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HISTOPATHOLOGICAL AND BIOCHEMICAL EVALUATION OF HEPATOTOXICITY AND NEPHROTOXICITY INDUCED BY 5-FLUOROURACIL IN RATS

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ABSTRACT

The goal of the study is to examine the potentially harmful histopathological and biochemical effects of 5- Fluorouracil (5-FU) on the liver and kidney. Thirty rats were divided into two groups. The control group was given physiological saline intraperitoneally for 5 days. The 5-FU group received 5-FU at a dose of 20 mg/kg b. wt. intraperitoneally for 5 days. Blood samples were collected and used for biochemical indexes. For histological analysis, samples of the liver and kidney were collected. There was a significant increase in the levels of serum creatinine, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT), malondialdehyde (MDA) in the 5-FU group when compared to the control group. Compared to the control group, there was a significant decrease in total antioxidants (TAO). Microscopic examination of the liver showed vascular changes, apoptosis, vacuolar degeneration, kupffer cell proliferation, focal inflammatory cell infiltration, hepatocellular necrosis and mononuclear cellular infiltration in the portal area. While the histopathological changes in kidneys varied from vascular changes, glomerular necrosis and atrophy and vacuolar degeneration of the renal tubules. It was concluded that the hepatotoxic and nephrotoxic effects were due to the oxidative stress induced by 5-FU.

Key words: 5-Fu, liver, kidney, histopathology

INTRODUCTION

Chemotherapy is an effective cancer treatment. Unfortunately, cancer treatment causes acute non-targeted organ damage (Maor & Malnick, 2013). Chemotherapy destroys both rapidly expanding cancer cells and other rapidly expanding body cells, such as blood and hair cells, without making a difference between them and healthy cells.

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(El-Sayyed *et al.*, 2009). The antimetabolic drug 5-fluorouracil (5-FU) inhibits the production of DNA and RNA in both normal and cancerous cells (Gelen *et al.*, 2018). It is essential for the treatment of pancreatic, colon, breast, gastrointestinal, head, and neck cancer (Longley *et al.*, 2003). 5-fluoro-2-deoxyuridine5-monophosphate (FdUMP), a metabolic by-product of 5-FU in the body, inhibits thymidylate synthase and hinders DNA replication (Peters *et al.*, 1994). Severe toxicity and undesirable side effects are induced following its use (Cabellos *et al.*, 2007). Some of the common clinical side-effects include myelosuppression, diarrhoea,

vomiting, mucositis, leukopenia, stomatitis, alopecia, cardiotoxicity, nephrotoxicity, and hepatotoxicity (Abou-Zeid, 2014). With the use of 5-FU, renal damage, which is characterized by changes in serum renal indicators, is a significant problem. Additionally, serious kidney structural changes such as tubular necrosis, renal lesions, and glomeruli atrophy may take place (Isaka & Rakugi, 2009). 5-FU is also a hepatotoxic, resulting in elevated tissue levels of aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) with histopathological alteration in hepatocytes (Gelen *et al.*, 2018). According to the studies, reactive oxygen species (ROS) is the cause of the toxic effects of 5-FU (Afolabi *et al.*, 2016). This study was done to evaluate the histopathological and biochemical changes in the liver and kidney induced by 5-FU.

MATERIALS AND METHODS

Materials:

Animals:

The study used thirty male adult Sprague-Dawley rats that weighed 200–220 gm. The animals were bought from the animal house, located in the Department of Pathology and Clinical Pathology, Faculty of veterinary medicine at Assiut University in Egypt. The ethics committee of the Faculty of Veterinary Medicine, Assiut University gave its approval to the study.

Chemicals:

- 5-Fluorouracil was purchased from Hikma specialized pharmaceuticals, Badr city, Cairo, A.R.E).
- Kits for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) analysis were purchased from SPINREACT S.A./S.A.U, Ctra.Santa Coloma , SPAIN .
- Kits for urea and creatinine analysis were purchased from MDSS GmbH, Schiffgraben 41, 30175 Hannover, Germany.

Experimental design:

Two groups of rats were used:

Group 1 (**5-FU group**): 15 rats received 5-FU with a dose of 20 mg/kg b. wt. intraperitoneally for 5 days.

Group 2 (**control group**): 15 rats received physiological saline intraperitoneally for 14 days.

Methods:

1. Collection of blood and tissue samples:

Under ether anesthesia, rats were slaughtered at the end of the experiment. Through the heart, blood samples were retrieved, centrifuged at 1500 rpm for 14 min, and the serum samples were collected to calculate biochemical indices. Specimens from the liver and kidneys were collected for histopathological examination.

2. Biochemical evaluation:

2.1. Evaluation: of liver function indices: Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were measured using commercial kits following the manufacturing procedure by Murray (1984).

2.2. Evaluation: of kidney function indices: Urea and creatinine levels were evaluated using commercial kits following the manufacturing procedure by Koller & Kaplan (1984) and Murray (1984) respectively.

2.3. Evaluation: of oxidative stress indices: The levels of malondialdehyde (MDA) were evaluated with a commercial kit by the method of Ohkawa et al. (1979). The approach of Koracevic et al. (2001) was used to evaluate total antioxidant (TAO) enzymes using a commercial kit.

3. Histopathology: Liver and kidney samples were fixed by neutral buffered formalin fixation, normal processing, dehydration in ascending ethyl alcohol series, clearing in xylene, embedding in paraffin, and sectioning (5 µm). Hematoxylin and eosin stain was used to

stain the sections of tissues. The appropriate parts of the stained sections were photographed after being inspected under a light microscope.

4. **Statistical analysis**: The values were represented as mean ± standard error (SE) using student's t-test. The values are supposed significant when the P value <0.05.

RESULTS

1. **Biochemical results:** Table 1 demonstrated the effect of 5-FU on the levels of AST, ALT, urea, creatinine and oxidative stress indices.

1.1. **ALT and AST levels:** The 5-FU treated group demonstrated a significant rise in serum AST and ALT levels as compared to the control group, as seen in Fig. 1A and Fig. 1B, respectively.

1.2. **Urea and creatinine levels:** According to Figs. 1C and 1D, there was a considerable increase in the levels of serum urea and creatinine in 5-FU group as compared to the control group.

1.3. **Oxidative stress indices (MDA and TAO):** When compared to the control group, the serum MDA level in the 5-FU group was significantly increased (Fig. 1E). When compared to the control group, the 5-FU treated group's serum level of TAO was significantly lower (Fig. 1F).

Table 1: Effect of 5-FU on serum levels of AST, ALT, urea, creatinine, MDA and TAO in 5-FU and control groups.

	5-FU group	Control group
AST (U/L)	254.6±9.2 *	161.7±3.4
ALT (U/L)	106±2.9*	57.6±1.2
Urea (mg/dl)	60.8±0.8 *	58.0 ±0.6
Creatinine (mg/dl)	1.1±0.06 *	0.71±0.01
MDA (nmol/ml)	11.61±0.38*	9.41 ±0.21
TAO (mM/L)	0.79±0.11*	0.82±0.01

The values were expressed as mean ±SE. * significant when compared with the control group (P<0.05).

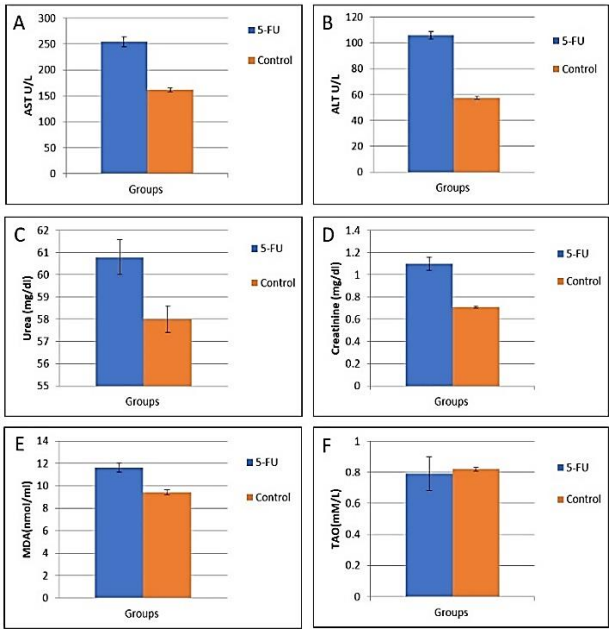

Fig 1: Effect of 5- FU on the levels of AST (A), ALT (B), urea (C), creatinine (D), MDA (E) and TAO (F). The letters show the statistical differences among groups (P<0.05). The values were expressed as mean ±SE (n-15).

Histopathological results:

Histopathological lesions in the liver and kidneys induced by 5-FU were summarized in Table 2. Examination of liver specimens from rats received 5-FU at a dose of 20mg/kg.bwt showed vascular changes and parenchymatous changes. Vascular changes were observed in the form of hyperemia of blood vessels (Fig. 2A), endothelial damage which was observed in both central and portal veins (Fig. 2C) and thrombosis (Fig. 2D). Parenchymatous changes were in the form of apoptosis (Fig. 3A), vacuolar degeneration (Fig. 3B), kupffer cell proliferation (Fig. 3C), oval cel proliferation (Fig. 3D), focal inflammatory cell infiltration and hepatocellular necrosis (Fig. 3E). Examination of liver specimens from control group demonstrated normal architecture (Fig. 3F).

Histopathological examination of kidney specimens from rats received 5-FU at a dose of 20mg/kg.bwt showed vascular changes, glomerular changes and tubular changes. The changes in blood vessels were in the form of congestion (Fig. 4A) and hemorrhage (Fig.

4B). Changes in the glomerulus included vacuolation of the mesangial, endothelial and glomerular epithelial cells (Fig. 4C), thickening of glomerular basement membrane (GBM) (Fig. 4D), necrosis of glomerular capillaries and mesangial cells associated with a hyaline cast (Fig, 4E) and atrophy of the glomerulus (Fig. 4F) . Changes in the renal tubular changes were in the form of vacuolation of the renal tubular epithelium observed in the epithelium of proximal convoluted tubule, distal convoluted tubules and collecting tubules (Fig. 5A&B) and focal interstitial infiltration of mononuclear inflammatory cells (Fig. 5C). Examination of kidney specimens from control group demonstrated normal architecture with normal glomeruli and renal tubules (Fig. 5D).

Table 2: Histopathological lesions induced by 5-FU in livers and kidneys of rats.

Lesions	5-FU group	Control group
Liver		
Vascular changes		
Congestion	14 (93.3%)	0
Hemorrhage	3 (20%)	0
Endothelial injury	14 (93.3%)	0
Thrombosis	7 (46.6%)	0
Dilatation of sinusoid	8 (53.3%)	0
Parenchymal changes		
Apoptosis	6 (40%)	0
Vacuolar degeneration	10 (66.6%)	0
Focal area of inflammatory cellular infiltration	7 (46.6%)	0
Kupffer cell hyperplasia	14 (93.3%)	0
Oval cell proliferation	8 (53.3%)	0
Infiltration of inflammatory cells in portal area	4 (26.6%)	0
Kidney		
Vascular changes		
Congestion	5 (33.3%)	0
Hemorrhage	10 (66.6%)	0
Changes in glomerulus		
Vacuolated glomeruli	13 (86.6%)	0
Thickening of glomerular basement membrane	12 (80%)	0
Glomerular atrophy	5 (33.3%)	0
Necrosis of the glomeruli	14 (93.3%)	0
Hyaline cast	3 (20%)	0
Changes in renal tubules		
Vacuolar degeneration	4 (26.6%)	0
Interstitial infiltration of inflammatory cells	13 (86.6%)	0

Values are presented as N(%)

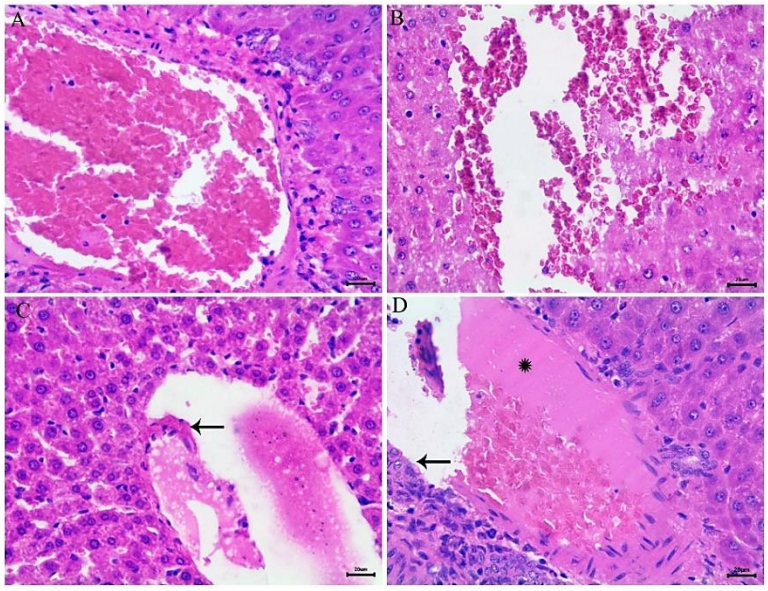

Fig. 2: Photomicrograph of liver from rats exposed to 5-FU (20 mg/kg b.wt). A. Congestion of blood vessel. B. Dilatation of blood sinusoid. C. Endothelial injury (arrows) D. Thrombosis formed of Rbcs, WBcs and fibrin (star). HE

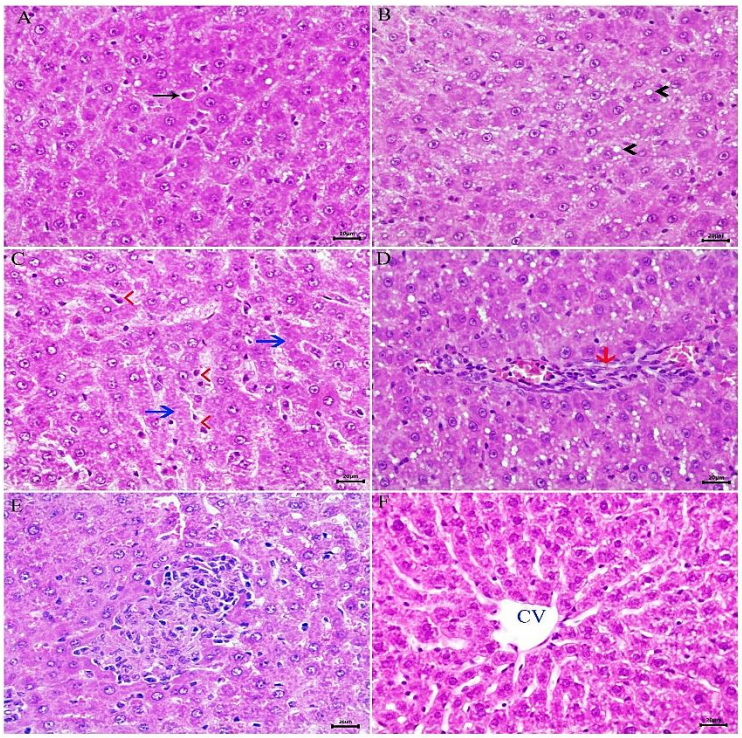

Fig. 3: Photomicrograph of liver from 5-FU and control groups. A. Apoptotic cells are characterized by shrinkage of the cells, condensation of the nuclei and eosinophilic cytoplasm (black arrows). B. Vacuolar degeneration of hepatocytes. The hepatocytes contain clear vacuoles (arrowheads). C. Proliferation of Kupffer cells (arrowheads). necrosis of hepatocytes (Blue arrows). D. Oval cell proliferation (red arrow). E. Focal area of necrosis associated with mononuclear cellular infiltration. F. Control liver. The normal architecture of liver. CV; central vein. HE

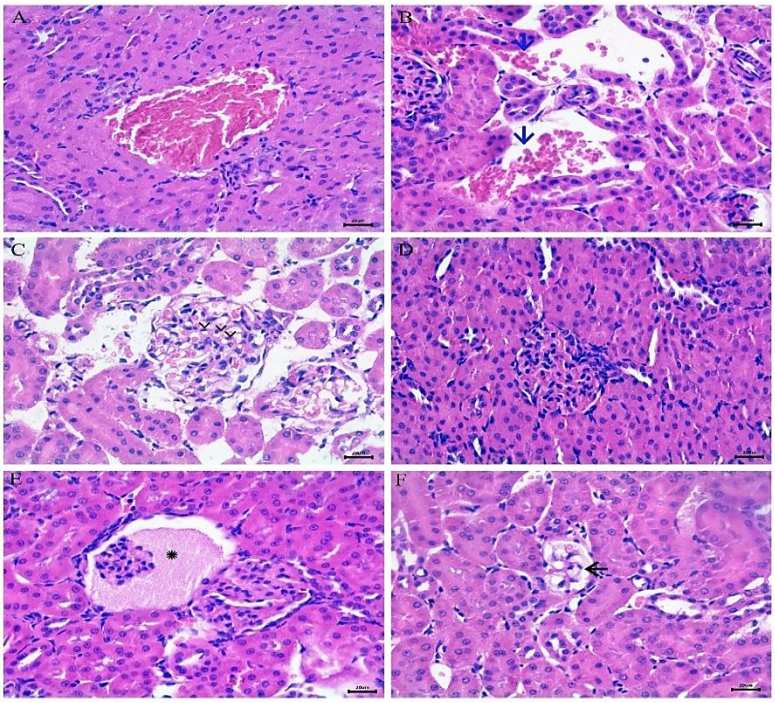

Fig. 4: Photomicrograph of kidney from rats exposed 5-FU (20 mg/kg b.wt). A. Congestion. B. Hemorrhage (blue arrows). C. Vacuolation of the epithelial cells of the glomerulus (arrowheads). D. Thickening of the glomerular basement membrane. E. Necrosis of the mesangial and epithelial cells of the glomeruli. Hyaline cast (star). F. Atrophy of the glomerulus. HE

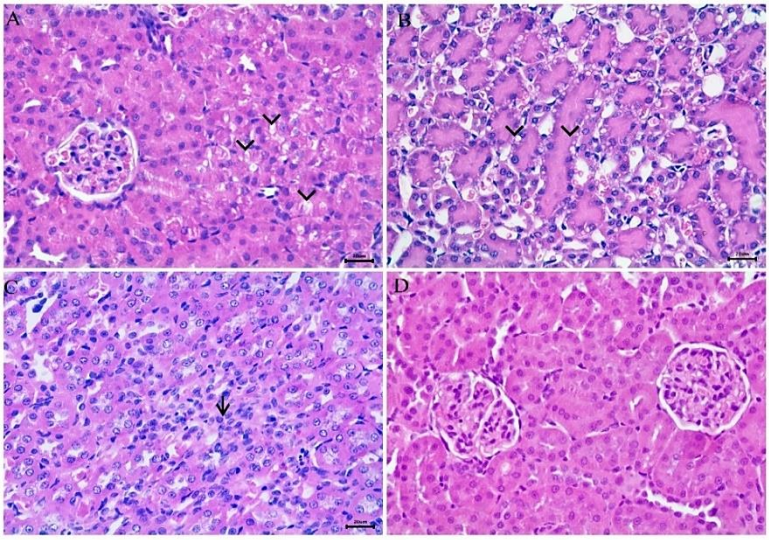

Fig. 5: Photomicrograph of kidney from 5-FU and control groups. A. Vacuolation of the renal tubular epithelium in the cortex (arrowheads). B. Vacuolation of the renal tubular epithelium in the medulla (arrowheads). Mononuclear cellular infiltration (arrow). D. Control kidney. Normal kidney architecture. HE

DISCUSSION

The main treatment for cancer patients is chemotherapy, but its therapeutic application is limited by serious clinical side effects. (Ramadori & Cameron 2010). The serious topics related to chemotherapy are liver and kidney damage (Maor & Malnick, 2013). As a severe adverse reaction, 5-FU, a pyrimidine antimetabolite used in chemotherapy, has been linked to renal

and liver damage. The toxicity of these organs is joined with increased apoptosis and oxidative stress (Rashid *et al.,* 2014). The most sensitive tissues to injury caused by ROS are liver and kidneys (Abou Asa *et al.,* 2018).

In our study, we explored the histopathological and biochemical effects of 5-FU on the liver and kidneys. Fifteen rats got 5-FU intraperitoneally 5 days with a dose of 20 mg/kg body weight. Histopathological examination of the liver showed marked vascular changes and parenchymatous changes. Vascular changes were observed in the form of hyperemia, dilatation of blood sinusoid, hemorrhage, endothelial damage and thrombosis. The current findings concur with those of Klatskin and Ocean (1993), who postulated that the blood sinusoids' dilatation would be caused by the direct toxic effect of 5 -FU on the blood sinusoids.

Parenchymatous changes were in the form of apoptosis, vacuolar degeneration, kupffer cell proliferation, focal inflammatory cell infiltration, hepatocellular necrosis and mononuclear cellular infiltration in the portal area. The current findings are consistent with those of Abou-Zeid *et al.* (2014), who observed that 5-flourouracil-treated hepatocytes displayed vacuolated cytoplasm, dilated hepatic sinusoids, and hyperplasia of Kupffer cells, pyknotic nuclei, a lack of the hepatocytes' typical architecture and inflammatory cells infiltration in between the hepatocytes. Similar histopathological changes were described by El-Sayyad *et al.* (2009) including apoptotic cell death, infiltration of inflammatory cells, hepatic cord disorganization and enlarged blood sinusoids. Similar findings were reported also by (Gelen *et al.,* 2018) who found coagulative necrosis in the hepatocytes and infiltration of inflammatory cells in the portal region. In the existing study, the cytoplasm of hepatocytes was vacuolated, According to Zhang and Wang (1984) the cytoplasmic vacuolation is due to a disturbance in the metabolism of lipids and fat. Jacquemyn *et al.* (2017) & Kunitomi *et al.* (2020) suggested that disorders of lipid metabolism can result from 5-FU treatment which induced endoplasmic reticulum stress; a crucial location for lipid synthesis. In the present study, comparing the 5-FU treated group to the control group, a significant rise in the levels of serum ALT and AST was observed. These results agreed with Shehab *et al.* (2015) who mentioned that hepatocyte necrosis and membrane damage caused by 5-FU allows leakage of intracellular enzymes ALT, AST into circulation and elevate their concentrations in the serum which suggests that the membrane of the hepatocytes has lost some of its function.

Regarding our histopathological observation in the kidney after administration of 5-FU at a dose of 20 mg/kg b. wt. intraperitoneal were manifested as vascular changes, glomerular changes and tubular changes. the changes in blood vessels were in the form of hemorrhage and congestion. Concerning the glomerular lesions, they were in the form of vacuolation of the mesangial, endothelial and glomerular epithelial cells, thickening of glomerular basement membrane (GBM) associated with the absence of Bowman's space, necrosis of the glomerular capillaries and mesangial cells, hyaline cast and atrophy of the glomerulus. The renal tubular changes were in the form of vacuolation of the renal tubular epithelium and focal interstitial infiltration of mononuclear inflammatory cells. Badawoud *et al.* (2017) reported that the kidneys of 5-FU-treated rats showed vacuolization of tubular epithelial cells, congestion,

hemorrhage, interstitial mononuclear cellular infiltration, areas of glomerular degeneration, glomerular atrophy, and periglomerular leukocyte infiltration. Rashid *et al.* (2014) found that 5-FU treatment disrupted the normal renal architecture. Our findings are in line with those previously published by Gelen *et al.* (2021) who describe renal tubule dilatation, tubular epithelial degradation, and necrosis in kidney tissue from the 5-FU group. Similar findings were also obtained by Adikwu *et al.* (2019) who reported atrophic glomerulus with thin glomeruli basement membrane, widen Bowman's space and tubular necrosis and vacuolation.

In the current investigation, the 5-FU-administered group showed a substantial rise in serum urea and creatinine levels. These results corroborated those of Adikwu *et al.* (2019), who found that 5-FU administration to rats resulted in decreased kidney TAO levels and increased kidney MDA levels, as well as compromised renal function shown by elevated blood creatinine and urea levels. Famurewa *et al.* (2019) showed that 5-FU can cause nephrotoxicity by encouraging oxidative stress and apoptosis. 5-FU slows down the kidneys' ability to filter out waste which results in higher blood levels of urea and creatinine (Longley *et al.,* 2003; Rashid *et al.,* 2014; Al-Asmari *et al.,* 2016).

In our study following the injection of rats with 5-FU, the concentrations of TAO were significantly decreased and the oxidative stress marker (MDA) increased. This agrees with previous reports by Al-Asmari *et al.* (2016) who mentioned that the increased level of serum MDA is a valuable marker of oxidative stress in rats given 5-FU, and is used to evaluate lipid peroxidation after tissue destruction through ROS generation. In addition to reducing TAO, 5-FU was found to induce lipid peroxidation and its related harmful effects to cellular membranes (Abraham *et al.,* 2010 & Tedesco and Haragsim, 2012). As well as Fahmy *et al.* (2020) explained the high level of MDA with a minimum TAO level point toward the accumulation of ROS and oxidative impairment.

CONCLUSION

The administration of 5-FU induced serious histopathological lesions in the liver and kidneys in rats. The lesions were associated with an increase in oxidative stress and a decrease in antioxidant enzymes. It was concluded that these lesions were due to the oxidative stress induced by 5-FU.

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التقييم الهستوباثولوجى والبيوكيميائى لتسمم الكبد والكلى المحدث ب ٥- فلورويوراسيل في الجرذان

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هدفت الدراسة إلى معرفة التأثير السام لمادة ٥- فلورويوراسيل(5-FU) على الكبد والكلى. تم تقسيم ثلاثين من الجرذان لمجموعتين. تلقت المجموعة الضابطة محلول ملحي فسيولوجي داخل الصفاق (البريتون) لمدة 5 أيام. تم حقن مجموعة ال-5 FU بجرعة ٢٠ مجم / كجم بالوزن داخل الصفاق لمدة خمسة أيام. تم جمع عينات الدم واستخدامها في القياسات البيوكيميائية. تم أخذ عينات من الكبد والكلى للفحص الهستوباثولوجي .أظهرت النتائج البيوكيميائية أن الكرياتينين، اليوريا، انزيمات الكبد (AST, ALT) Malondialdehyde (MDA), كانت مرتفعة بشكل ملحوظ في مجموعة 5-FU بالمقارنة مع المجموعة الضابطة. بينما كان هناك انخفاض كبير في مضادات الأكسدة بالمقارنة مع المجموعة الضابطة. أظهرت التغيرات النسيجية المرضية في الكبد تغيرات في الأوعية الدموية، موت الخلايا المبرمج، تنكس فجوي، تكاثر خلايا كوبفر، تسلل الخلايا الالتهابية البؤرية، نخر الخلايا الكبدية، التسلل الخلوي وحيد النواة في منطقة المدخل. بينما تباينت التغيرات النسيجية المرضية في الكلى من تغيرات في الأوعية الدموية ونخر كبيبي وضمور وتنكس فجوي في الأنابيب الكلوية. استنتج أن التأثيرات السامة للكبد والكلية كانت بسبب الإجهاد التأكسدي الناجم عن لـ 5-FU.