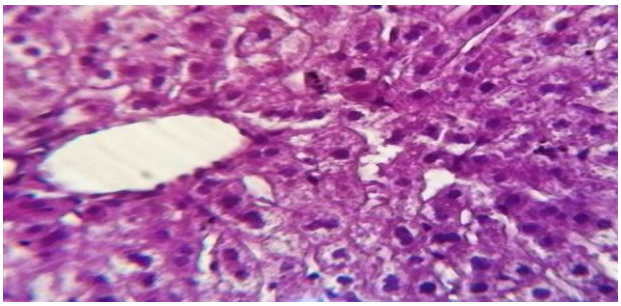

Figure 9. Histological section of a rabbit liver for the control group shows normal histological structures (H&E, stains, 400x).

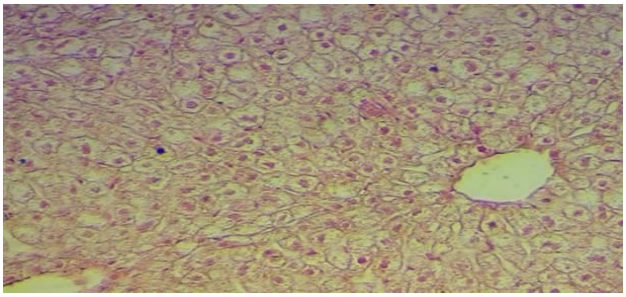

Figure 10. Histological section of a rabbit liver for the control group shows negative results (no deposition of iron) (Prussian bleu stain,100x).

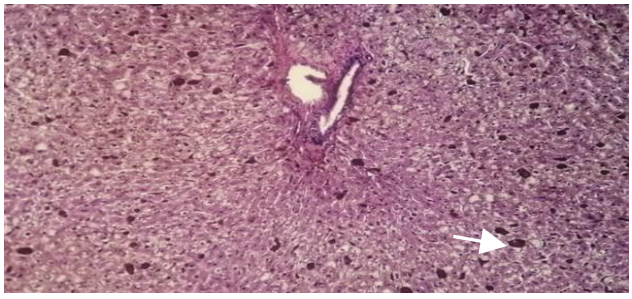

Figure 11. Histopathological section of a rabbit liver in theT1 group shows severe iron overload (white arrow) (H&E, stains, 100x).

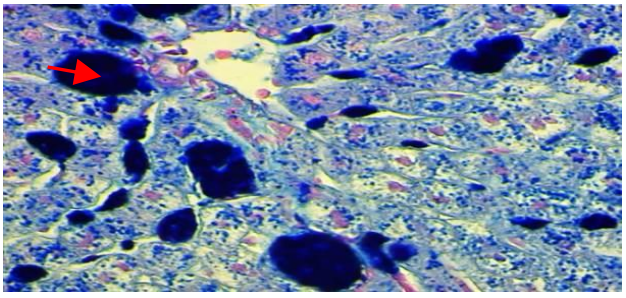

Figure 12. Histopathological section of a rabbit liver in the T1 group shows positive result (increase in iron overload appear as blue color) (red arrow) (Prussian bleu stain,100x).

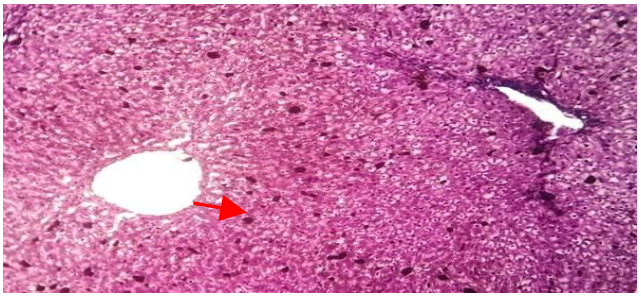

Figure 13. Histopathological section of a rabbit liver for the T2 shows decrease in iron overload (yellow arrow) (H&E, stains, 100x).

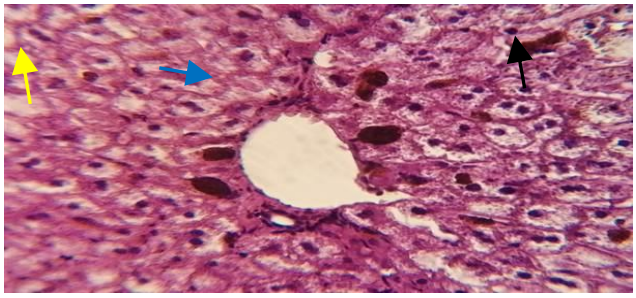

Figure14. Histopathological section of a rabbit liver for the T2 group shows vacuolation of hepatocyte (yellow arrow) and decrease in iron overload (blue arrow) with increase in mitotic division (black arrow) (H&E, stains, 400x).

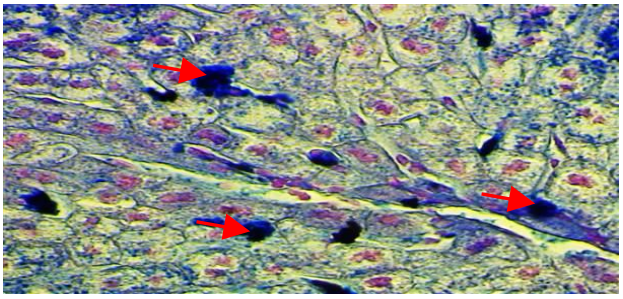

Figure 15. Histopathological section of a rabbit liver for the T2 group shows positive result (moderate iron overload appear as blue color) (red arrows) (Prussian bleu stain,100x).

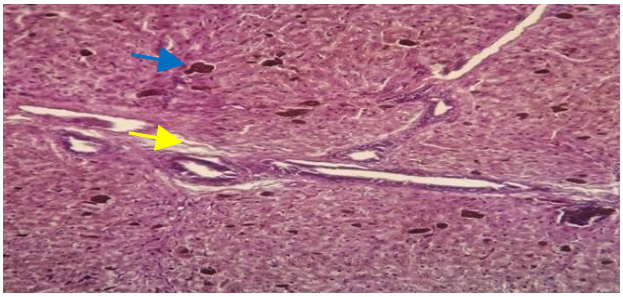

Figure16. Histopathological section of a rabbit liver for the T3 group shows decrease iron overload (blue arrow) with fibrosis around the portal area (yellow arrow) (H&E, stains, 100x).

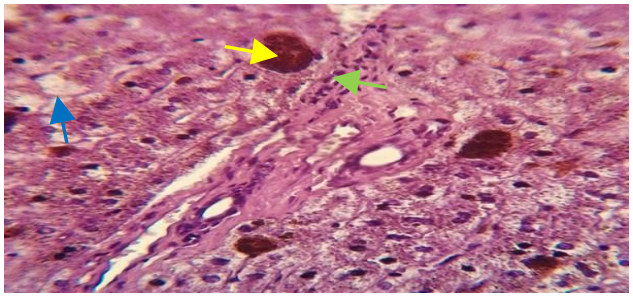

Figure17. Histopathological section of a rabbit liver for theT3 group shows vacuolation of hepatocyte (blue arrow), decrease iron overload (yellow arrow) with fibrosis and inflammatory cells around the portal area (green arrow) (H&E, stains, 400x).

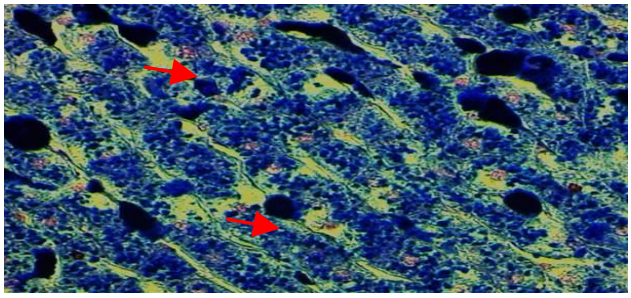

Figure 18. Histological section of a rabbit liver for the T3 group shows positive result (increase iron overload appear as blue color) (red arrows) (Prussian bleu stain,100x).

Histopathological Changes of Duodenum

Duodenum sections of iron overload T1 group show hemochromatosis with inflammatory cells infiltration and a positive result for the Prussian blue stain (increase in iron overload) (Figures 21, 22), when compared with control group (Figures 19, 20). While the T2 group show mononuclear cells infiltration with mild deposition of iron particles and a negative result for the Prussian blue stain (no deposition of iron) (Figures. 23-25), compared with control and T1 groups. Histopathological sections of duodenum rabbits T3 were treated with DFO group show fibrosis in the submucosa layers with inflammatory cells infiltration and mild deposition of iron as well as a positive result for the Prussian blue stain (moderate iron overload) (Figures 26, 27) compared to the T2 group).

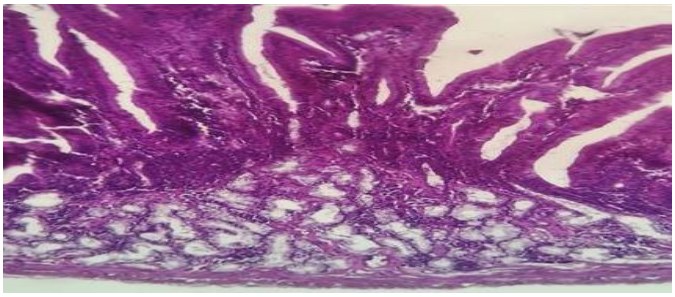

Figure 19. Histological section of a rabbit duodenum for the control group shows normal histological structures (H&E, stains, 100x).

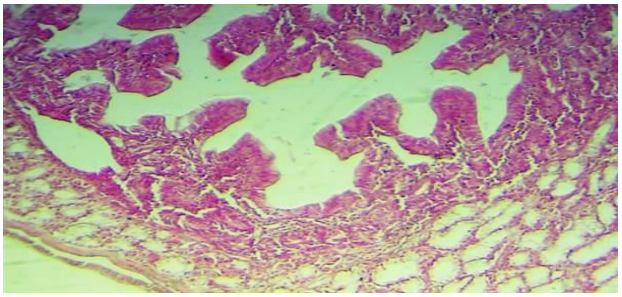

Figure 20. Histological section of rabbit duodenum for the control group shows negative result (no deposition of iron) (Prussian bleu stain,100x)

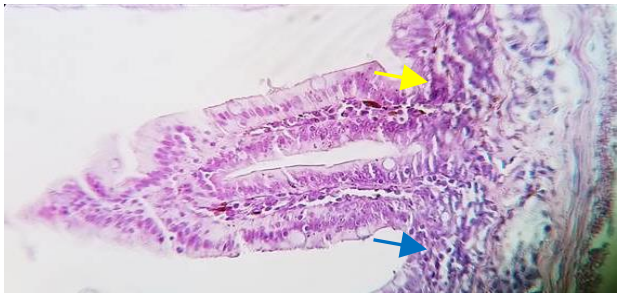

Figure 21. Histopathological section of a rabbit duodenum for the T1 shows hemochromatosis (yellow arrow) with inflammatory cells infiltration (blue arrow) (H&E, stains, 400x).

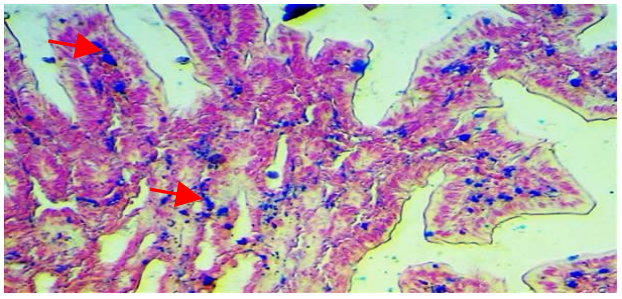

Figure 22. Histological section of a rabbit duodenum villi for the T1 group shows positive result (increase in iron overload appear as blue color) (red arrows) (Prussian bleu stain,100x**)**

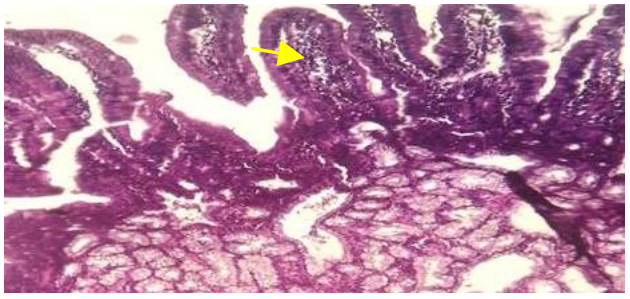

Figure 23. Histopathological section of a rabbit duodenum for the T2 group shows mononuclear cells infiltration (yellow arrow) (H&E, stains, 100x).

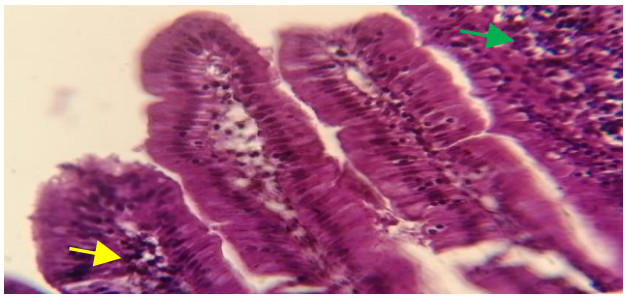

Figure 24. Histopathological section of a rabbit duodenum for theT2 group shows mild deposition of iron particles (green arrow) with mononuclear cells infiltration (yellow arrow) (H&E, stains, 400x).

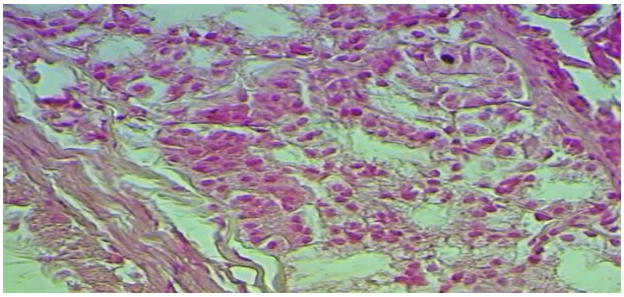

Figure 25. Histological section of a rabbit duodenum for the T2 group shows negative result (no iron deposition) (Prussian bleu stain,100x)

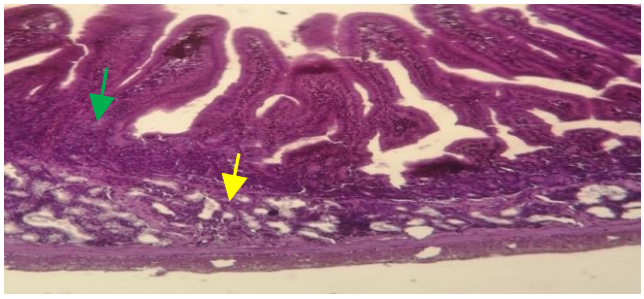

Figure 26. Histopathological section of a rabbit duodenum for the T3 group shows fibrosis in sub mucosa layers (yellow arrow) with inflammatory cells infiltration (green arrow) (H&E, 100x).

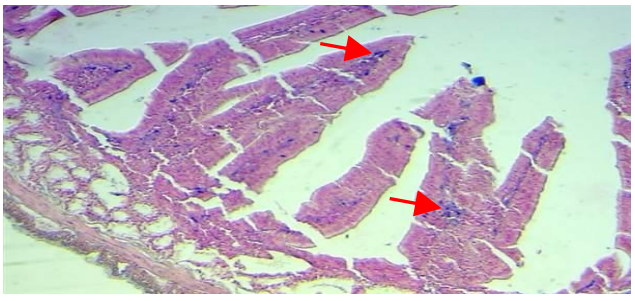

Figure 27. Histological section of a rabbit duodenum for the T3 group shows positive result (moderate iron overload appear as blue color) (red arrows) (Prussian bleu stain,100x).

DISCUSSION

In biological systems, iron is involved in a catalytic reaction that is mediated by free radicals' production, and oxidative damage and developing many organs dysfunction (22, 23).

Current study used iron overload by iron dextran intraperitoneal injection to mimic heavy iron overload. Myocardial muscles and hepatocytes microscopic features agreed with (24, 25).

Histopathological changes in cardiac muscle in the T1 group are characterized by cardiomyopathy related to high iron levels, increased acute myocardial infarction risk, and a suggested, iron contributes in the lipid-ROS generation and ferroptosis, results in the damage-associated molecular patterns release from dead cells, which may promote inflammation through the receptors for advanced end products of glycation Receptor for Advanced Glycation End products (RAGE) to activate Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) (26). The Fenton reaction is a key process that underpins cell growth and mitogen-activated protein kinase (MAPK) activation (27).

Myocytes store iron as hemosiderin, ferritin, and free iron, the most active one leads to ROS production, which converts Fe^{+2} to Fe^{+3} with the formation of the toxic OH radical by the Fenton reaction, resulting in LPO formation, also, increased Fe^{+2} transport via the L-type calcium channels leads to ventricular dysfunction and cardiomyopathy characterized mainly by left ventricular dysfunction (28), and, iron overload enhanced cardiac hypertrophy in rats (29).

In the current study, the histological sections of the T3 group clearly showed that iron chelators reduced heart iron content and reversed the cell damage, abnormal cells architecture, and inflammation, the DFO ability to bind iron in linoleic acid suspension, explanation its mechanism as antioxidant by an electron donor and its ability to react with the OH or the O_2 (30).

In animals treated the over dose of iron, there was a related dose accumulation of iron within hepatocytes or intra sinusoidal cells, stimulates the formation of fibrous septa similar to alcoholic cirrhosis, resulting in hepatocellular carcinoma and micronodular cirrhosis (7). In liver inflammation, iron activation Kupffer cells and increase mononuclear cells chemotaxis toward the damaged area and increases monocyte adhesion to endothelial cells (31, 32).

lymphocytes in the liver activates cytokines in Kupffer cells, leads to increased growth factor production, and stellate cell activation results in the development of fibrosis (33).

In the current study iron caused duodenal pathological alterations such as, iron deposits in the lumen, hemochromatosis and inflammatory cell infiltration in the duodenum histological sections of group T1, these results were in agreement with (19). These pathological alterations were affected intestinal hemostasis by OS, altering GIT flora or by inflammation (34, 35).

In current study, the T2 group, iron levels in liver and cardiac muscle were dramatically reduced due to quercetin able to combination with non-haem iron, and transport it to the blood stream for excrete it from body (36-38)

Quercetin can mitigate iron overload by various mechanisms, including transferrin receptor 1 inhibition, downregulation of ferroportin 1 expression, enhancement of divalent metal transporter 1 expression, and increased hepcidin transcription level that is related to the binding site of STAT3, which indirectly reduces iron saturation (for example, ferritin and transferrin) (37).

The primary sites of chelating action of DFO were the reticuloendothelial in the liver sinusoid and the intercellular spaces of cardiac muscle (39). It is known that DFO iron complexes are excreted through the bile (40). So, the pathologic and metabolic alteration in the liver may influence the excretion of iron (41).

Furthermore, the current study showed more elevation in the iron of duodenum mucosa, while the T2 and T3 groups showed a significant reduction in the duodenum iron level, emphasizing quercetin is potency as a chelator, these results are consistent with (42). There have been few studies on the DFO and quercetin effects on intestinal mucosa in patients with iron overload. However, quercetin might be attributable to reduced iron absorption in acute iron overload by chelating iron inside the intestine via the 3-hydroxyl group, and in the long-term by directly regulating ferroportin expression (43). Or it enhanced iron excretion by forming a complex with iron that was transported by glucose transporter 1 and decreased cellular OH production (44).

The results suggest that quercetin mitigates histological changes induced by iron overload due to its properties as an iron chelating compared to DFO in rabbits.

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N/A.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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التغيرات النسيجية المرضية للقلب والكبد والاثني عشري في الحمل الزائد للحديد: مقارنة بين الكيرستين والديفيروكسامين

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الخلاصة

كان الهدف من هذه الدراسة هو إجراء مقارنة بين الكيرستين والديفيروكسامين في التخفيف من تأثير الحديد الزائد على عضلة القلب والكبد والاثني عشري . تم استخدام أربع مجاميع من الأرانب البالغة (سبعه في كل مجموعة) وعولجت على النحو التالي لمدة ٢٨ يومًا: المجموعة C: تم حقن الحيوانات داخل الصفاق بمحلول ملحي طبيعي كل ٧٢ ساعة + محلول ملحي طبيعي عن طريق الفم يوميًا، تم حقن مجموعات T1 و T2 و T3 بديكستران الحديد ١٠٠ مجم/كجم كل ٧٢ ساعة. المجموعة T2 جرعت بمادة الكيرسيتين ٣٥٠ مجم/كجم عن طريق الفم يوميًا ، والمجموعة T3 حقنت بـ الديفيروكسامين ١٢٥ مجم/كجم بالعضلة يوميًا. في نهاية التجربة تمت التضحية بالحيوانات ، وجمعت عينات انسجة من القلب والكبد والاثني عشري لدراسة التغيرات النسيجية المرضية. أظهرت نتائج الفحص لمقاطع القلب في المجموعة T1 وذمة في عضلة القلب وترسب للحديد. أظهرت مجموعة T2 وذمة طفيفة بين ألياف عضلة القلب. بينما أظهرت مجموعة T3 وذمة بين ألياف عضلة القلب ، وتضخم واحتقان في الأوعية الدموية ، كل المجاميع اظهرت نتيجة ايجابية لصبغه بروسين الزرقاء مقارنة بمجموعه السيطرة. أظهرت المقاطع النسيجية للكبد للمجموعة T1 وجود زيادة حادة من الحديد في سيتوبلازم الخلايا الكبدية ، وتليف مع سماكة المنطقة البوابيه ، ونخرفي الخلايا الكبدية. وأظهرت مجموعات T3 وT2 تفجي خلايا الكبد مع انخفاض في الحديد. وتليف حول المنطقة البوابية ، ، كل المجاميع اظهرت نتيجة ايجابية لصبغه بروسين الزرقاء مقارنة بمجموعه السيطرة. أظهرت مقاطع الاثني عشري في المجموعة T1 ترسب الأصبغة. واظهرت مجموعة T2 ترسب خفيف للحديد. اظهرت المجاميع T1وT3 نتيجة ليجابية لصبغه بروسين الزرقاء مقارنة مع مجموعة السيطرة ومجموعة T2 . الاستنتاج: أن الكيرسيتين يخفف من التغيرات النسيجية المرضية الناتجة عن زيادة الحديد بسبب خصائصه كمخلب للحديد مقارنة بـ الديفروكسامين في الأرانب.

الكلمات المفتاحية: الكيرستين ،الديفروكسامين، الحديد، القلب ،الكبد ،الاثنى عشري