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STUDY OF THE EFFECT OF *SALVIA OFFICINALIS* LEAVES EXTRACT AND XENICAL DRUG ON SOME OF THE BIOCHEMICAL AND HISTOLOGICAL PARAMETERS IN THE RATS INDUCED WITH HYPERLIPIDEMIA

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Abstract

The objective of the study was to determine the effect of *Salvia officinalis* leaves alcohol extract and Xenical drug in some of the biochemical and histological parameters in the males white rats induced with hyperlipidemia by studying the following criteria: Biochemical parameters including lipid profiles (cholesterol, triglycerides, LDL, VLDL, HDL) (AST, ALT, ALP), kidney function (urea, creatinine) and a histological study of liver and kidney. The study included (40) adult male white rats randomly divided into four equal groups with each group (10 animals). The first group is the control group (C): the physiological solution was pumped and the normal diet was given. The second group was the first treatment group (T1): which contains the animal fat at a concentration of 30% the high-fat diet for 60 days. The third group was the second treatment group (T2): Was given the high-fat diet with the alcohol extract of the leaves of the *Salvia officinalis* leaves with a concentration of 100 mg/kg of body weight at the same time for 60 days. The fourth group was the third treatment group (T3): Was given the high-fat diet and the Xenical drug a concentration of 5 mg/kg of body weight at the same time for 60 days. The results showed a significant increase in the levels of cholesterol, triglycerides, LDL, VLDL with a significant decrease at the level of HDL in the first treatment group T1 compared with the control group, while T2 and T3 showed a significant decrease in the level of cholesterol, triglycerides, LDL, VLDL, with a significant increase in HDL compared with T1. The results showed a significant increase in the levels of liver enzymes AST, ALT and ALP for the first treatment T1 compared to the control group, while the treatment T2 showed a significant decrease compared with T1, while the treatment T3 showed none significant differences compared to T1. The results of the current study showed that there was a significant increase in the level of urea and creatinine ($P < 0.05$) in the first treatment T1 compared to the control group, while the treatment T2 significant decrease compared to T1, while the treatment T3 showed none significant differences compared to T1. The histological sections of the liver in of the group T1 showed a marked and severe fatty degeneration with bleeding in the hepatic tissue, infiltration of the inflammatory cells, and central vein congestion. The histological sections of the liver of the group T2 showed a marked improvement in liver tissue which showed a high degree of repair, where it is possible to observe the radiation arrangement of hepatic cells around the natural central vein. While The histological sections of the liver of the group T3 showed that hepatic cells experienced fatty degeneration and infiltration of inflammatory cells with a clear expansion of hepatic sinusoid.

Keywords : Salvia officinalis leaves extract, xenical drug, histological parameters etc.

Introduction

Obesity is one of the most common health problems in the world. More than 1.6 million people are overweight and at least 400 million people are suffering from clinically obese (Misra, 2013). They are exposed to heart disease, high blood pressure, stroke, Type 2 diabetes, hyperlipidemia, and malignant vascular disease that make them more at risk of early death (Kang and Park, 2012). Obesity results from high levels of fat in the body and is the main cause of hyperlipidemia due to incorrect eating habits, with other factors such as smoking, alcohol, and lack of exercise, which in turn raises the risk of atherosclerosis, kidney disease and hypothyroidism (Gotto and Moon, 2010).

As a result of the increase in the prevalence of obesity and health problems that affect more than one third of the world's population increased the interest of people with obesity by the use of slimming drugs as a quick and effective treatment against obesity, which varied in terms of effectiveness, mechanism of action and the side effects of the treatment (Padwal and Majumdar, 2007). Xenical drug is an effective anti-obesity drug by its effect on the metabolism of fat in the intestinal cavity. It reduces the absorption of about 30% of the fat in the diet that comes out with the stool in conjunction with a moderate diet (Zhi *et al*., 2013). Orlistat is the active compound in the drug and is derived from the chemical compound of lipstatin. It is a natural product isolated from *Streptomyces toxytricini* (Birari and Bhutani, 2007). Its mechanism depends on the inhibition of the pancreatic lipase enzyme, Leading to the non-breakage triglycerides in the intestine and thus prevents its transformation into free fatty acids and monoglyceride (Zhi *et al*., 2013). As with all degenerative drugs, Xenical drug has a range of side effects, mainly fatty feces, diarrhea, abdominal pain, bloating, headache, cholelithiasis, cholestatic hepatitis and subacute liver failure (Yang *et al*., 2011). As a result of the negative effects of the treatment of dermatological drugs, the recent interest in medicinal herbs has been increased as a safer alternative to slimming drugs in the treatment of obesity as well as its wide role in the prevention and treatment of various diseases because these plants contain ingredients with antioxidant properties Because there is a wide spectrum of active compounds involved (Misra *et al*., 2009). *Salvia officinalis* is one of these medicinal plants classified in the oral family Lamiaceae (Labiatae), which belongs to a large number of plants known to be important medical and therapeutic The plant has a wide range of active compounds included in the composition of essential oils, turbines, phenols, Proteins, carbohydrates and vitamins, including vitamin C and E, as well as B vitamins and various elements such as zinc, iron, copper and selenium, which have proven therapeutic effectiveness against a wide range of diseases and in the elimination of oxidizing free radicals (Lu and Yeap Foo, 2001) As well as its effective role in the treatment of obesity because of the presence of a group of chemical compounds within the plant composition has a inhibitory effect of the Lipase enzyme Carnosic acid and the

most important and Carnosol, Saponin in addition to the role of Ursolic acid, oleanolic acid, lectin and Thujone in lowering cholesterol, triglycerides and LDL with increased HDL level (Azevedo *et al*., 2010).

Material and Methods

Preparation of the high fat diet

The high fat diet was prepared after grinding a fine grinder with an electric grinder. The animal fat was added 30% (Altunkaynak, 2005) after being completely melted, then mixed with the ground diet and left for a suitable period until the water evaporated.

Xenical drug

Xenical drug obtained from a pharmacy in the city of Diwaniyah. The dose was used 5 mg/kg of body weight (Alagbada Bukola, 2016). After the full daily dose of Xenical drug was dissolved in distilled water, each animal was given 1 ml orally, using a special syringe for this purpose

Preparation of alcohol extract of the *Salvia officinalis*

The leaves of the plant were ground using the electric grinder and filtered to obtain a fine powder. The alcohol extract was obtained by (Hajzadeh *et al*., 2011) The animals were given an extract at a dose of 100 mg/kg of body weight (Khashan and Al-khefaji, 2015).

Experimental Design

In this study, the male Albino Rats were used, whose weights ranged from 150 to 250 grams and their ages between 3-4 months. Experiment animals were placed in special plastic cages designed for this purpose and equipped with a special water-drinking system. Experimental animals were subjected to appropriate laboratory conditions at 20-25 °C.

Ues in this experiment, 40 animals of male white rats were divided randomly into four groups. Each group included 10 animals as follows:

1. The first group (C) Was given the saline (NaCl) at a concentration of 0.9% and given a normal diet for 60 days and was promised as the control group.
2. The second group (T1): Was given The high fat diet which contains the animal fat at a concentration of 30% for 60 days.
3. group 3 (T2): Was given the high fat diet and the extract *Salvia officinalis* a concentration of 100 mg/kg body weight daily and synchronously for 60 days by oral dosage with a special syringe for this purpose.
4. group (T3): Was given high fat diet and Xenical drug a concentration of 5 mg/kg body weight and synchronously daily for 60 days by oral infusion with a special syringe for this purpose.

After the experiment ended, chloroform was used to anesthetize the animals, draw blood from the heart directly by a disposable 5-ml Disposable syringe and put blood in a clean glass test tube free of anticoagulants, and left for 15-20 minutes at laboratory temperature, Then put in the Centrifuge at 3000 cycles / min for 15 minutes. The serum was isolated and placed in new plastic tubes for biochemical tests. The serum was kept at -20 °C until use.

Standards Parameters

Estimate the level of total cholesterol in the serum

The Kits produced by the English Rondox company were used to measure the serum total cholesterol level (Friedwold *et al*., 1972).

Estimation of serum triglyceride levels

The concentration of triglycerides in the serum was measured using the kits produced by Randox company, according to the method adopted (Friedwold *et al*., 1972)

Measuring the concentration of high density lipoproteins (HDL) in the serum

Method Demacherp (1980) was used to estimate the level of high-density lipoprotein (HDL) in the serum using the enzymatic method and using the Kits produced by Randox company.

Measuring the level of low-density lipoproteins (LDL)

The concentration of LDL was estimated using the method (Friedwold *et al*., 1972).

Measuring the level of very low density lipoproteins (VLDL) in the serum

The level of VLDL was estimated using a method (Tietz, 1999).

Determination of the level Aminotransferase Enzymes AST, ALT in serum

Determination of the Effectiveness of the ALT and AST Enzymes by the colour method of (Reitman and Frankel, 1957) was followed by the use of kits prepared by the Italian Giesse company.

Determination effectiveness of alkaline phosphatase Enzyme ALP in serum

Using the colour method followed by (Belfeld and Goldberg, 1971), the efficacy of ALP was estimated by using kits prepared from the Italian Giesse company.

Estimation of serum creatinine level

The colour method (Henry, 1974) and the kits produced by the English Randox company was used to measure the level of serum Creatinine.

Estimation of serum urea level

Enzymatic Method was used to measure the level of urea in the serum by using the kit made by the French BioMerieux. company

Histological preparations

The (liver, kidney) samples were initially saved after being removed from the animal in a 10% formalin solution and after 48 hours removed from formalin and washed some time by water followed by a series of processes depending on the method described in (Humason *et al*., 1997).

Statistical analysis

The results of the experiments were analyzed using the SPSS statistical program. The ANOVA test was used to compare the studied groups and the control group. The least significant difference (LSD) was calculated to test the significance of the results (Schielfer, 1980).

Results and Discussion

Lipid Profiles

The results indicated that the treatment of high-fat diet led to a significant increase in the levels of total cholesterol and triglycerides, LDL and VLDL in the blood with a significant decrease in the level of HDL compared with the control group and these results agreed with the study (Kong *et al*., 2018). The reason for this increase in morbidity can be attributed to several reasons, for example, that eating rats high-fat diet causes oxidative stress, which can lead to the generation of large amounts of reactive oxygen species (ROS) (Furukawa *et al*., 2017). This is confirmed by (Munshi *et al*., 2014) noting that giving mice high-fat diet caused elevated levels of cholesterol, triglycerides, LDL and VLDL with decrease HDL level due to increased lipid per-oxidation due to delayed gastric emptying of the stomach due to accumulation of fat in the small intestine compared with the time needed to process Healthy digestion, which affects the defense mechanism of antioxidants causing oxidative stress. This may be due to an increase in the amount of cholesterol in the diet and thus increase the rate of absorption of cholesterol from the intestine (Mathe, 1995) leading to increased deposition of fat in the liver, which increases the processing of liver cells in quantities greater than Acetyl CoA to form cholesterol and triglycerides (Rapaport and Havel, 1995). High fat diet may also stimulate enzyme 3-Methyl Glutaryl-Coenzyme A reductase (HMG-CoA reductase), which is primarily responsible for the synthesis of cholesterol (Wu *et al*., 2013). The decrease in HDL may be since high fat diet reduces the activity of the enzyme Lecithin-Cholesterol Acyl Transferase (L-CAT), a binding enzyme and a carrier that plays an important role in the formation of HDL and the flow of cholesterol from cell membranes to HDL (Al-Awadi *et al*., 2013). On the other hand, the current results showed a significant decrease in the level of animal fat in the animal blood which given the extract of the *Salvia officinalis* leaves and Xenical drug (T2, T3) with high fat diet compared with animals that ate high-fat diet only (T1). And that the reason may be due to the high content of saponin and lectin in the plant because of their role of hypolipidemia, Marrelli and his group (Marrelli *et al*., 2016) confirmed that the hypoallergenic effect of the saponin compound to the cholesterol level came from its formation of insoluble complexes with cholesterol in the gastrointestinal tract, inhibiting its absorption and thus being excreted in the feces. The reason may be due to the containment of the *Salvia officinalis* plant on effective compounds inhibit the synthesis of the triglycerides such as single turbines, the most important of which Thujone, which is known to reduce cholesterol and triglycerides. Also the decrease in the level of fat may be due to the containment of the *Salvia officinalis* plant on the compounds of flavonoids lowering blood lipids through its role of antioxidant (Kianbakht *et al*., 2011), flavons play a direct role in increasing the LDL receptor in the liver and its association with Apolipoprotein B and thus removing it from the blood (Joshi and Uniyal, 2008). This may also be explained by the containment of (Alwakeel, 2008), which plays an active role in lowering cholesterol levels by increasing the activity of Cholesterol 7-α-hydroxylase, an enzyme that works to lower blood cholesterol level by converting it to bile salts (Ueteng *et al*., 2006), In addition, the decrease in the level of lipids in animal which given Xenical drug may be due to the effect of the chemical compound of lipstatin, the main component of Xenical drug and inhibitor of the Lipase enzyme, which prevents the breakdown of fat in the stomach and intestines, which inhibits their transformation into free fatty acids and monoglycerides Absorption (Sladic *et al*., 2014) and thus reduces intestinal absorption of fat. This may be explained by the inhibitory action of the Xenical drug to the HMG-CoA reductase, which is primarily responsible for cholesterol synthesis (Al-Kuraishy and Al-Gareeb, 2016). This may be due to the role of the Xenical drug in inhibiting the secretion of Cholecystokinin (CCK) which causes the contraction of the bile sac and loosens the pancreatic hepatic to allow the passage of bile and the enzyme-rich pancreatic amyloid toward the duodenal. (Alqahtani *et al*., 2015), thus, lowering the level of the CCK hormone reduces the secretion of bile and pancreatic enzymes, which leads to a reduction in the process of digestion of fat. This may be due to the effect of the Xenical drug in reducing cholesterol uptake by inhibiting Niemann-Pick C1-like1 protein (NPC1L1), a protein responsible for the transport of cholesterol through the intestinal membrane and thus plays an important role in controlling the level of blood cholesterol (Altmann *et al*., 2004).

Table 1 : Showing the effect of the *Salvia officinalis* leaves extract and Xenical drug on fat images in male rats with hyperlipidemia.

Parameters					
VLDL(mg/dl)	**LDL(mg/dl)**	**HDL(mg/dl)**	**TG(mg/dl)**	**Chole.(mg/dl)**	**Groups**
66.354±0.113 f	43.641±0.520 f	44.955±0.341 a	42.255±0.274 f	74.392±0.265 f	C
83.272±0.129 a	60.125±0.294 a	30.71±0.368 f	67.98±0.377 a	95.284±0.167 a	T1
73.365±0.198 c	51.282±0.241 c	37.206±0.460 d	51.62±0.352 c	83.151±0.294 c	T2
69.796±0.292 e	45.527±0.197 e	42.335±0.178 b	45.513±0.15 E	76.664±0.219 e	T3
0.985	1.025	0.969	1.754	2.015	LSD

Liver Enzymes

The results of the statistical analysis showed a significant increase ($P < 0.05$) in the level of liver enzymes ALP, ALT, AST in the first group T1 treated with the high fat diet compared with a control group. These results have been agreed with (Shawky, 2015). The rise in the level of liver enzymes is due to the damage done to the body, especially the tissue of the liver by a high fat diet. This is confirmed by our study of tissue and the resultant damage

and necrosis with inflammation of the liver causing the release of these enzymes into the bloodstream (Uthandi and Ramasamy, 2011), Zhang and his group (Zhang *et al*., 2014) also confirmed that high-fat diets have a positive relationship with liver disease by fatty degeneration and increased saturated fatty acids in the liver, which coincide with acute hepatic tissue injury, increasing the release of liver enzymes into the bloodstream. This may be explained by the occurrence of oxidative stress and the formation of free radicals in the rats with hyperlipidemia (Noeman *et al*., 2011). In the same direction, high fat diet causes an increase in peroxidation in the liver, heart, and kidney, the liver is rich a tissue in mitochondrial. It is, therefore, more susceptible to oxidative damage that affects mitochondrial function, thereby impairing the efficiency of the electron transport chain, which leads to apoptosis of cells (Amirkhizi *et al*., 2010). Poli and his group (Poli *et al*., 1987) pointed to the changes that result from an increase in MDA in hepatocytes, which negatively affects mitochondrial functions, causing lipid peroxidation, nucleotide oxidation, endoplasmic reticulum enzymes, notably Glucose-6-phosphatase and cytochrome p-450, Levels of calcium absorption. As a result, several enzymes are released from Lysosomes, which increase the permeability of the plasma membrane, leading to damage to the liver cells and thus releasing their enzymes. On the other hand, the current results showed a significant decrease ($P < 0.05$) in the level of liver enzymes of the treatment group with the *Salvia officinalis* leaves extract compared with the T1 group treated with high fat diet, while this improvement was not observed during the treatment with Xenical drug. These results agreed with the study (Sá *et al*., 2009) which confirmed the role of *Salvia officinalis* leaves extract against the destruction of liver cells in the treatment of rats with a high fat diet. That the low level of liver enzymes in the treatment of rats with the extract of the leaves is due to the range of antioxidant compounds within the structure of the plant and its role in the protection of tissues and organs from the damage caused by oxidative stress caused by high-fat diet (Kolac *et al*., 2017). Phenols and flavonoids are known as antioxidants, which protects the fats in cell membranes from high oxidation and degradation and thus protects the enzymes from release into the serum (Kianbakht *et al*., 2011). This may be due to catechol, one of the compounds involved in the synthesis of Caffeic acid and Rosmarinic, which in turn is known to destroy the free radicals in the body's cells by breaking free radical chains by inhibiting initiation and thereby preventing growth and reproduction of sequential free radicals, which prevents the damage of liver cell and preservation of enzymes from release into the bloodstream (Bors *et al*., 2004). *Salvia officinalis* plant also contains selenium and zinc (Alwakeel, 2008), Se protects the liver and kidney from oxidative damage caused by increased free radicals by increasing the effectiveness of antioxidants such as SOD, GR and GSH (Erkekoglu *et al*., 2014). It was also observed that the addition of Se and vitamin E to rat diets contributed to the inhibition of hepatic stellate cells (HSCs), which play an important role in liver fibrogenesis, thus reducing hepatic fibrosis (Shen *et al*., 2005). Zinc also has an important role in the formation of Metallothionein (MT), a protein rich in amino acid Cysteine who has antioxidant properties by binding heavy metals in the thiol group with the terminals of the Cysteine (Ruttkay-Nedecky et al., 2013). In the case of Xenical, Amin and his group (Amin *et al*., 2015) observed that the treatment of rats with Xenical drug did not reduce the effect of high-fat diet in increasing liver lipid aggregation, and Heck and his group (Heck *et al*., 2000), noting severe liver damage and hepatic failure in people who received of Xenical drug as a result of its side effects (Heck *et al*., 2000). This may be due to damage to the liver due to the role of the drug inhibiting the efficacy of CES-2 carboxylesterase-2, an enzyme that stimulates the hydrolysis of drugs with the removal of toxins secreted in the liver by activating its metabolism, limiting the accumulation of toxic substances in the liver (Alves *et al*., 2016). It also explains the damage caused by the drug by increasing the risk of bile stone, which is produced by the effect of the inhibitory drug of the secretion of CCK, preventing the passage of the contents of the bile and the pancreatic juice rich digestive enzymes to the digestive tract with the inhibition of constriction of the gallbladder to reduce digestion of fat (Alqahtani *et al*., 2015). The cause may be due to the tissue damage caused by the drug in liver cells due to the overlap of the drug or its products with the metabolic processes in hepatocytes either by its direct toxic effect on the basic structures or by the injury of immune reactions that lead to necrosis with damage and destruction of hepatic cells. In the release of enzymes and thus into the bloodstream (Douglas *et al*., 2013).

Urea and Creatinine level

The results showed a significant increase ($P < 0.05$) in the level of urea and creatinine in animal serum treated with high fat food compared to the control group. These results were agreed with (Ahangarpour *et al*., 2018). The increase in urea and creatinine levels may be attributed to increased peroxidation of total fat and thus lower levels of SOD and CAT oxidative enzymes, resulting in oxidative stress associated with increasing the generation of free radicals with the effect of high-fat diet (Noeman *et al*., 2011), Yao and his group (Yao *et al*., 2017) in their study on the effect of obesity on renal function in rats when treating high-fat foods indicated that renal disorders caused inflammation and enlargement of the renal connective tissue, which affected renal function and its antioxidant defenses causing oxidative stress, Free. Or perhaps due to the condition of tissue damage confirmed by the current tissue study when treating rats with high-fat food, including necrosis and complete damage in some renal tubules, which is reflected on kidney function causing a decrease in glomerular filtration rate (Chade *et al*., 2003), the results of this study showed a significant decrease ($P < 0.05$) in the level of urea and creatinine for the second treatment T2 compared to the (T1) treatment with high-fat food, while this improvement was not observed during treatment with Xenical. This may be because the plant contains antioxidant vitamins C and E (Ibrahim and Wali, 2014). Vitamin C protects the kidney tissue from the damage of oxidative stress by reducing the free radicals and their harmful effects in the kidney tissue, which improves their function by restoring their natural structure Thus returning urea and creatinine to normal levels (Dennis and Witting, 2017). Also, vitamin E has a direct effect on improving kidney function by protecting its tissue from lipid peroxidation and free radicals. Vitamin E has a synergistic action with vitamin C and Se, Ajith and his group (Ajith *et al*., 2009) confirmed their evaluation of the protective effect of aseparate doses And double-vitamin C and E against acute renal failure caused by cisplatin in mice, they observed that the low double doses of antioxidant vitamins E and C had a

better effect than the high separate doses of these vitamins in protecting rat kidneys from the toxic effect of cisplatin, which in turn reflected in improved kidney function and lower levels of urea and creatinine and MDA with a high level of GSH. Vitamin E is a synergistic act with Se in kidney protection and improved function. Selenium is the main component of the GPX enzyme, which enters into the protection of cellular membranes from lipid peroxidation and its detrimental effect on unsaturated fatty acids and thus reduces its end products, including MDA (Teodor *et al*., 2011).

In the case of Xenical drug, the results were agreed with Tousson and his group (Tousson *et al*., 2018). They observed the role of this drug in causing toxicity in the kidneys of obese rats, which was associated with high levels of urea, creatinine, sodium, potassium, and chlorine. Ions this may be due to kidney failure due to the effect of hyperoxaluria, which results from renal dysplasia with calcium oxalate, leading to excretion in renal tubules, causing acute kidney disease, which is associated with elevated urea level and creatinine (Buysschaert *et al*., 2016). This may be due to the role of Xenical drug in inhibiting the absorption of a group of lipid-soluble vitamins, which in turn are known as antioxidants capable of free radicals(Hollywood and Ogden, 2010). The most important is vitamin D, which is associated with chronic kidney disease (CKD) due to the negative relationship between the glomerular filtration rate and the oxidative stress condition that stimulates cytotoxicity, which contributes to the generation of oxidizing free radicals leading to the release of inflammatory cytokines that stimulate acute kidney disease (Mokhtari *et al*., 2017).

Table 2 Showing the effect of the *Salvia officinalis* leaves extract and Xenical drug on some liver enzymes and urea and creatinine white male rats with hyperlipidemia

Parameters					
Cr. (mg/dl)	**Urea(mg/dl)**	**ALP(U/L)**	**ALT(U/L)**	**AST(U/L)**	**Groups**
0.643±0.0278 D	21.532±0.259 d	80.85±0.202 D	10.661±0.128 D	15.377±0.176 d	C
0.862±0.01 a	35.194±0.22 a	96.11±0.019 A	22.43±0.026 A	26.563±0.024 A	T1
0.702±0.06 c	24.919±0.247 c	83.55±0.015 C	13.543±0.07 C	18.518±0.129 C	T2
0.823±0.05 a	33.921±0.154 a	93.822±0.010 A	20.864±0.02 A	24.869±0.03 A	T3
0.044	1.212	2.302	1.652	1.857	LSD

Changes in the histological sections of the liver

The histopathological of first treatment (T1), which was treated with a high fat diet for two months, showed clear fatty degeneration, with hepatic hyperplasia with the site's peripheral nucleus. These results here combined with Altunkaynak and Ozbek (Altunkaynak and Ozbek, 2009) in hypertensive liver cells and alteration in the cytoplasm of the liver when treating rats with high fat diet for 90 days. Fatty degeneration was explained by excessive fat in the liver and imbalance between synthesis and secretion of triglycerides in the liver, which results in the accumulation of unsaturated fatty acids with elevated LDL, VLDL and low HDL (Zhang *et al*., 2014). It is also due to oxidative stress caused by hyperlipidemia, which increases the free radicals and reduces the level of antioxidants, causing a decrease in SOD, GTS and CAT, which is reflected in damage to liver tissue and functions (Carmiel-Haggai *et al*., 2005) infiltration of inflammatory cells may be due to increased concentration of white blood cells in the blood and directed towards the affected area in the liver with congestion in the central vein, which occurs as a result of the accumulation of fat in the liver, which stimulates inflammatory response with increased blood entry to the area of inflammation and central vein blocked with Stopping blood flow due to an increase in the number of stellate hepatic cells may explain the congestion in the central vein. On the other hand, the results of the histological examination showed the T2 groups were treated with the *Salvia officinalis* leaves extract at the same time showed a high degree of repair and improvement in the presence of the normal radiation arrangement of the hepatocytes with the proliferation of most hepatic cells which appear binuclear. This improvement explains the role of the *Salvia officinalis* leaves extract of the plant in Protecting the liver tissue from degeneration when treated with high-fat diets and resulting from oxidative stress through its role as anti-oxidant, destroy the free radical and activator of cellular antioxidants (Placha *et al*., 2015). The improvement may also be due to the effectiveness of the flavonoids found in the *Salvia officinalis* extract, one of the most active compounds in the plant plays an active role in protecting the cellular membranes of the liver by activating the antioxidants CAT, SOD, GSH due to its protective role in preventing lipid peroxidation and minimizing damage Oxidative stress (Van *et al*., 2017) On the other hand, the histological study of the groups that treated with Xenical drug showed inflammatory cell infiltration and degeneration with hyperplasia in the bile ducts and a simple proliferation of Kupffer cells. These results agreed with Youssef (Youssef, 2018) in the occurrence of liver cell dysfunction and fatty degeneration in rat liver When treated with Xenical drug at a concentration of 23 mg/kg body weight. The role of the drug inhibiting the efficacy of carboxylesterase-2 (Nwobodo, 2015), which stimulates the hydrolysis of drugs and detoxifies the liver by activating its metabolism processes, may limit the accumulation of toxic substances in the liver (Alves *et al*., 2016), the enzyme also increases the oxidation of fatty acids and triglycerides, preventing the accumulation of fat in tissue and liver cells (Ruby *et al*., 2017). Therefore, inhibition of the CES-2 enzyme due to drug therapy leads to fat accumulation in the liver (Li *et al*., 2016). This may be due to the liver dysfunction caused by the side effects of the drug, including the acute liver injury associated with the use of the drug and confirmed by the results of our current study that there is none significant difference in the level of

aminotransferase enzymes compared to the group of hyperlipidemia is an indicator of dysfunction in the functions Liver, which may lead to chronic liver injury with long duration of dosage (Douglas *et al*., 2013).

Changs in the histological sections of the kidney

The results of the renal tissue showed histopathological changes in the kidneys of rats treated with high-fat diet showed atrophy and necrosis in most renal glomeruli with fatty degeneration in the glomerulus and dissociation of the renal tubules. These results were agreed with Salim and his group (Salim *et al*., 2018) in renal glomerular degeneration and blockage in some renal tubules with damage and dislocation in the internal lining of renal tubules in male rats when treated with high fat diet. and that the cause of the damage and glomerular obstruction, which in turn affected the process of glomerular filtration resulting from the high level of fat, which causes the state of oxidative stress due to lipid peroxidation in cellular membranes, which leads to change the permeability of cellular membranes by affecting the entry and exit of ions of renal tubules, which is reflected in metabolic processes Cellular in conjunction with the reduction of antioxidant enzymes causing an increase in the generation of free radicals due to oxidative stress. Yao and his group (Yao *et al*., 2017) confirmed that kidneys had disorders of their function, resulting in infections and histological changes in the treatment of rats with high-fat diets for 8 weeks. Oxidative stress resulted in the generation of high doses of ROS with high MDA and low CAT. The expansion of renal tubules may be due to structural changes in the tissue of the kidney due to treatment with a high fat diet, which adversely affected the level of blood flow and blood circulation, causing damage to renal tissue, which in turn reflected on renal function (Yurt *et al*., 2013). Or perhaps the reason for the effect of high-fat food is to reduce the activity of the enzyme active protein kinase AMP (AMPK), an enzyme that plays an important role in the balance of cellular energy by stimulating the pathways of power generation in the case of ATP deficiency in cells through the oxidation of fatty acids and glucose (Declèves *et al*., 2011), where Szeto and his group (Szeto *et al*., 2016) confirmed that the treatment of rats with high fat diets may cause mitochondrial damage in kidney cells with the loss of membranes of cristae due to oxidation of unsaturated fats in their membranes causing oxidative stress which resulted in the generation of free radicals that adversely affected the effectiveness of the chain Transfer of electrons and thus decrease in level ATP. On the other hand, the histological study of the T2 group showed clear improvement with the regeneration of most of the glomeruli that appeared normal round and large. The noticeable improvement in the role of the effective *Salvia officinalis* plant may be attributed to the protection of the kidney and restoration of damaged tissue due to the effect of high fat diet by activating the antioxidants with elevated GSH and reduced MDA, which helped protect the mitochondria from the harmful effect of free radicals and thus reduce programmed death of renal cells, as well as being a rich extract of natural antioxidants, the most important of which are phenols in addition to the vitamins and elements that contributed to reduce changes in the kidney tissue due to its effective role in reducing fat peroxidation (Placha *et al*., 2015). This is due to the role of flavonoids, which play an active role in destroying free radicals by inhibiting the start-up phase of the free-radical chain of reactions as a result of their ability to interfere with the lipid membranes of the cell membrane (Saija *et al*., 1995). Ashour and his group (Ashour *et al*., 2017) also pointed out that the *Salvia officinalis* extract has an effective role in improving kidney tissue with the return of the natural structure of the renal tubules and the Bowman's capsule through its protective role in the treatment of renal toxicity and oxidative stress caused by the toxic substances of Chlorpyrifos and Methomyl. While the histological study of the T3 group showed a state of atrophy with fatty infiltration in the glomeruli, some glomeruli also disappeared with the appearance of others. The cause of the side effects of the drug is acute kidney injury (Beyea *et al*., 2012), which was confirmed by the results of our current study that there was none significant difference in the concentration of urea and creatinine compared to the T1 group. The cause of damage, degeneration, and expansion of the renal tubules and glomeruli is due to hyperoxaluria, which is caused by the lack of intestinal calcium, which is used by Xenical drug in the formation of calcium soap resulting from the association of non-absorbent fats in the small intestine by the Xenical drug with calcium. Thus calcium Linking oxalates inside the intestine increases the absorption of oxalate intestinal and thus increases the excretion of oxalate in the renal tubules, which results in acute renal injury with necrosis and damage of renal glomeruli and renal nephropathy (Beyea *et al*., 2012).

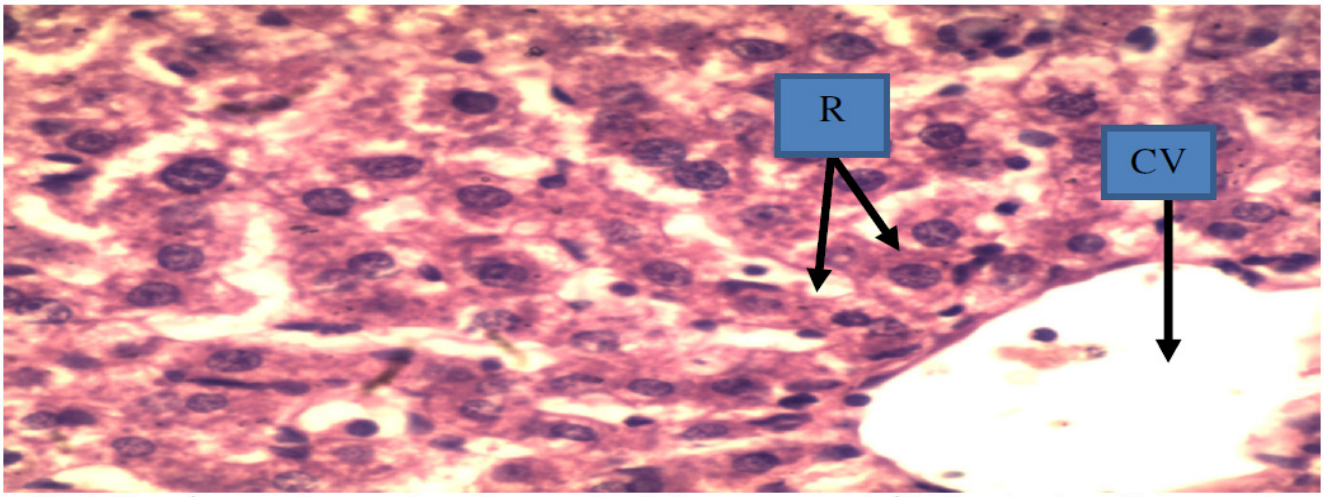

Fig. 1: Liver for control group shows the normal radiation arrangement of the hepatocytes, which appear in the order of ligaments (R) around the central vein (Cv) (40X H & E)

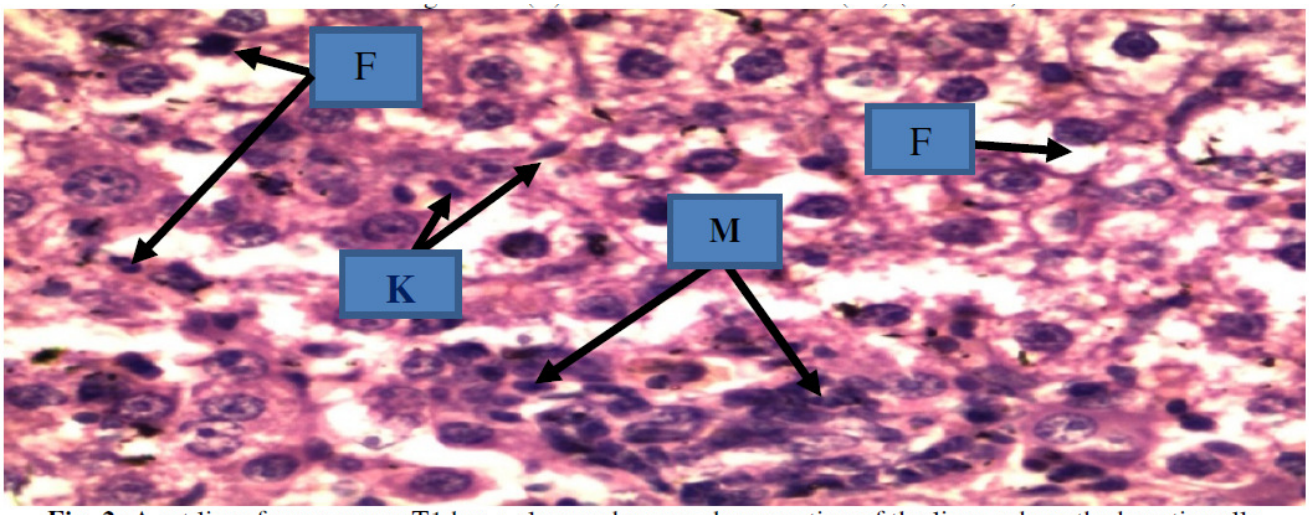

Fig. 2: A rat liver from a group T1 has a clear and severe degeneration of the liver, where the hepatic cells appear swollen and peripheral nucleus, giving them the shape of the ring (F), with the proliferation of kupffer cells and the release of Inflammation of the inflammatory cells (M) (40X H & E).

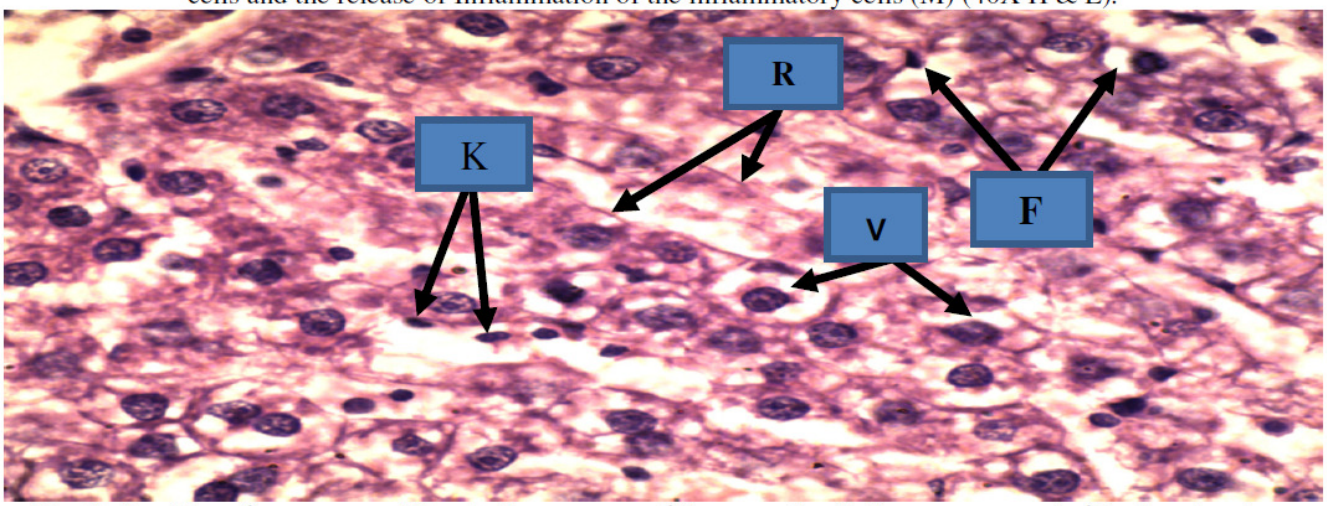

Fig. 3: A rat liver from a group T2, note the presence of the normal radiation arrangement of the hepatocytes around the central vein (R) also apparent. Some hepatic cells are swollen with bubbles (V) with a proliferation of Kupffer cells (K). Very slight fatty degeneration of some hepatocytes (F) (40xH & E).

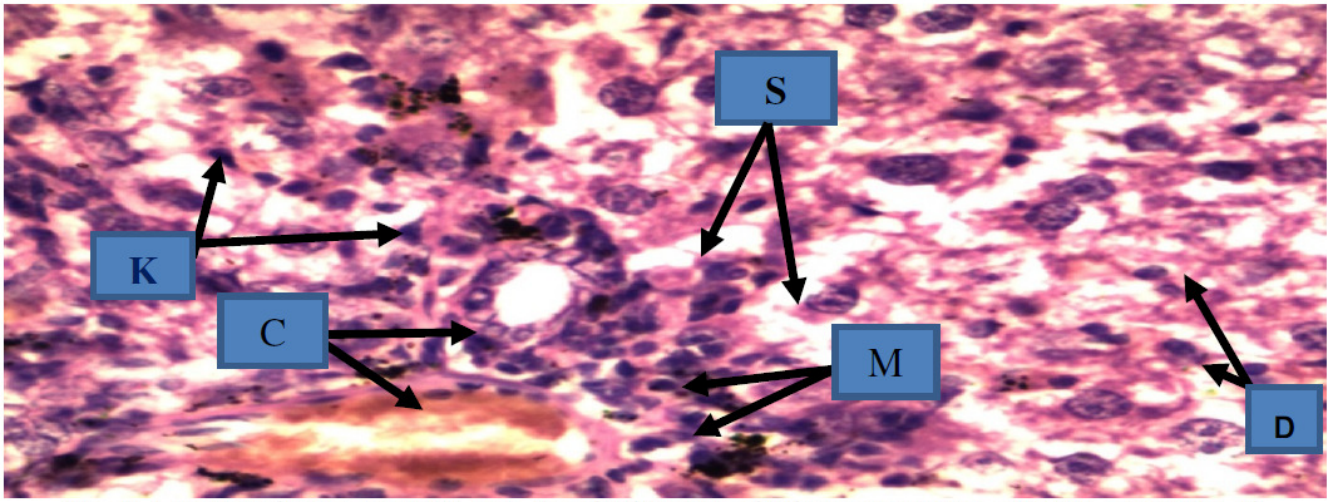

Fig. 4: A rat liver from a group T3, note the of infiltration of inflammatory liver cells (M), expansion of hepatic sinusoid (S), with proliferation of Kupffer cells (K), Bile ducts appear to be slightly proliferative with congestion (C) and fatty degeneration in some hepatocytes (D) (40xH & E).

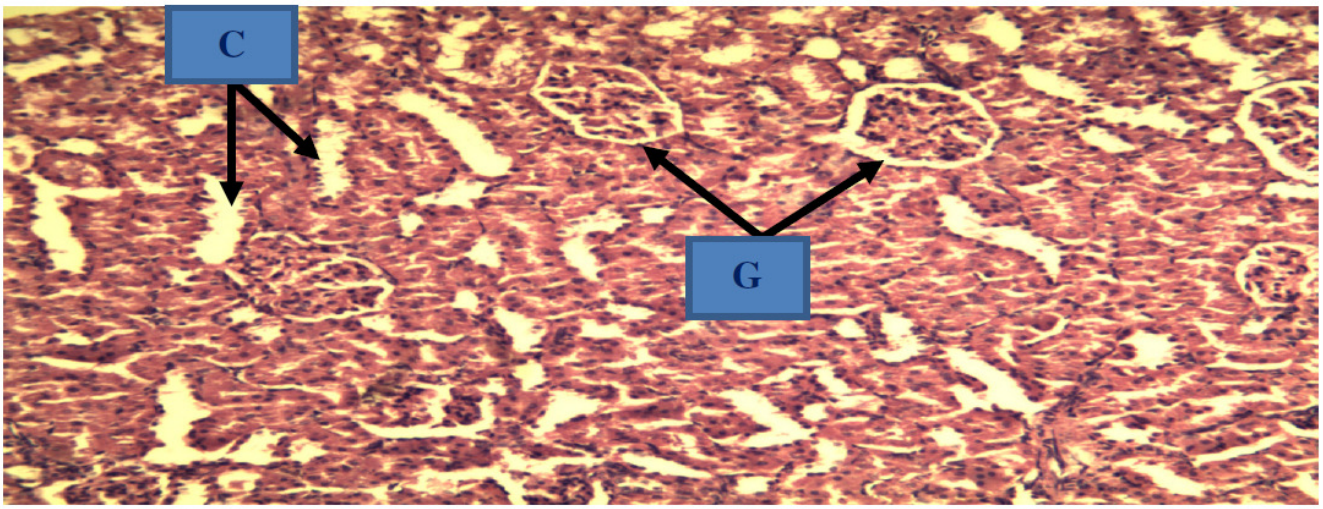

Fig. 5: Kidney for control group, where normal glomeruli (G) are surrounded by normal renal tubules and lined with cubic and natural epithelial cells (C) (10xH & E)

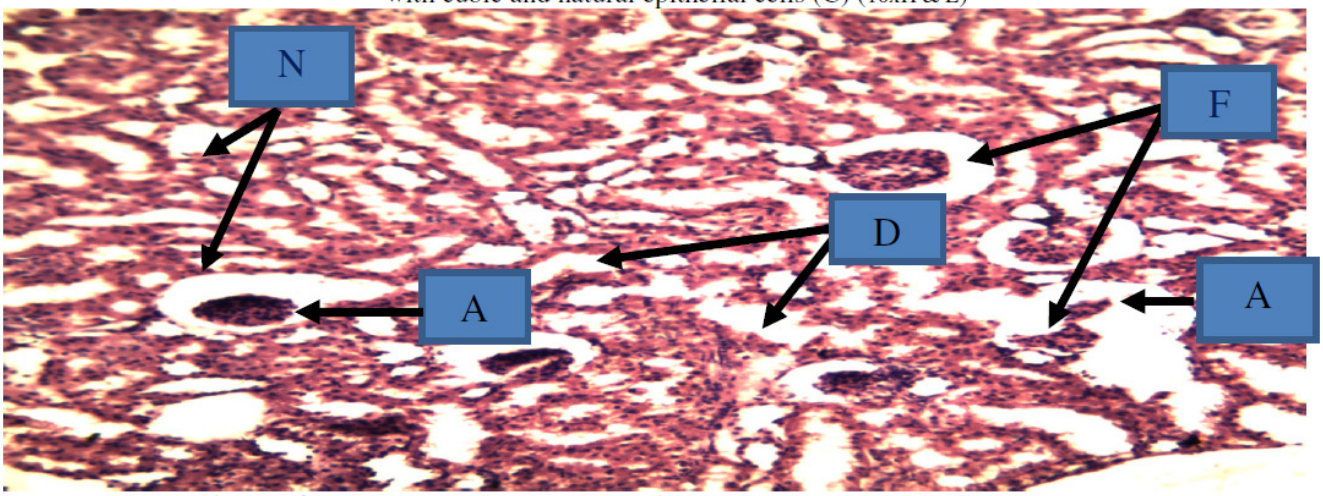

Fig. 6 : A rat kidney from a group T1, There is a marked atrophy in most glomeruli (A) with degenerative degeneration of the glomerulus (F), a clear expansion of twisted glomerular tubules (D), and necrosis of the cells lining the twisted tubes (N) (10xH & E).

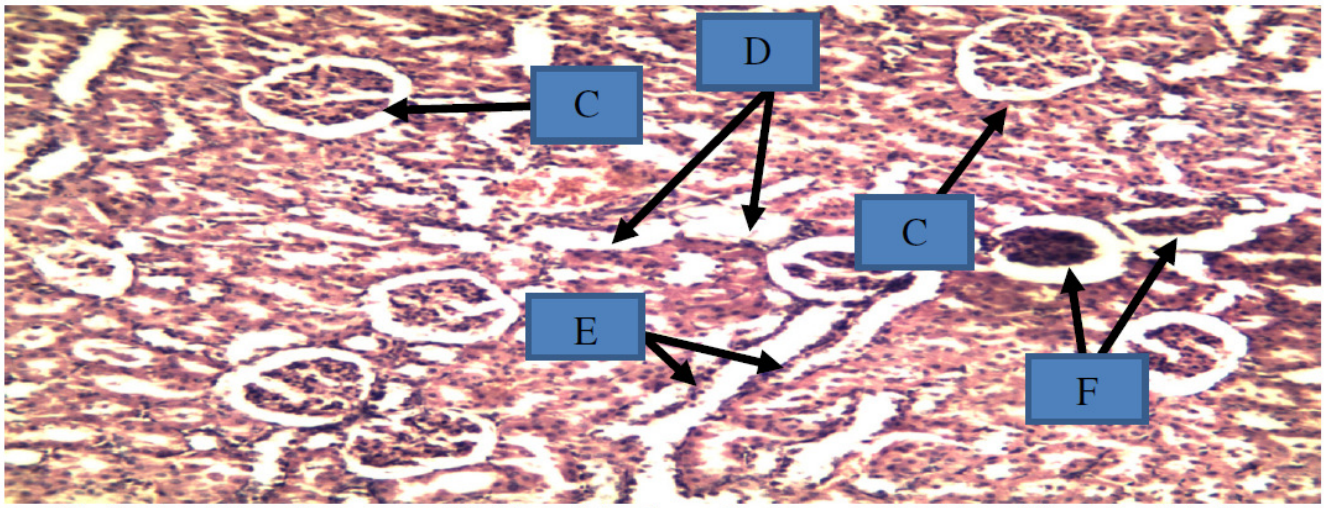

Fig. 7 : A rat kidney from a group T2, Most of the glomeruli appear round and large (C), with a slight fatty eruption observed in very few glomeruli (F). The twisted tubules appear to be lined with normal cells (E) with a small expansion (D) (10xH & E).

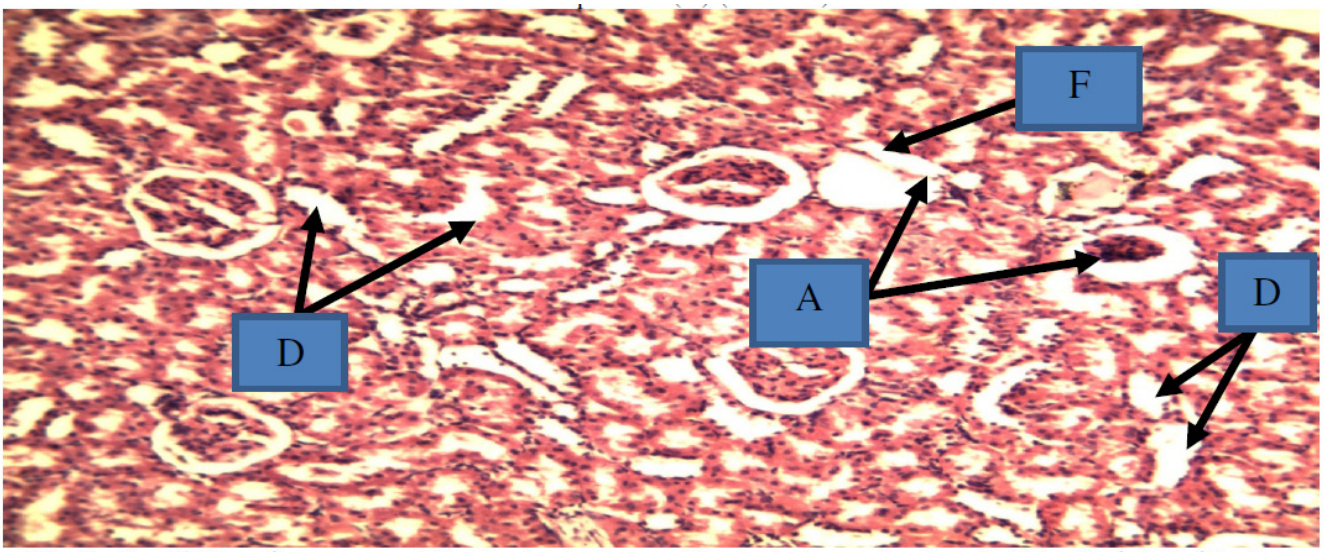

Fig. 8 : A rat kidney from a group T3, atrophy is observed in most glomerulosclerosis (A) with fatty infiltration in the glomeruli (F) and expansion of twisted renal tubules (D) (10xH & E)

Conclusion

The histological sections of the kidney of the group T1 showed fatty atrophy in most glomeruli with necrosis and dissection of the lining cells of the twisted tubules. The histological sections of the liver of the group T2 showed that most of the glomeruli were round and large, and the renal tubules appeared to be lined with normal cells. While the histological sections of the liver of the group T3 it has atrophied in most glomeruli with fatty infiltration and expansion of the renal tubules and some glomeruli appear completely hidden with clear necrosis, as well as bleeding and infiltration in some renal tissue cells. It can be concluded that the treatment of alcohol extract of *Salvia officinalis* leaves had positive effects on hyperlipidemia through the studied parameters in addition to the apparent improvement in the liver and kidney tissues compared to the Xenical drug

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