Histopathological evaluation of the 4,4 -(4,5,6,7-Tetrahydro- [1,2,3-] Selenadiazolo [4,5 E] Pyridine-4,6-Diyl) Bis(Benzene-1,3-Diol) on female rats in comparison with Dipyrone.

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Histopathological evaluation of the 4,4̄-(4,5,6,7-Tetrahydro-[1,2,3-] Selenadiazolo [4,5 E] Pyridine-4,6-Diyl) Bis(Benzene-1,3-Diol) on female rats in comparison with Dipyrone.

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Abstract

Selenium (Se) is one of the vital nutritional components with main biological roles. It acts as a prosthetic group in many enzymes like glutathione peroxidase enzyme and thioredoxin reductase enzyme. The aim of the present study to investigate the histological effects of 4,4̄ -(4,5,6,7-Tetrahydro- [1,2,3-] Selenadiazolo [4,5 E] Pyridine-4,6-Diyl) Bis(Benzene-1,3-Diol)(T) compare with Dipyrone (Di) on kidney, liver and stomach. Healthy female rats divided into four groups received 50mg/kg BW of T (T group), Di (Di group), both T and Di (T&Di) dissolved in 2 ml of distilled water(DW), the forth group control received 2 mL of (DW) for 30 days. The samples of liver, kidney and stomach were fixed in 10%formalin, and the histological sections and staining were prepared in the pharmacy college central lab for histopathological examination. The results indicated that Di group showed disarrangement of hepatic architecture and sinusoids narrowed of the liver. Section of the kidneys reveal shrinkage in glomerular content and misshaped of cuboidal lining epithelial. Stomach sections showed destruction of gastric pits and increased number of fundic glands. T group liver sections incomplete disappearance of hepatocyte radiation. Renal Section of T treated group rat's disappearance of Bowman's capsule; stomach Sections showed complete disappearance of epithelial cells of the gastric pit. T&Di group sections exhibit disappearance of hepatocytes normal radiation architecture phenomena, also there is some hemorrhages. Renal histological sections showed absences of walls of cuboidal lining epithelium with enlarged nuclei. It can be concluded that T compound has low destructive effects on the test organs compare with Di and control group. Administrations of both treatments have no benefit effects.

Key wards: selenadiazole, Dipyrone, histopathology

1- Introduction

Selenium (Se) is one of the vital nutritional components with main biological roles. It acts as a prosthetic group in many enzymes like glutathione peroxidase enzyme and thioredoxin reductase enzyme [1]. Environmental selenium can found in an organic form in which directly attached to carbon; such as methyl compounds $(CH_3)_2Se$ $(CH_3)_2SeO_2$, or an inorganic form like selenite and elemental Selenium. In living organisms Se commonly selenomethionine and selenocysteine [2]. Organic selenium compounds have substantially greater bioavailability, significantly less toxic than inorganic compounds for example selenomethionine bioavailability greater than selenite up to twice. The organic form more effective, more safes that encouraged to synthesis and identifications of novel selenium created pharmaceuticals used as anticancer, antimicrobials and antioxidants [3]. Selenium-organic compounds have many advantages like; more absorption, less cytotoxicity than inorganic forms, consequently rising attention for study organoselenium compounds. Selenoproteins have an antioxidant, anticancer, antimicrobial, anti-inflammatory, neuro-protectors, construction of active thyroid hormones, cytokine inducers and immunomodulatory [4].

It has been confirmed that selenium -toxicity can be assigned to chemical forms; thus, the dangerous harmfulness was detected as selenious acid or selenium oxide. Reviews have revealed that synthetic selenium displays minor toxicity related to other oxidative states[5]. This study was aimed to assess the 4,4̄ -(4,5,6,7-Tetrahydro- [1,2,3-] Selenadiazolo [4,5 E] Pyridine-4,6-Diyl) Bis(Benzene-1,3-Diol) (T) toxicity on liver, kidney and stomach, the results were compared with Dipyrone (Di) effects.

2- Material and Methods

2.1 Animal's preparation

Forty healthy female rats were obtained from University of Basrah/Veterinary Medicine College. The rat's weight 240-254g, retained in polypropylene-cages padded with sawdust (3-4rats/cage). The diet provided was usual pellet diet for rats and tap water. They were adapted to laboratory circumstance, natural day and light (12 hr. days and 12 hr. nights). Room temperature 21±4°C[6]. Then the cages were labeled and separated as groups and then Body weight of all rats was measured.

2.2 Experiment design

The animals divided into four groups, three groups T group, Di group, and T&Di group. Each group administered 50 mg/kg body weight (BW) dissolved in 2mL distilled water (DW) of T compound synthesized by the authors at pharmaceutical chemistry research lab/College of Pharmacy/Basrah University; the composite was branded at University of Al al-Bayt, Al-Mafraq-Jordan. The second group (Di group) treated with 50 mg/kg BW of Di (provided from Shaanxi pioneer Biotech. China) dissolved in 2mL DW. The third group (T&Di) received 50

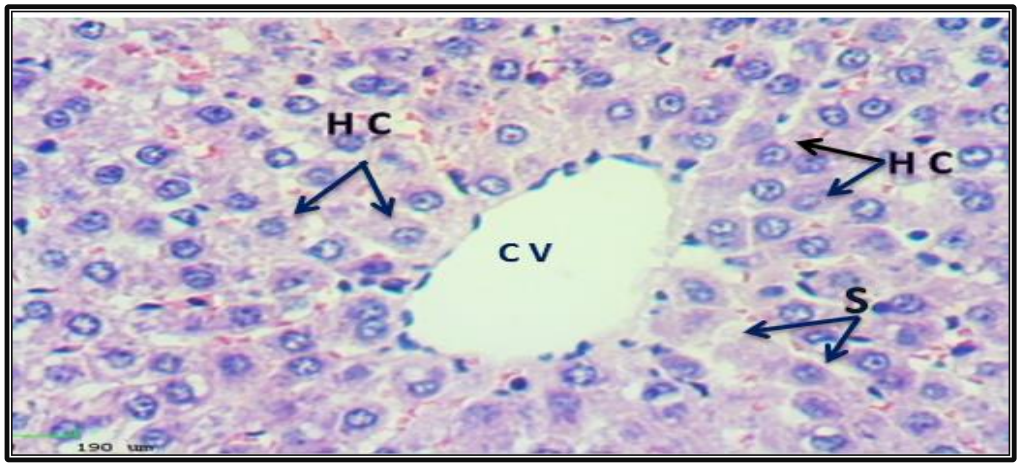
mg/kg BW of T and 50 mg/kg BW of Di, the forth group (control or DW group) received only 2mL of DW. All Compounds are administered orally using a mouth gavage, for 30 days.

Under the effects of chloroform, organs were separated from the body and washed with normal saline. The samples were fixed in 10%formalin, and then the histological sections and staining were done in the pharmacy college central lab. The samples prepared in embedded paraffin for histopathological analysis, the silds stained with hematoxylin eosin[7].

3- Results

3.1 DW group

Histological analysis of Liver section in DW group, as in a figure (1) showed that liver parenchyma was healthy, hepatic plates radiating normally disconnected by blood sinusoids. The Renal cross section of DW treated group revealed that kidney structure, glomeruli size, cubiodal cells size of epithelial lining of renal tubules and lumenal renal tubules were normal, Renal cells have a natural cytoplasm and bright nuclei. No signs of Inflammation or necrosis, and tubules have a normal visage as visible in the figure(2). Stomach section of female rats in DW group appeared that gastric pits epithelial cells, and the number and size of the glands of fundic region were normal. Also, the muscular mucosal layer was normal as in the figure(3).



Figure(1):- section in the liver from DW treated rats group, showed normal hepatic cell HC and central vein CV. 400X (Hand E stain)

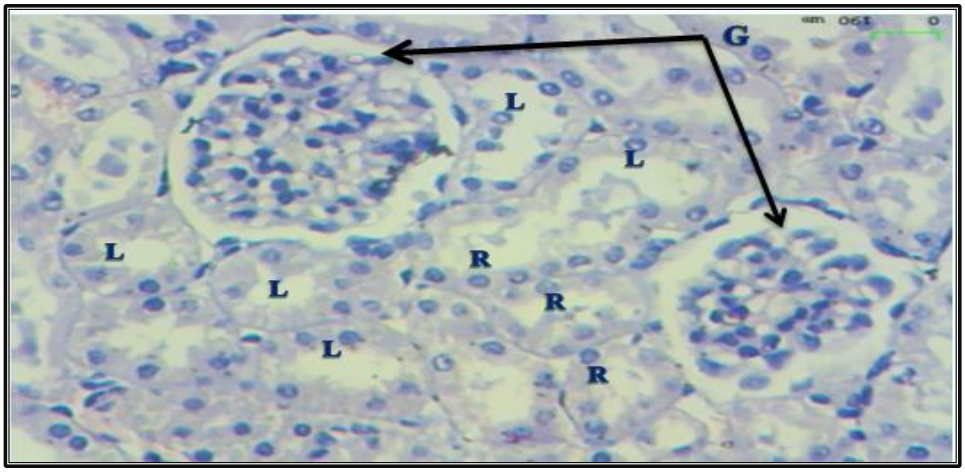


Figure (2):- Section in the kidney of DW treated rats group, revealed glomeruli (G), renal tubule(RT) and lumenal renal tubules(L). (H and E stain). 400X

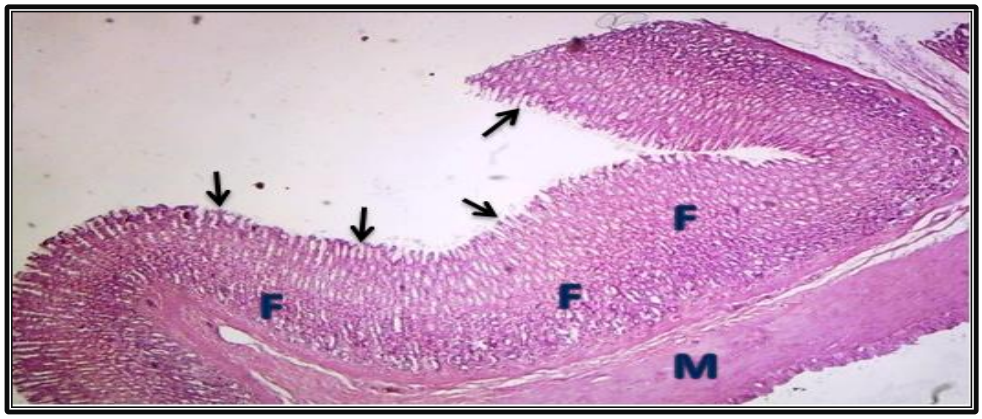


Figure (3):- Section in the Stomach of DW group, showed gastric pits (arrows) and normal number and size of fundic glands (F) of fundic region. The muscular mucosal layer is normal (M). (H and E stain), 100X.

3.2 Di group

Histological examination of the liver from Di group revealed as in the figure (4) elongated central vein, hepatocytes were flattened, pyknotic hepatic nuclei enlarged and sinusoids narrowed, with disarrangement of hepatic architecture. Kidney from the same rats as in the figure(5) revealed shrinkage in glomerular content and misshaped of cuboidal lining epithelial cells of the renal tubule, besides to enlarge pyknotic nuclei of cuboidal cells. Figure (6) shows stomach Section from the same group; there were destructions of the gastric pit epithelial cells and increased number of fundic glands, also muscular mucosa was thickening.

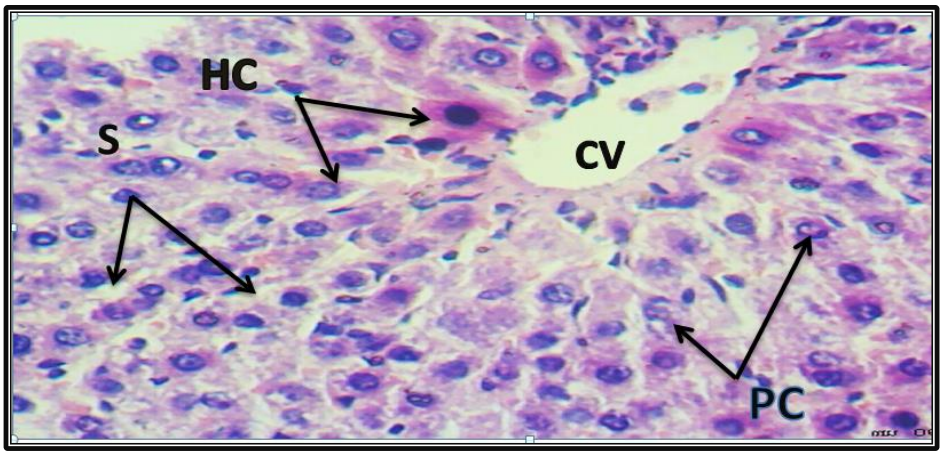


Figure (4):- Cross Section of liver from Di treated rats. Central vein (CV), sinosoid (S) and hepatocytes(HC) arranged in hepatic rays architecture. (H and E) stain.400X

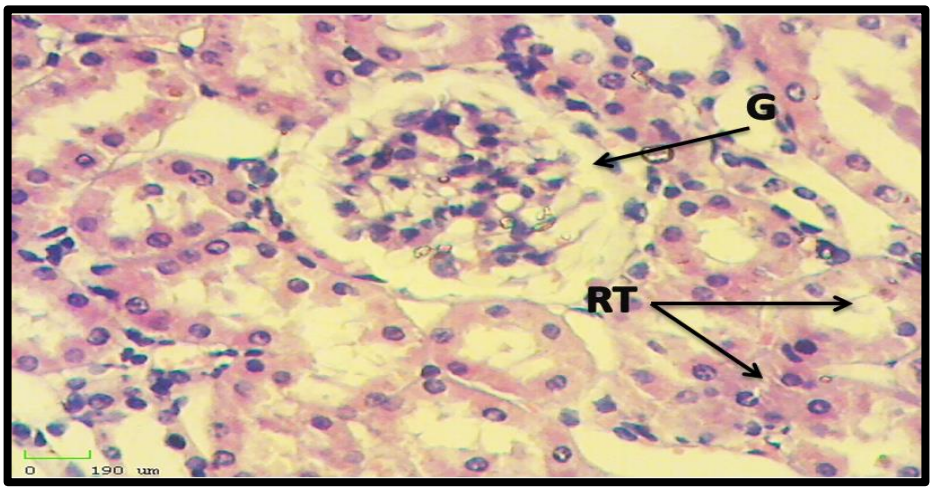


Figure (5):-Cross section in the Kidney from Di Treated rats revealed. glomeruli (G), renal tubules(R) and lumenal renal tubules. (H and E) stain.400X

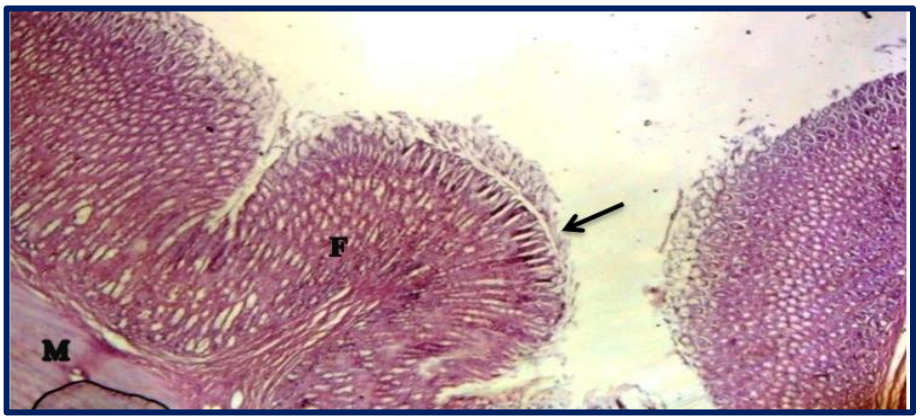


Figure (6):- sections in the gastric region of Di group rats. The cells of the gastric pit (arrow) and muscular mucosa (M). (H and E stain)100X.

3.3 T Group

The liver from (T) group rats section as shown in a figure (7) reveled normal central vein (CV) disarrangement of hepatocyte architecture and incomplete disappearance of hepatocyte radiation. Renal Section of same group, as in Figure (8) revealed; disappearance of Bowman's capsule and shrinkage of the glomerulus. Gastric sections of T treated group rats, figure (9), reveals complete disappearance of epithelial cells of the gastric pit, in addition less number, size of fundus region, while there was more thickening of the muscular mucosa.

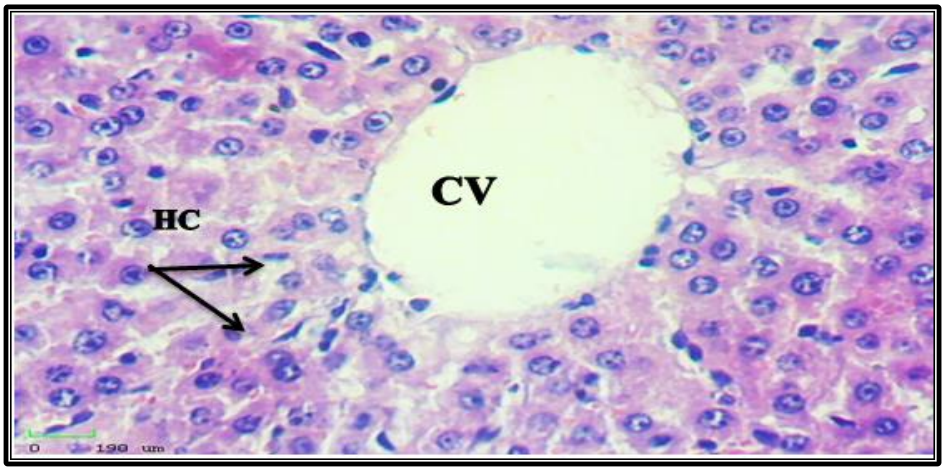
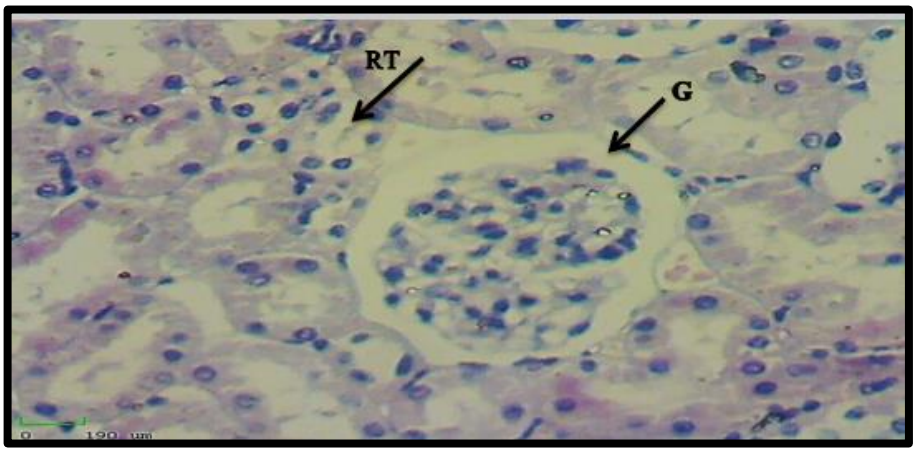


Figure (7):- Cross section in the liver of rats treated with (T) synthesized compound showed disappreance of hepatocyte radiation. (H and E stain)100X.



Figure(8):- Section in the kidney from (T) group showed, Glomerulus (G), some destructive changes of renal tubules (RT).(H and E stain) 400X

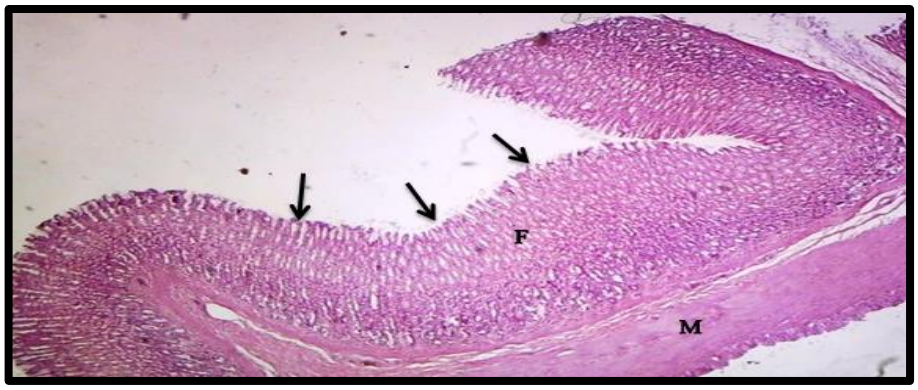


Figure (9):- Section in the stomach from T group, Epithelial cells of the gastric pit(arrows), fundus region(F), muscular mucosa (M). using H and E stain (100X).

3.4 T&Di group

Liver section from T&Di group showed in figure (10) reveals a normal central vein, but there is complete disappearance of hepatocytes boundaries. Also, there is homogenization of liver parenchyma containing enlarged nuclei with clear nucleoli. Disappearance of hepatocytes normal radiation architecture phenomena, also there is some hemorrhages. Renal histological section (11) showed irregular shape of renal tubules, with absence of walls of cuboidal lining epithelium with enlarged nuclei. Besides there are some hemorrhages. Section of stomach as in the figure (12) shows partial destruction of epithelial cells of the gastric pit and nearly normal number and size of fundic glands, thickening of the muscular mucosa.

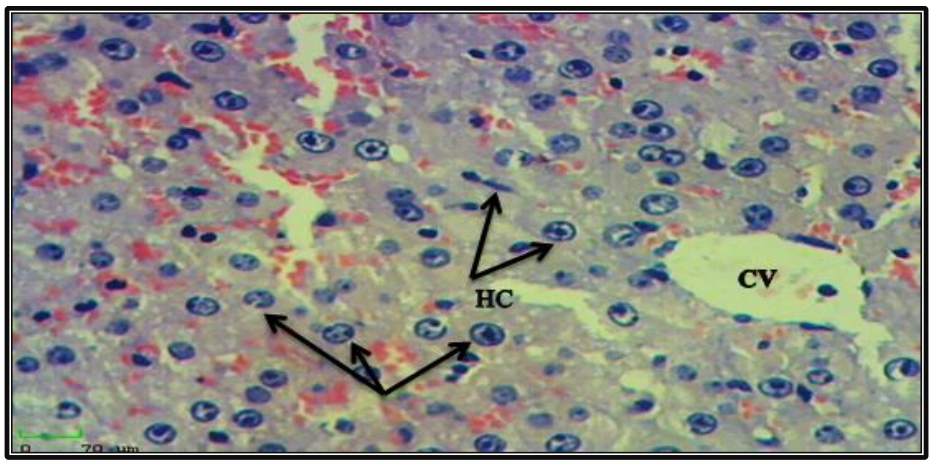


Figure (10):-Section in the liver from of T&Di group, showed disappearance of hepatocytes boundaries. (H and E stain) 400X.

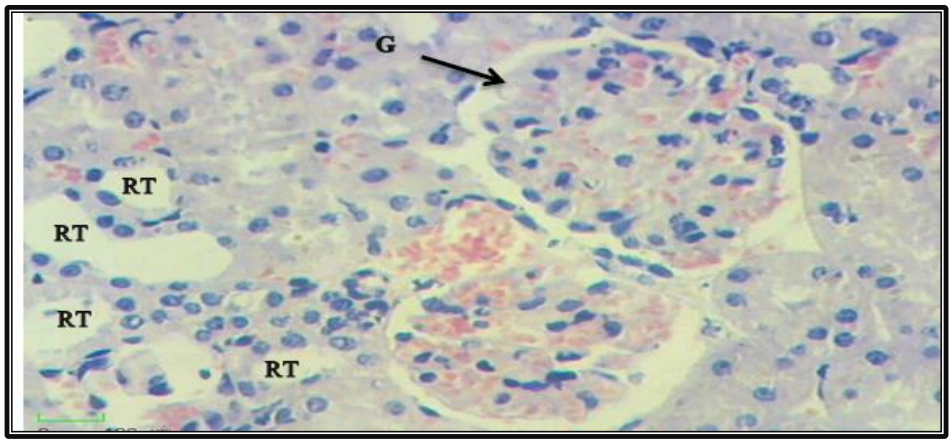


Figure (11):-Section in the kidney from T&Di group, revealed irregular shape of renal tubule (RT), degeneration of lining epithelial of glomerulus(G) (H and E stain)400X.

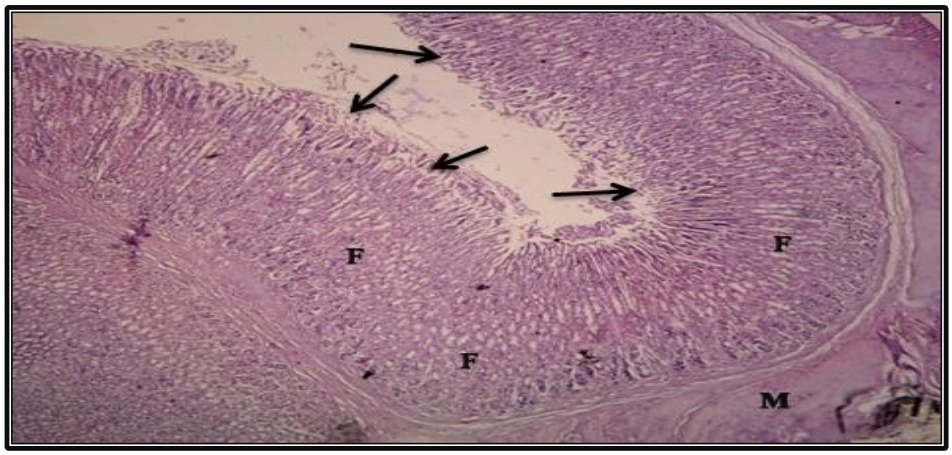


Figure (12):- Section in the stomach of T&Di group showed destruction of gastric pits, normal fundic glands(F) and thickening of muscular mucosa(M) . (H and E stain) 100X.

4- Discussion

The Liver of Di group rats section showing elongated central veins. While the main histopathological changes of hepatocytes were flattened, pykonotic, hepatic nuclei enlarged and sinusoids narrowed, with disarrangement of hepatic architecture. Kidney of Di group rats quite revealing shrinkage in glomerular content and cuboidal lining epithelial cells of the renal tubule were misshaped, besides to enlarged pyknotic nuclei of cuboidal cells. Whereas the stomach Section of Di group rats illustrated main changes include destruction of the gastric pit epithelial cells, increased number of fundic glands, also muscular mucosa was thickening. A study by[8] found that histopathological investigation, which is in agreement with the results of the present study. The histopathological sections revealed that toxic alterations had identified in Pyrazolone derivatives treated rats. The structural alterations such as cytoplasm vacuolation, hepatic cells

degranulation of the nucleus were detected. Also renal globules were dilated and atrophied glomeruli. Also [9] found that, Di causes lower hemorrhage and ulcers compared to acetaminophen, which is in good agreement with the results of the current study.

The liver of T group rat's sections showed there was no remarkable change such as disarrangement of hepatocyte architecture and incomplete disappearance of hepatocyte radiation. The Renal Sections of (T) group rats illustrated the main histopathological alteration included disappearance of Bowman's capsule and shrinkage of the glomerulus. Stomach section of (T) group rats reveals histological change includes complete disappearance of epithelial cells of the gastric pit, also less number, size of fundus region, while the muscular mucosa was more thickening. Consistent with findings by[10] , found that hepatic sections of rats treated with Se and VitE shows only mild inflammatory infiltration. Also [11] reported that rats liver sections (Se-treated) showing normal hepatocytes and central vein similar to control. Despite prior evidence[12]founded that acute and high exposure to Se produced noticeable deleterious modification in liver sections include interstitial edema, and focal. Also [5] obtained conclusions confirmed that no significant hepatic pathological change in mice treated with 2.5, 5, 10 and 20 mg/kg doses was observed; but 30 mg/kg doses group there was cellular infiltration of mononuclear lymphocytic around the portal and hepatocellular degeneration. [13] Reported that renal tissue of rats given cadmium, the distinctive changes in rats given cadmium Vit C, E, Se, and Cd. Se presented some protective effect on the rat kidney. Studies revealed that serum Se value decreased in acute renal damage patients. Though, to date, few surveys have studied the association of serum Se values, and morbidity, mortality inpatient with renal failure [14]. Also [15] reported that compounds of organo-selenium have no damaging effect on the gastric mucosa. Gastric mucosa suffers most damage as side effect of all non-steroidal anti-inflammatory drugs (NSAIDs).

The liver section of rats of T&Di group reveals some disappearances of hepatocytes boundaries. Also disappearance of normal radiation architecture phenomena, furthermore there are some hemorrhages. Section of kidney displays irregular shape of renal tubules with absence of walls of cuboidal lining epithelium with enlarged nuclei. Besides there are some hemorrhages. Section of stomach shows partial destruction of epithelial cells of the gastric pit and nearly normal number and size of fundic glands, thickening of the muscular mucosa. Data from the present study agree relatively well with that from [10] liver sections of rats treated with Se and VitE combined with Bisphenol A, improved toxic effects of Bisphenol A, many of parameters such as normal hepatocyte, portal vein. Similar results by [16] illustrating that Morphological analysis indicated that the pathologic changes extent in the liver were less extensive in the zinc selenium tea group versus the normal green tea group. Also [17] showed that slight variations in hepatic physiological state between the control group and Se treated groups. From histopathological examination they observed protective activity of Se nanoparticles against d-gal induced liver damage. Furthermore [18] illustrate that hepatocytes fatty alteration, lymphocytic infiltration in the liver parenchyma were significantly reduced in high-fat diet + selenium powder treated rats. The maximum improvement was detected in the

group receiving1 mg/kg selenium. Results of [11] study clarify that liver section of rat treated with Se+Ag nanoparticles showing cellular appearance was normal and reduction in toxicity.

The study of [19] revealing that histological investigation of rodents renal sections indicated that Se administration reduced renal damaged after ischemia-reperfusion I/R and lipid peroxidation. They concluded that Se protected tissues against oxidative damage.

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تقييم التاثير الهستوباثولوجي للمركب

4,4-(4,5,6,7-Tetrahydro- [1,2,3-] Selenadiazolo [4,5 E] Pyridine-4,6-Diyl) Bis(Benzene-1,3-Diol)

في اناث الجرذان بالمقارنه مع الديبارون.

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المستخلص

السيلينوم هو احد العناصر الغذائية الحيوية الذي له ادوار بايلوجية مهمة, حيث يعمل كمجموعة صناعية في العديد من الانزيمات مثل انزيم كلوتاثيون بيروكسيديز وانزيم ثيوروكسين المختزل. الهدف من هذه الدراسة هو استكشاف الآثار النسيجية لمركب

4,4-(4,5,6,7-Tetrahydro- [1,2,3-] Selenadiazolo [4,5 E] Pyridine-4,6-Diyl) Bis(Benzene-1,3-Diol)(T)

مقارنة مع تاثير الديبايرون على الكلى والكبد والمعدة. قسمت اناث الجرذان الى اربع مجاميع تلقت كل مجموعة 50 ملغم/كغم وزن الجسم من المركبان T (مجموعة T), الديبايرون (مجموعة Di), والاثنان Tوكذلك Di (مجموعة Di&T) مذاب ب 2 مل من الماء المقطر , اما مجموعة التحكم DWاعطيت 2مل من الماء المقطر لمدة 30 يوما. ثبتت عينات الكبد والكلى والمعدة بمادة الفورمالين وتم عمل المقاطع النسيجية والتصبيغ في المختبر المركزي في كلية الصيدلة . اظهرت النتائج ان مجموعة Di اظهرت عدم انتظام بنية الكبد , اما مقاطع الكلى تظهر تشوه المحتوى الكبيبي والبطانة الظاهرية ,مقاطع المعدة اشارت الى تحطم في حفر المعدة وزيادة غدد فونيك. اما مجموعة T اظهرت مقاطع الكبد اختفاء غير كامل للشعاع الكبدي, مقاطع الكلى لمجموعة الجرذان T اظهرت اختفاء كبسولة بومان , واشارت مقاطع المعدة اختفاء تام للخلايا الظهارية من حفر المعدة. تظهر مجموعةDi&T اختفاء البناء الاشعاعي الطبيعي لخلايا الكبد مع وجود نزيف, واظهرت المقاطع النسيجية الكلوية غياب جدران بطانة الظهارة المكعبة مع توسع بالنويات. يمكن الاستنتاج ان مجموعة T لديها اضرار تدميرية منخفضة مقارنة مع المجموعة Di ومجموعة التحكم DW . اما اعطاء الادوية T مع Di ليس له تاثيرات مفيدة.