

EFFECT OF CORIADRUM SATIVUM ON EXPERIMENTALLY IDUCED HEPATOTOXICITY OF CARBON TETRACHLORIDE IN RATS

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ABSTRACT

Key words:

Coriandrum sativum (CS) ;
 Liver fibrosis; Anti-oxidant
 activity ; Haematology.

Objective: The aim of this study was to investigate the possible anti-fibrotic effect and antioxidant role of Coriandrum sativum (CS) extract against Carbon tetrachloride (CCL₄) induced liver fibrosis in adult male rats. **Method:** The extracted CS was proved by phytochemical analysis (thin layer chromatography (TLC)). This study was carried out on (72) rats these animals were divided into six groups of (72) rats The first group is negative control group. The second group is Positive control group. The third group is Preventive group. The fourth group is Therapeutic group. The fifth group is Silymarine group. The sixth group is Combination group. **Result:** The TLC analysis revealed the presence of some important polyphenolic compounds as Kaempferol, Quercetin, 3'-OMe quercetin, 4'-OMe quercetin, Acacetin and some of phenolic acids e.g. Vanillic acid, p-Coumaric acid, Cis-Ferulic acid, Trans-Ferulic acid which could be responsible for the anti-oxidant activity. Treatment with CS significantly decreased the elevated plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) while increased the albumin level. It also inhibited the formation of lipid peroxidative products Malondialdehyde (MDA) and nitric oxide (NO) during CCl₄ administration. Moreover, treatment with CS extract brought significant restoration of the haematological parameters to values that were comparable to those of the control. CS treatment enhances the liver and kidney health (which confirmed by histopathological studies). **Conclusion:** The present study indicates that the coriandrum sativum extract possesses significant anti-fibrotic and antioxidant activity in liver against experimental hepatotoxicity and nephrotoxicity in vivo. Increasing CS consumption is recommended, especially in cases of heavy contaminants and hepatic and renal disorder.

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INTRODUCTION

Liver is an organ of paramount importance as it plays an essential role in maintaining the biological equilibrium of vertebrates. The spectrum of its functions includes metabolism of carbohydrates, lipids and

proteins, blood coagulation and immunomodulation¹. It also has a great capacity to detoxify toxic substances and synthesize useful ones. Therefore, damage

on the liver inflicted hepatotoxic agent is of grave consequences. Hepatic diseases represent the major cause of human mortality in the world, they are characterized by a progressive evolution from steatosis to chronic hepatitis, fibrosis, cirrhosis and hepatocellular carcinoma². A major cause of these disorders is due to exposure to different environmental pollutants and xenobiotics such as alcohol, paracetamol, carbontetrachloride and thioacetamide³. The kidneys possess the common xenobiotic metabolizing enzymes, localized in proximal tubular cell⁴. A number of environmental contaminants, chemicals and drugs dramatically alter the structure and function of the kidneys⁵.

Carbontetrachloride (CCl₄) an industrial solvent, cleaner and degreaser. It is proved to be hepatotoxic as well as nephrotoxic to human^{6,7}. The initial step in biotransformation of CCl₄ is reductive dehalogenation and by formation trichloromethyl and trichloromethylperoxyl radicals⁸. As electrophils, these free radicals initiate the lipid peroxidation process and induced damage and dysfunction of DNA and proteins^{9,10}. Also, CCl₄ upregulates the gene expression of many inflammatory markers¹¹, **mean** –while down regulates the gene expression of many antioxidant enzymes triggering an oxidative stress¹².

Conventional or synthetic drugs used in the treatment of liver diseases are inadequate and can have serious adverse effects. Thus there is a world-wide trend to return to traditional medicinal plants to treat liver ailments¹³. Anti-fibrotics from natural products used in traditional medicine may reduce the risk of toxicity and maintain the therapeutic effectiveness when the drug is used clinically^{14, 15}. Various phytochemical components especially polyphenols such as flavonoids, phenyl propanoids, phenolic acids, tannins and others. Polyphenolic compounds are widely distributed in plants and known to be excellent antioxidants in

vitro and have the capacity to scavenge free radicals and protect antioxidant defence¹⁶.

Since dietary polyphenols have been reported to be inversely associated with lipid peroxidation and cytotoxicity, an attempt was made to study the effects of the extracts of *Coriandrum sativum* on the activities of antioxidant enzymes in CCl₄ treated liver. Coriander is available throughout the year providing a fragrant flavour, originated around the Mediterranean and is cultivated mainly in the tropical areas. The seeds contain an essential oil “linalool” a monoterpenoid and the leaves contain good amount of caffeic acid, ferulic acid, gallic acid and chlorogenic acid¹⁷. The seeds and aerial parts of the plant are extensively used in traditional system of medicine for various ailments like spasm¹⁸ rheumatism, neuralgia, gastric complaints¹⁹ bronchitis, diarrhea, dysentery, gout, dyspepsia and giddiness. Moreover, coriander has been shown biological activities as anti-tumor, chemopreventive and anti-inflammatory agents and may play a role in regulating the activity and/ or expression of certain enzymatic systems that are included in apoptosis, tumor promotion, intracellular signal transduction or xenobiotic metabolizing enzymes²⁰.

The plant is known to possess hypoglycemic²¹ antibacterial, antifungal²² free radical scavenging and lipid peroxidation activities²³.

The search for novel natural antioxidants of plant origin has ever since increased. It is not known which constituents of plant are associated in reducing the risk of chronic diseases, but antioxidants appear to play a major role in the protective effect of plant medicine. The present study was designed to investigate *in vivo* antioxidant activities of ethanolic extract of Coriander. Results were compared to a standard antioxidant drug silymarin. Silymarin (SMN), an extract of *Silybum marianum*, has well established hepatoprotective properties. It is a standardized mixture of

flavonolignans including silybinin, isosilybinin, silydianin and silychristin. SMN effectively scavenges free radicals, antagonizes lipid peroxidation, and stabilizes cell membranes²⁴. At the molecular level, SMN stimulates RNA and protein synthesis leading to faster regeneration, repair, and renovation after liver injury. SMN also modulates inflammation and TNF- α production in vitro and in vivo²⁵ and binds to hepatocellular receptors, preventing toxins from binding to those sites, therefore, it seems of interest to evaluate the antioxidant activity and hepato-protective effect of coriander sativum in comparison with silymarin against CCl₄ – induced hepatic injury in rats.

MATERIAL AND METHODS

Materials:

Carbon tetrachloride and chemical kits for biochemical analysis were obtained from El-Gomhorya Pharmaceutical Company, Cairo, Egypt.

Plant Material:

The fresh leaves and stem of coriander overall, were purchased from the local market at Cairo, Egypt. The plant sample were kindly identified and proved by Herbarium unit of Potany Department faculty of Science Zagazzege University . The plant samples were airdried for 10 days and powdered. The powdered samples were placed in air tight container for future use.

Extract Preparation:

The dried and powdered plants (2kg) were extracted successively with mixture of ethanol: water (3:1) in a soxhlet extractor for 48 hours at 60°C. After extraction, the solvent was evaporated to dryness at 50-55°C using a rotary evaporator. Finally, the lyophilization of the dried extract was done to yield the Coriander²⁶ The extract was stored at 4°C in avacum for future till the analysis of different parameters.

Animals:

Adult male Sprague-Dawely rats (n=72) weighing 180-260 gm were purchased

from Animal House of the National Research Center (NRC), Dokki, Giza, Egypt. They were kept individually in stainless steel wire bottomed cages at room temperature (25 \pm 2 °C) under 12 hr dark light cycle. Animals were fed balanced diets. Rats had free access to food and water. They were used after acclimatization period of one week.

Phytochemical analysis:

The chromatographic profiles were developed for ethanolic extract using in triplicates for the identification of the polyphenols by paper chromatography²⁷. The Polyphenol separation included the isolation and identification of (a) Flavonoids (b) Phenolic Acids (c) Glycoflavones. The standard analytical procedures involving interaction with diagnostic reagents and paper chromatographic separation of compounds and their UV/Visible spectroscopic studies including hypsochromic and bathochromic shifts with reagents such as AlCl₃, AlCl₃/HCl, NaOMe, NaOAc and NaOAc/H₃PO₃ were followed for the identification of flavonoids and other phenolics. The identities of all the compounds were confirmed by co-chromatography (paper and thin-layer chromatography) with authentic samples²⁸.

Behaviour and toxic effects:

Different groups of rats were treated with graded doses of the coriandrum sativum extract (100 mg, 200 mg, 500 mg and 750 mg, p.o). One group was maintained as control and was given 0.5% Tween-80. They were observed continuously for 1 h for any gross behavioural changes and death, if any and then, intermittently for the next 6h, and then again at 24 h after dosing with C. sativum extract²⁹.

Experimental Design:

Animals were randomly assigned to six groups each of twelve rats as follow:

Group 1: Negative control group, Rats injected i.p. with saline once daily for 7days.

Group 2: Positive control group, Rats injected i.p. with CCl₄ in a dose of 0.5ml/kg b.wt i.p once daily for 7 days³⁰.

Group 3: Preventive group, Rats were injected i.p with coriander extracted dose of 200mg/kg b.wt orally by gavages at the beginning of the experiment, at the second day Rats were injected i.p. with CCl₄ in a dose of 0.5of ml/kg b.wt i.p once daily for 7 days, and then Rats were received orally by gavages the coriander extracted in a dose of 200 mg/kg once daily for 15 days.

Group 4: Therapeutic group, Rats were injected i.p. with CCl₄ in a dose of 0.5of ml/kg b.wt i.p once daily for 7 days, and then Rats were received orally by gavages the coriander extracted in a dose of 200 mg/kg once daily for 15 days.

Group 5: Silymarine group, Rats were injected i.p. with CCl₄ in a dose of 0.5of ml/kg b.wt i.p once daily for 7 days, and then rats were received silymarin in a dose of 25 mg /kg b.wt orally by gavages once daily for 15 days.²⁹

Group 6: Combination group, Rats were injected i.p. with CCl₄ in a dose of 0.5of ml/kg b.wt i.p once daily for 7 days, and then rats were received orally by gavages a combined dose of 200mg/kg the coriander extracted and 25mg/kg silymarine once daily for 15 days.

Blood collection and tissue homogenate:

At the end of 15th day, blood samples were collected from the retro-orbital vein plexus and direct cardiac puncture, under ether anesthesia. Whole blood used for haematogram was collected into tubes containing the anticoagulant, ethylene diamine tetra-acetic acid (EDTA) while samples for biochemical analysis were collected into plain sample tubes. Sera samples were separated by centrifugation at 600 x g for 15 min. and were stored in the -80 °C freezer before they were analyzed.

Liver and kidney tissues were excised from each rat and divided into 2 parts, part of liver tissue from each group was collected in sample tubes contains phosphate buffer saline (PBS) pH 7.4; for

biochemical analysis, The second part of tissue from each group was preserved in 10% neutral formalin solution for histological examination.

Biochemical Analysis:

The biochemical analysis include determination of ALT and AST levels³¹, liver malondialdehyde level³², serum albumin level³³, liver nitric oxide level³⁴ and haematological parameters were determined by auto haematology analyzer (**Diatron Abacus 380**)

Histopathological Study:

Liver and kidney of the sacrificed rats were taken and immersed in 10 % formalin solution. The specimens were then trimmed, washed and dehydrated in ascending grades of alcohol. Then cleared in xylol, embedded in paraffin, sectioned (4-6 microns) and stained with Heamtoxylin and Eosin for histopathological examination³⁵.

Statistical Analysis:

Statistical analysis of data was performed by using SPSS 14.0 version using T-test (2- tailed) was applied to compare between groups and one way analysis of variance (ANOVA) according to the method described by³⁶ followed by post-hoc test using Graphpad Prism-5 software. numerical data were expressed as mean \pm SD, P values < 0.05 were considered to be statistically significant.

RESULTS

Extraction of plant:

Coriander sativum (2 kg) after undergoing extraction yielded deeply green paste (60g) of the extract.

Phytochemical constituents and toxicity studies:

The extract revealed the presence of various phytoconstituents of polyphenolslike flavonoids and phenolic Acids. The flavonoids that were identified are kaempferol, quercetin, 3'-OMe quercetin, 4'-OMe quercetin and acacetin as shown in table (1). The phenolic acids that were identified vanilic acid, ferulic acid (cis and trans form) and p-coumaric acid as shown in table (2).

Toxicity study:

In acute toxicity, no mortality was observed up to a dose of 750 mg/kg body weight.

Biochemical result:

There was significant decrease in the level of ALT, AST, MDA and NO and significant increase appeared in albumin level in combination, preventive, therapeutic and silymarine groups compared to positive control group as shown in Table (3) and Figs 1,2,3,4 and 5 .

Hematological result:

There was significant increasing in RBC counts , Hb concentration , platelet counts and total WBC counts in combination, preventive , therapeutic and silymarine groups compared to positive control group as shown in Table (4)

Histopathological results :

The negative control groups showed normal central vein (star) with radiating cords of normal hepatocytes showing central uniform nuclei, and finely granular cytoplasm (**Figure 7a**). The positive control rat liver showing dilated congested hepatic sinusoids (star), early hepatocellular dysplasia with nuclear pleomorphism and hyperchromasia (arrow head), with occasional binucleation of hepatocytes (bold arrow) (**Figure 6b**). Interestingly, treatment with coriander sativum extract reduced most of the pathological alterations induced by CCL4 in rats. The combined group rat liver showing slightly dilated central veins (star) with normal liver cords and sinusoids (**Figure 6c**). The preventive group rat liver showing slightly dilated hepatic sinusoids (star), normal hepatocytes (**Figure 6d**). The therapeutic group rat liver showing dilated portal tract with mild portal fibrosis (bold arrow) surrounded by normal hepatocytes (**Figure 6e**). The silymarine rat liver showing dilated congested hepatic sinusoids (star), and areas of hemorrhage (bold arrow) (**Figure 6f**).

Microscopically, kidneys of rat from negative control group showing normal renal tubules lined by single layer of

cuboidal epithelium (**Figure 7a**). kidneys of rat from the positive control group showing diffusely infiltrating chronic non-specific inflammatory cellular infiltrates mainly lymphocytes, (**Figure 7b**). kidneys of rat from the preventive group showing normal renal cortex with normal glomerulus (arrow) with normal capillary tufts, and surrounded by normal renal tubules (**Figure 7c**). Kidneys of rat from the silymarin treated group showing renal medulla with near normal renal tubules apart from mild cloudy swelling of renal tubular epithelium (**Figure 7d**). Kidneys of rat from the therapeutic group showing renal medulla with normal renal tubules and mild interstitial inflammation (**Figure 7e**). Kidneys of rat from the combined group showing normal renal tubules lined by single layer of cuboidal epithelium with rounded uniform nuclei (**Figure 7f**).

DISCUSSION

Coriandrum sativum (Coriander) of family Umbelliferae is a well known plant derived from the traditional system of medicine in India and a native of Mediterranean region³⁷. CS is considered as a rich source of biologically active compounds mainly polyphenolic compounds. It has been reported to possess diuretic, carminative, digestive, anthelmintic, antioxidant²², antibacterial and antifungal activities³⁸. An interest has increased in naturally-occurring antioxidants that can be used to protect from oxidative stress damage induced by CCl₄³⁹. This is largely due to the afford ability of these products along with no or fewer side effects they produced as compared to conventional drugs. CS is commonly used as a food ingredient, is claimed to be useful for various ailments via its antioxidant activity⁴⁰. The present studies indicate that Polyphenol separation by co-chromatography (paper and thin-layer chromatography) included the isolation and identification flavonoids and Phenolic Acids. In Coriander leaves the flavonoids that were identified are quercetin, kaempferol and aldehydes, which are common in coriander structures,

phospholipids, phytosterols, flavonoids and active phenol are found to help fighting inflammation and free radicals. Coriander contains about 1% volatile oil mainly linalool, 20% oleic, petroselinic and linolenic fatty acids, monoterpene hydrocarbons, up to 26% flavonoid glycosides⁴¹. Quercetin is found in abundance in onions, apples, broccoli and berries. Thus coriander leaves, rich in quercetin, can be an important food source for the prevention of chronic degenerative diseases. The flavonol quercetin (3, 3', 4', 5, 7- pentahydroxy flavone) is one of the most abundant dietary flavonoids. Quercetin and other flavonoids have been shown to modify eicosanoid biosynthesis (antiprostanoic and anti-inflammatory responses), protect low density lipoprotein (LDL) from oxidation (prevention of atherosclerotic plaque formation) and promote relaxation of cardiovascular smooth muscle (antihypertensive, antiarrhythmic effects)²⁸. In addition, flavonoids have been shown to have antiviral and anticarcinogenic properties⁴². Generally, some flavonoids exert a stimulatory action on transcription and gene expression of certain antioxidant enzymes that play an important role against oxidative insults⁴³. Flavonoids can activate or inhibit the biotransformation and resulting toxicity of drugs^{44,45}. The current study demonstrated that coriander contains several phenolic acids that were identified vanilic acid, ferulic acid (cis and trans form) and p-coumaric acid as can be seen from Table 2. Vanillin, a polyphenolic compound, in CS was found to be effective in preventing DNA fragmentation caused by CCl₄⁴⁶. Phenolic compound ferulic acid has added health benefits as it battles cancer. Ferulic acid is the predominant bound phenolic form. The fact that ferulic acid could be identified in CS, emphasizes their potential role in the fight against cancer⁴⁶.

Carbon tetrachloride (CCl₄) is a potent hepato and nephro toxin that mimics oxidative stress in many physiological

situations³⁷. Hepatotoxicity produced by CCl₄ seems to be mediated by reactive metabolite trichloro methyl free radical (.CCl₃) formed by the hemolytic cleavage of CCl₄ or even by more reactive species trichloro methyl peroxy free radical (Cl₃COO.) formed by the reaction of .CCl₃ with O₂ caused membrane damage of hepatocytes and resulted in centrilobular necrosis⁴⁸. Meanwhile, some studies showed that the nephrotoxic effects of CCl₄ are associated with free radical production⁹. These free radicals attack microsomal lipids leading to its peroxidation and also covalently bind to microsomal lipids and proteins. This results in the generation of reactive oxygen species (ROS), which includes the superoxide anion O₂^{•-}, H₂O₂ and the hydroxyl radical⁴⁹.

The current study revealed that CCl₄ administration caused severe hepatic damage through a substantial increment in the blood levels of hepatic biochemical markers like ALT and AST⁷. When liver cell membrane is damaged, a variety of enzymes normally located in the cytosol are released into blood stream like, (AST) and (ALT) are found in higher concentrations in the cytoplasm and AST in particular also exists in mitochondria. AST is found in the liver, cardiac muscle, skeletal muscles, pancreas, kidney and others, meanwhile, ALT level is highest in the liver and therefore, it appears to be more sensitive test for hepatocellular damage than AST⁵⁰. However, the elevated activities of AST and ALT are indicative of cellular leakage and loss of functional integrity of cell membranes in liver¹.

Our data in table 3 and fig 1 and 2 showed that CS has significant decrease on the elevation of plasma levels of ALT and AST due to its antioxidant effect as it was observed that CS lowered ALT and AST activities by 51.6 % and 51.1% of combination group, by 43.04 % and 43.6 % of preventive group, by 30.09 % and

31.8 % of therapeutic group and by 18.8 % and 21.4 % of silymarin group all groups in comparison with positive group . This is in agreement ³⁷ who reported that pretreatment with CS before introduction of CCl₄ had significantly reduced the elevated plasma enzyme significantly reduced the elevated plasma enzyme indicating a hepato- protectant activity of CS via its antioxidant activity quenches ROS produced by CCl₄ , reserves antioxidant enzymes and restores their levels and protects cellular organelles from CCl₄ damage such as cell membrane, lysosomes, mitochondria and microsomes .Moreover ²⁹ observed that administration of CS to rats induced a significant decrease in the levels of the above enzymes which may be due to the stabilization of plasma membrane as well as repair of hepatic tissue damage caused by CCl₄ and this is supported by the view that serum levels of transaminases return to normal with the healing of hepatic parenchyma and regeneration of hepatocytes .

⁵¹ reported that, silymarin has an anti-hepatotoxic activity against CCl₄ induced hepatotoxicity in rats. Silymarin protects liver against the increase in serum ALT and AST. Silymarin is known to have Hepato-protective effect ⁵².

CCl₄ caused decrease in total serum protein that might be due to the decrease in the number of hepatocytes which in turn, may result in decreased hepatic capacity to synthesize protein ⁸. Also Significant decrease in serum albumin had been associated with active cirrhosis and biliary liver damages ⁵³. The present study in table 3 fig 3 showed a significant decrease in serum albumin due to oxidative stress by CCl₄ on hepatocyte to synthesize albumin. Our data reflect the antioxidant activity and hepatoprotective effect by elevation of serum albumin by 33.3 %, 25.9%, 18.5 % and 11.1 % in combination, preventive, therapeutic and silymarin groups respectively in comparison with positive group. This is in agreement ⁵⁴ who revealed that the

administration of coriander and silymarin pre-treatment effectively prevented these alterations of serum albumin and maintained the antioxidant status. In another study ⁸ who stated that the treatment of aqueous leaf extract of *Cnidioscolus aconitifolius* (CA) can make the restoration of the level of albumin level the hepatoprotective nature of CA.

Malondialdehyde (MDA) is a major reactive aldehyde that appears during the peroxidation of biological membrane polyunsaturated fatty acid ⁵⁵. Therefore, the hepatic content of MDA is used as an indicator of liver tissue damage ⁵⁶. MDA, an end product of lipid peroxidation, is widely used as a marker of lipid peroxidation. Lipid peroxidation (LP) is one of the main manifestations of oxidative damage and has been found to play an important role in toxicity and carcinogenicity. It is well documented that CCl₄ enhanced LP ^{57, 58} that is an indication of free radical mediated toxicity. Free radicals are known to attack the highly unsaturated fatty acids of the cell membrane and induce lipid peroxidation that is considered a key process in many pathological events induced by oxidative stress ⁵⁹. In the present study, MDA was found to be significantly higher in the animals treated with CCl₄ alone suggesting that this agent has a significant effect on LP and supported the earlier finding ^{60, 61}.

CCl₄ induced oxidative stress caused enhanced lipid peroxidation. Combination ,Preventive ,therapeutic and silymarin groups showed significant degree of protection against oxidative damage caused by CCl₄ by decreasing lipid peroxidation in comparison with positive control rats , as it was observed that CS has lowered the MDA level by 72.9%, 66.1% , 49.8% and 30.5% in liver combination ,preventive, therapeutic and silymarin groups in comparison with positive group. Hence, it may be possible that CS decreases lipid peroxidation level due to its antioxidant effect.

Moreover 56 who reported that the increase in (MDA) levels in liver was due to enhanced lipid peroxidation leading to tissue damage and failure of antioxidant defense mechanisms to prevent formation of excessive free radicals in CCl₄ induced hepatotoxicity in rats. Treatment with ethanol extract of CS significantly reversed these changes, and it may be possible that the mechanism of hepatoprotection by ethanol extraction of CS is due to its antioxidant effect.

⁵⁴ stated that Lipid peroxidation refers to the oxidative stress degradation of lipid in which (MDA) is one of its end products. It mostly affects polyunsaturated fatty acids causing tissue damage ⁶² and the elevation in MDA levels in both liver and kidney of irradiated rats may be due to the enrichment of cell membrane with polyunsaturated highly oxidizable fatty acids. The administration of C.S decreases in MDA level in irradiated rat liver and kidney, because of coriander has antioxidant property and it is valid to consider that it might be capable of protecting the liver and kidney tissues from irradiation induced injury changes ⁶³. The antioxidative property of coriander is related to the large amounts of tocopherols, carotenoids and phospholipids ⁶⁴, which act through different mechanisms.

²⁹ reported that most of the hepatotoxic chemicals including CCL₄ damaged liver mainly by inducing lipid peroxidation directly or indirectly. Therefore, the hepatic content of MDA is used as indicator of liver tissue damage involving a series of chain reactions. It has been accepted that lipid peroxidation of hepatocyte membranes is one of the principal causes of CCL₄ –induced hepatotoxicity, and is mediated by the production of free radical derivatives of CCL₄. Thus administration of Coriandrum sativum significantly decrease hepatic MDA concentration by reducing hepatic lipid peroxidation which may be due to an enhancement of antioxidant enzymes, these antioxidant enzyme system played an

important role in the defence of cells against oxidative insults and ameliorates the effect of the extracts from C.S, on oxidative stress induced by CCL₄.⁶⁵ Silymarin can prevent the absorption of toxins into the hepatocytes by occupying the binding sites as well as inhibiting many transport proteins at the membrane. These actions along with anti-peroxidative property make silymarin a suitable candidate for the treatment of toxic liver diseases ⁶⁶.

The excessive production of nitric oxide (NO) in the cell may be due to viral or bacterial infections and can promote pathogenesis by promoting oxidative stress, tissue injury and even cancer ⁶⁷. Nitric oxide (NO) is produced by macrophages and it plays an important role in tumor conditions ⁶⁸.

The generation of NO by the inducible nitric oxide synthase (iNOS) played a key role in the cytokine-mediated cell destruction ⁶⁹. In the current study, the ingestion of CCl₄ significantly increased NO suggesting that CCl₄ preferentially affects macrophage functions. It is well documented that excess ROS, a condition referred to as oxidative stress, is considered to be a major contributor to cell injury, although many studies have shown that higher levels of ROS can also activate specific genetic programs in various cells ⁷⁰.

Furthermore a significant inhibition on NO formation that might be due to its anti-inflammatory effect, as it was observed that CS lowered the NO level by 59.03%, 30.04%, 15.95% and 9% in liver of combination preventive, therapeutic and silymarin groups in comparison with positive group.

It is notable that, Several flavonoids, including quercetin resulted in a reduction in the ischemia-reperfusion injury by interfering with inducible nitric-oxide synthase activity. Nitric oxide reacts with free radicals, thereby producing peroxynitrite can directly oxidize LDL, resulting in irreversible damage to the cell

membrane. When flavonoids are used as antioxidants, free radicals are scavenged and, therefore can no longer react with nitric oxide, resulting in less damage. Coriander is also reported to be a chelating agent and reported to be effective as pharmaceutical agents in removing heavy metals⁷¹.

⁴⁹ found that treatment with Grape Vitisvinifera Seed (GSE) extract showed significant improvements in the antioxidant enzymes, oxidative stress markers, nucleic acids content and gene expression as indicated by the reduction of NO levels, this is due to GSE has the chemical properties of bioflavonoids, in terms of the availability of the phenolic hydrogens as hydrogen donating radical scavengers and singlet oxygen quenchers, predicts their antioxidant activity.

The Hematological alterations of acute and chronic experimental inflammation in adult rats were monitored because of their diagnostic significance. It was demonstrated clearly that CCl₄ administration produced pancytopenia (a generalized reduction in the cellular elements in the blood) as shown by erythrocytopenia, thrombocytopenia and leucocytopenia in the blood as evidenced by the reduction in the RBC, haemoglobin, platelets and total WBC counts, which believed that this reduction in the formed elements in the blood under stress⁷².

⁷³ consistent erythrocyte damage is presumed to be related to direct oxidative injury to the red cells by the chemicals or to the pitting function of the spleen. It may be assumed that the free radicals resulting from CCl₄ metabolism caused liver injury corroborated by the increased erythrocyte osmotic fragility which has also been reported to increase during oxidative stress⁷⁴. Thrombocytopenia is a common finding in advanced liver cirrhosis and is usually related to the congestive splenomegaly of portal hypertension and possibly to inadequate thrombopoietin synthesis by the failing liver^{75,76}.

The extract CS significantly reduced the oxidative damage caused by CCl₄ and altered the normal range of hematological parameters which may be due to its stimulatory action on antioxidative enzymes through significantly increasing in RBC counts, Hb concentration, platelet counts and WBC counts by 28.07%, 32.4%, 20.6%, 50.8% in combination group in comparison with positive group and by 26.3%, 27.9%, 15.6%, 44.2% in preventive group in comparison with positive group, by 21.05%, 15.3%, 11.3%, 31.1% in therapeutic group in comparison with positive group and by 15.7%, 6.8%, 8.5%, 26.2% in silymarin group in comparison with positive group respectively.

⁸ observed that aqueous leaf extract of *Cnidioscolus aconitifolius* showed significantly reduced the damaging effects of CCl₄ in the treated rats, by significantly increasing the PCV, RBC, Hb, platelets, MCV and MCH values it may be due to the antioxidant properties of the extract, because Vitamin E and other free radical scavengers such as black tea have been reported to reduce the toxic effects of CCl₄, especially on the liver⁶⁵.

Moreover ⁷⁷ found that acetone extract of *Rhodiola imbricate* rhizome against paracetamol induced liver toxicity in rats significantly increase hematological parameters (RBC, Hb, Platelet and WBC) which revealed that the extract is rich in these antioxidant compounds, which clearly support the antioxidant and other related pharmacological properties including hepatoprotective activity of *Rhodiola*.

The histological studies were carried basically to support the results obtained from serum enzymes assays²⁹. The normal control rat liver showing normal central vein (star) with radiating cords of normal hepatocytes showing central uniform nuclei, and finely granular cytoplasm as shown in fig(6 a) also rat kidney from normal control group showing normal

renal tubules lined by single layer of cuboidal epithelium as shown in fig (7a)

Positive control group of rat liver showing dilated congested hepatic sinusoids early hepatocellular dysplasia with nuclear pleomorphism and hyperchromasia, with occasional binucleation of hepatocytes as shown in fig(6b), rat kidney from the positive control group showing diffusely infiltrating chronic non-specific inflammatory cellular infiltrates mainly lymphocytes as shown in fig(7b).

This is in agreement with ⁵⁶ who stated that histopathological studies showed that CCL4 caused cytoplasmic vacuolization of centrilobular hepatocytes associated with leucocytic cells infiltration and kupffer cells activation. However, kidneys of rat revealed vacuolization of endothelial lining glomerular tufts as well as epithelial lining renal tubule. ²⁹ stated that the liver of CCL4 intoxicated rats showed massive fatty changes gross necrosis, broad infiltration of lymphocyte and kupffer cells around the central vein and loss of cellular boundaries. ⁴⁶ reported that CCl4 caused a significant damage to renal structure, manifested as marked glomeruli and tubular damages probably due to the generation of ROS. So, hydroperoxides accumulated in kidney could cause cytotoxicity associated with membrane phospholipids peroxidation, the basis for renal damage and necrotic renal cells. In addition, the vasoconstriction that induced by CCl4 produced a local ischemic environment aggravates cellular damages ⁶² However, CCl4 intoxication also altered the proximal tubular epithelial cells, mitochondria and lysosomes. The later released their contents into the tubular lumen with concomitant tubular damage ⁷⁸. For combination rats group, as a whole, the liver tissue showed to a large extent a normal appearance reflected by slightly dilated central veins with normal liver cords and sinusoids as shown in fig(6c), rat kidney from the combined group showing normal renal tubules lined by single layer

of cuboidal epithelium with rounded uniform nuclei as shown in fig(7c). For preventive group rat liver showing slightly dilated hepatic sinusoids, normal hepatocytes, as shown in fig(6d); rat kidney from the preventive group showing normal renal cortex with normal glomerulus (arrow) with normal capillary tufts, and surrounded by normal renal tubules, as shown in fig(7d). For therapeutic group rat liver showing dilated portal tract with mild portal fibrosis surrounded by normal hepatocytes, as shown in fig (6e) rat kidney from the therapeutic group showing renal medulla with normal renal tubules and mild interstitial inflammation, as shown in fig (7e). For silymarine group rat liver showing dilated congested hepatic sinusoids, and areas of hemorrhage, as shown in fig(6f), rat kidney from the silymarin treated group showing renal medulla with near normal renal tubules apart from mild cloudy swelling of renal tubular epithelium, as shown in fig (7f). Thus from obvious results CS extract show enhancement in the histology of the liver and modulate the histology features of the kidney. This is in agreement With ⁵⁶ who stated that CS showed slightly improvement in hepatocytes and fatty changes in liver tissue and also showed improvement of the histological structure of the kidney. ²⁹ revealed that the histopathological observations of the liver rats pretreated with CS and subsequently given CCL4 showed more or less normal architecture of the liver having reversed to a large extent, the hepatic lesions produced by the toxins, almost comparable to the normal control and silymarine group because of containing antioxidant properties that may enhance the liver condition.

The hepatorenal activity of CS against CCl4 as manifested from our data is attributed to various mechanisms; primarily, its antioxidant activity which results from the polyphenolic constituents in CS. Polyphenols of CS act

as anti peroxidative agents for the prevention of oxidative damage in living systems ⁷⁹. CS via its antioxidant activity quenches ROS produced by CCl₄, reserves antioxidant enzymes and restores their levels, improvement the histological structure of both liver and kidney and suppressing proliferation of liver and induced apoptosis in HSCs.

CONCLUSION

It could be concluded from the present results that, CCl₄ intoxication considerably damaged both the liver and kidneys depleted the antioxidant enzymes. CS antagonized CCl₄-induced acute hepatotoxicity as evidenced by restoration of the liver function enzymes and indicators of acute liver damage by conserving the endogenous antioxidant mechanism and scavenging free radicals and enhancement of the reduction in malondialdehyde. This study thus provides evidence that CS may be an alternative treatment for liver diseases caused by xenobiotics. Also CS may protect against microcytic hypochromic anaemia, thrombocytopenia and stress associated with CCl₄ administration in rats and reduce the hepatic damage in extrahepatic cholestasis by prevention of the oxidative stress, and the inflammatory process. As a result, CS as well as the reference drug silymarin enriched in phenolic compounds can protect humans against nephrotoxicity and hepatotoxicity induced by various xenobiotics and help maintain healthy liver and kidneys.

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Table 1 : Polyphenol content of coriander leaves

| Name of the compounds | Coriander leaves |
|------------------------|------------------|
| Apigenin | - |
| 3',4'-di-OMe luteolin | - |
| Kaempferol | + |
| 4'-OMe kaempferol | - |
| 7'4'-di-OMe kaempferol | - |
| Quercetin | + |
| 3'-OMe quercetin | + |
| 4'-OMe quercetin | + |
| 3',4'-di-OMe quercetin | - |
| Acacetin | + |
| Gossypetin | - |
| Quercetagenin | - |
| Proanthocyanidins | - |
| Anthocyanins | - |
| Coumarins | - |

+ : Present; - : Absen

Table 2 : Phenolic acids content of coriander leaves

| Name of the compounds | Coriander leaves |
|-----------------------|------------------|
| Vanillic acid | + |
| Syringic acid | - |
| p-OH benzoic acid | - |
| Melilotic acid | - |
| Gentisic acid | - |
| o-Coumaric acid | - |
| p-Coumaric acid | + |
| Cis-Ferulic acid | + |
| Trans-Ferulic acid | + |
| Phloretic acid | - |
| Chlorogenic acid | - |
| Resorcylic acid | - |

+ : Present ; - : Absent

Table 3: Effect of coriander leaves extract on some biochemical parameters in hepatotoxicity produced by CCL4 in rats .

| | ALT (U/ml) | AST (U/ml) | Albumin(mg/dl) | MDA (nmol/g) | NO (umol/g) |
|------------------|------------------------|--------------------------|-----------------------|--------------------------|------------------------|
| Negative control | 37.3±4.5 | 99.5±9.7 | 3.9±0.08 | 31.4±14.5 | 41.9±9.4 |
| Positive control | 105±9.3 ^{*a} | 264.9±37 ^{*a} | 2.7±.4 ^{*a} | 182.7±35.4 ^{*a} | 79.2±4.5 ^{*a} |
| Combination | 50.8±3 ^{*b} | 128.3±6.4 ^{*b} | 3.6±0.1 ^{*b} | 49.4±4.8 ^{*b} | 49.8±4.2 ^{*b} |
| % change | 51.6% | 51.1% | 33.3% | 72.9% | 59.03% |
| Preventive | 54.8±7.8 ^{*b} | 149.4±7.2 ^{*b} | 3.4±0.1 ^{*b} | 61.9±4.9 ^{*b} | 60.9±1.8 ^{*b} |
| % change | 43.04% | 43.6% | 25.9% | 66.1% | 30.04% |
| Therapeutic | 75.4±0.4 ^{*b} | 180.4±14.3 ^{*b} | 3.2±0.1 ^{*b} | 91.6±8.4 ^{*b} | 68.3±4.0 ^{*b} |
| % change | 30.09% | 31.8% | 18.5% | 49.8% | 15.95% |
| Silymarin | 85.2±4.3 ^{*b} | 208.1±7.1 ^{*b} | 3.0±0.1 ^{*b} | 126.8±13.5 ^{*b} | 72.3±1.7 ^{*b} |
| % change | 18.8% | 21.4% | 11.1% | 30.5% | 9% |

Values are expressed as mean±S.E.

a: Values significantly differ from negative control group.

b: Values significantly differ from positive control group.

*: P<0.001

% change: Values different from positive control group group.

Table 4: Effect of coriander leaves extract on some hematological parameters changes in experimentally induced hepatotoxicity in rats .

| | WBC(X10 ³) | RBC(X10 ⁶) | PLT(X10 ³) | Hb (g/dl) |
|------------------|------------------------|------------------------|--------------------------|------------------------|
| Negative control | 9.1±0.75 | 7.7±1.1 | 165.9±16 | 14.3±1.1 |
| Positive control | 6.1±0.7 ^{*a} | 5.7±0.5 ^{*a} | 116.7±11.5 ^{*a} | 11.1±1.6 ^{*a} |
| Combination | 9.2±0.7 ^{*b} | 7.3±0.9 ^{*b} | 140.8±14 ^{*b} | 14.7±1.3 ^{*b} |
| % change | 50.8% | 28.07% | 20.6% | 32.4% |
| Preventive | 8.7±0.7 ^{*b} | 7.2±0.76 ^{*b} | 135±9.9 ^{*b} | 14.2±1.6 ^{*b} |
| % change | 44.2% | 26.3% | 15.6% | 27.9% |
| Therapeutic | 8±0.7 ^{*b} | 6.9±0.7 ^{*b} | 130±11.2 ^{*b} | 12.8±.6 ^{*b} |
| % change | 31.1% | 21.05% | 11.3% | 15.3% |
| Silymarin | 7.7±0.8 ^{*b} | 6.6±0.6 ^{*b} | 126.7±12.3 ^{*b} | 11.9±1.1 ^{*b} |
| % change | 26.2% | 15.7% | 8.5% | 6.8% |

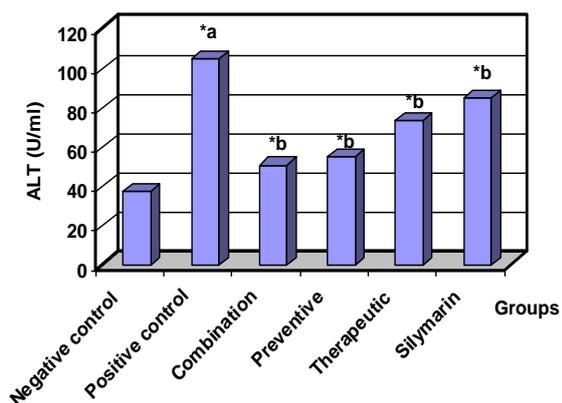
Values are expressed as mean±S.E.

a: Values significantly differ from negative control group.

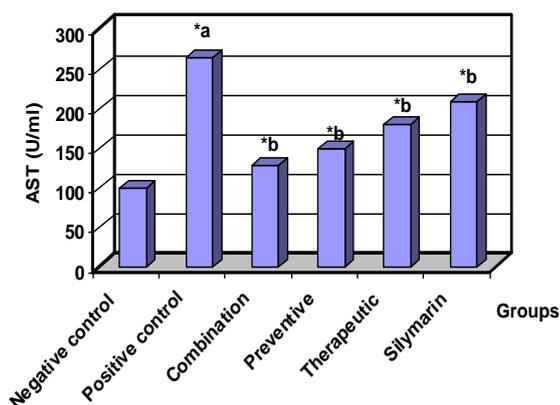
b: Values significantly differ from positive control group.

*: P<0.001

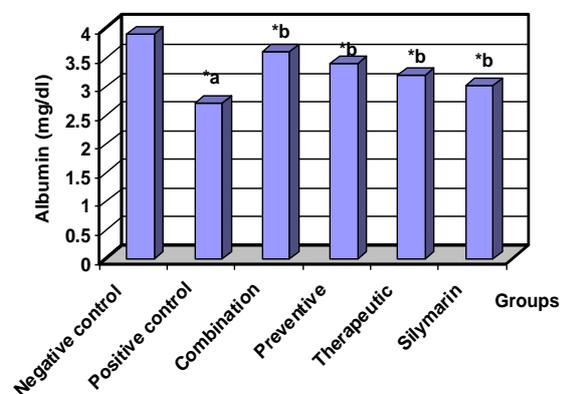
% change: Values different from positive control group.



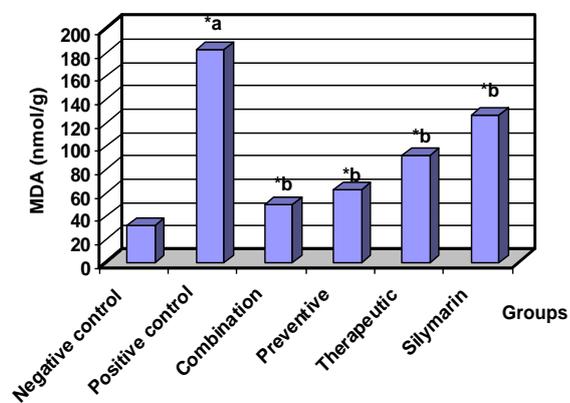
Graph 1: Relation between ALT level and all groups



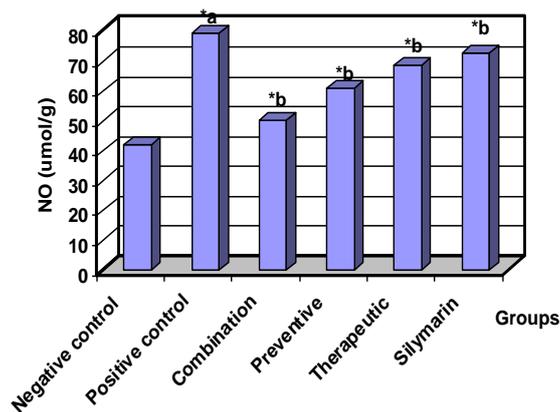
Graph 2: Relation between AST level and all groups



Graph 3: Relation between Albumin level and all groups



Graph 4: Relation between MDA level and all groups



Graph 5: Relation between NO level and all groups

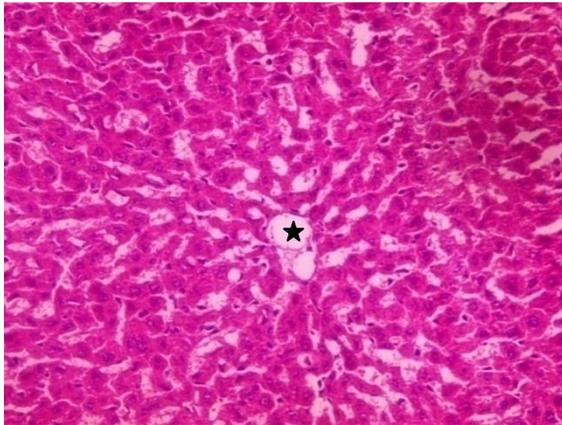


Fig. (6a): Photomicrograph of rat liver from negative control group, (H&E,X 400).

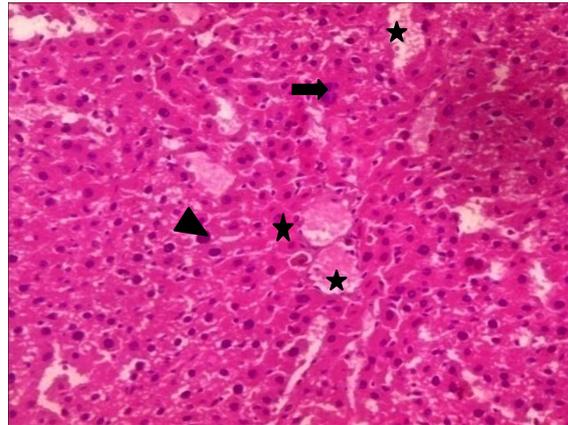


Fig. (6b): Photomicrograph of rat liver of positive control group, (H&E,X 400)

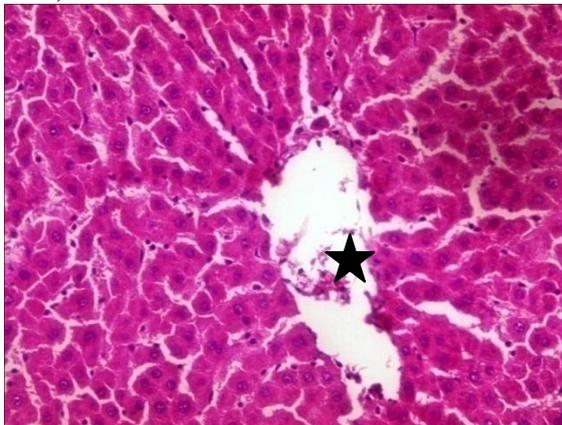


Fig. (6c): Photomicrograph of rat liver from the combined group, (H&E,X 400).

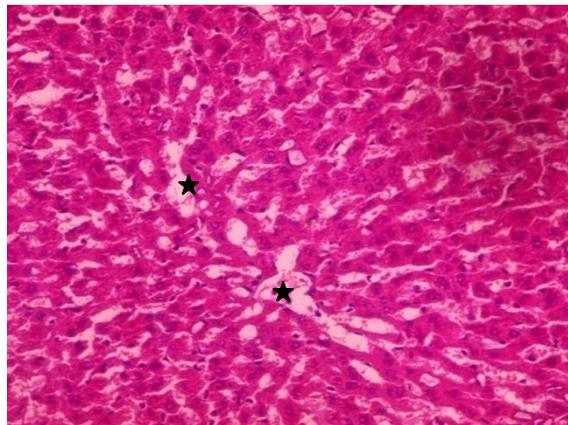


Fig. (6d): Photomicrograph of rat liver from the preventive group, (H&E,X 400).

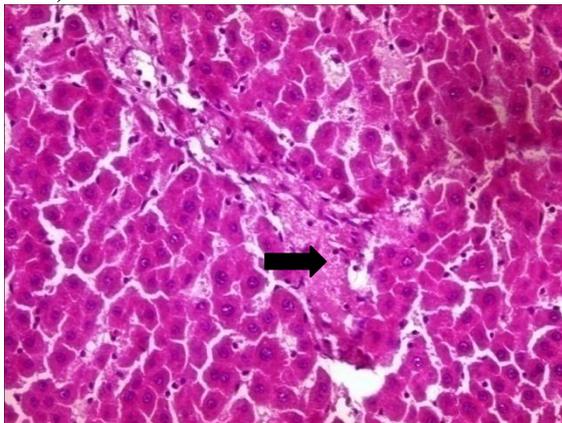


Fig. (6e): Photomicrograph of rat liver from the therapeutic group showing, (H&E,X 400).

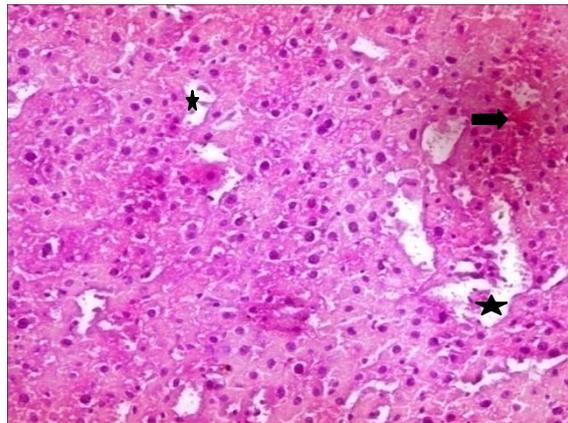


Fig. (6f): Photomicrograph of rat liver of sylimarine control group showing, (H&E,X 400).

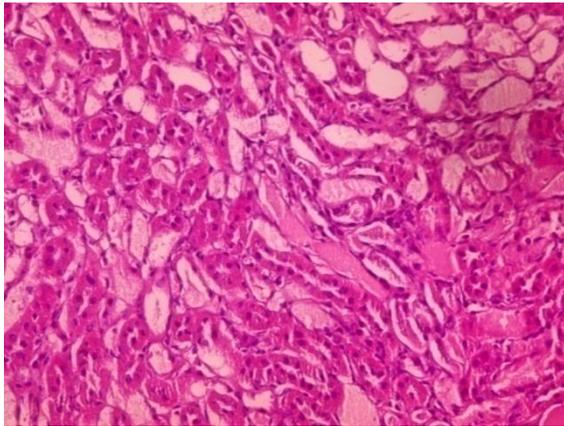


Fig. (7a): Photomicrograph of rat kidney from negative control group, (H&E,X 400).

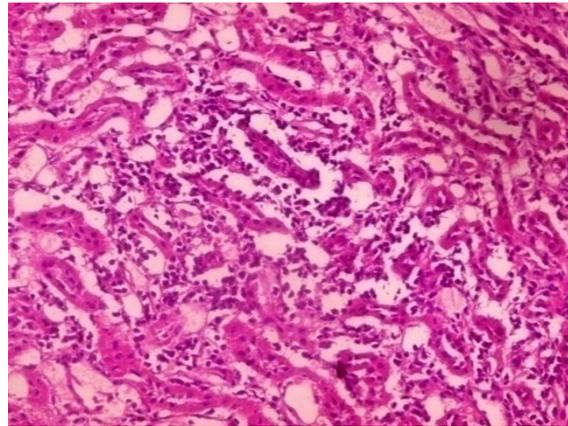


Fig. (7b): Photomicrograph of rat kidney from the positive control group, (H&E,X 400).

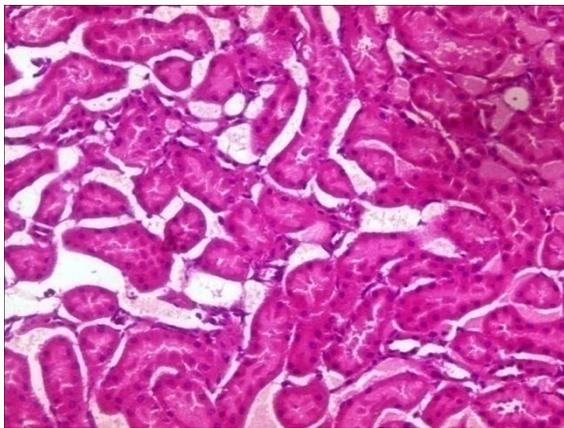


Fig. (7c): Photomicrograph of rat kidney from the combined group, (H&E,X 400).

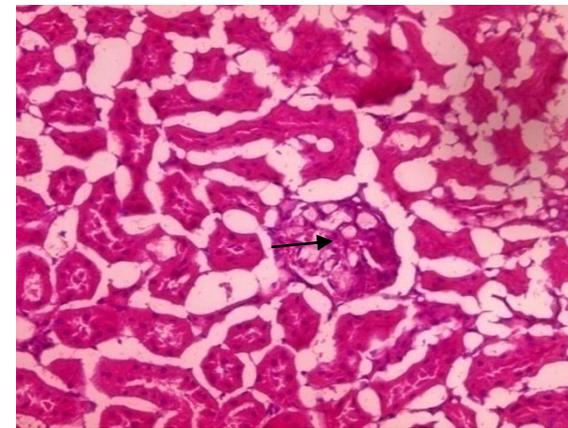


Fig. (7d): Photomicrograph of rat kidney from the preventive group, (H&E,X 400).

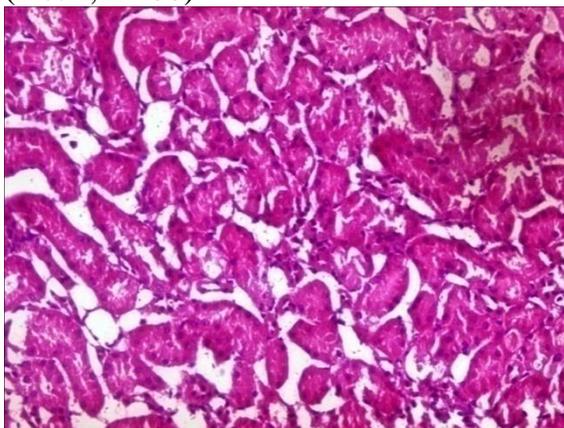


Fig. (7e): Photomicrograph of rat kidney from the therapeutic group, (H&E,X 400).

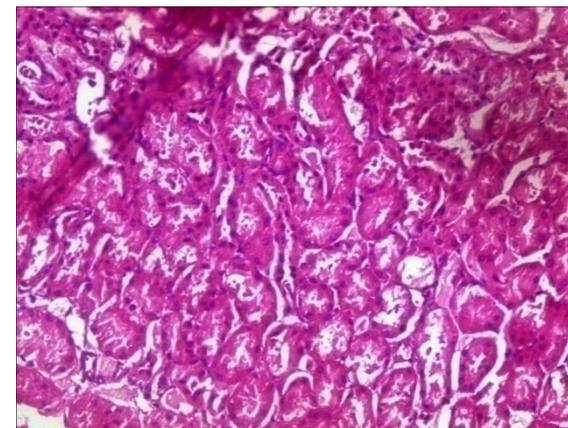


Fig. (7f): Photomicrograph of rat kidney from the sylimarin group, (H&E,X 400).