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ORIGINAL ARTICLE

The Potential Ameliorative Role of Wheat Germ Oil on Subchronic Cadmium chloride-induced hepato-renal Toxicity in adult male albino rats

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ABSTRACT

Background: Cadmium (Cd) is a hazardous non-essential transition metal that can be harmful to both human and animal health. Wheat germ oil (WGO) is a by-product of the milling of grain into flour which is believed to have anti-oxidant properties contributing to its protective effect against different toxins. So we aimed to study the toxic effects of cadmium on the liver and kidneys in adult male albino rats and to evaluate the protective effect of wheat germ oil against these toxicities through biochemical, histopathological, and PCR studies.

Methods: The study was conducted on 50 adult male albino rats, divided into a negative control group that received regular diet and tap water; the positive control group received 0.25 ml corn oil; the cadmium group received 3.5 mg/kg CdCl2 daily; a WGO group received 100 mg/kg WGO daily; and combined Cd + WGO group for 12 weeks. Blood samples and target organs were collected for biochemical, gene expression, and histopathological studies.

Results: Cadmium administration significantly elevated levels of ALT, AST, ALP, LDH, bilirubin, urea, and creatinine while decreasing total proteins, and albumin. Cd increased Bax, Caspase-3, and TNF-α and decreased Bcl-2 and IL-10 gene expression. Histopathological studies revealed that cadmium exposure caused hepatic and renal damage. Co-administration of WGO resulted in partial improvement.

Conclusion: Cadmium exposure causes significant biochemical and histopathological damage to the liver and kidneys. WGO administration significantly ameliorated biochemical parameters and histopathological findings, indicating its potential as a protective agent in reducing cadmium toxicity.

Keywords: Wheat germ oil, Subchronic cadmium chloride, hepato-renal toxicity, Adult male albino rats.

INTRODUCTION

Cadmium is a heavy metal that is very dangerous to people and the earth. Cigarette smoke, inhaled dust, cutaneous absorption, and oral consumption of tainted food and water are the main ways that people become exposed to Cd. Apart from smoking and some occupational activities, the population's primary exposure to cadmium is derived from their diet **[1].** Research has shown that the body eliminates cadmium relatively slowly. Due to its prolonged half-life in the body, cadmium has a variety of harmful health consequences on both people and animals, particularly on the liver and kidneys **[2].** The studies of Cd-induced hepatotoxicity in experimental animals have yielded that cadmium causes hepatotoxicity injury, either directly by itself which causes ischemia due to endothelial cell injury, or indirectly by inflammatory injury **[3].** On the other hand, cadmium's deposition and accumulation on kidneys occur mainly in proximal tubules and damage occurs because of the development of proximal tubular epithelial cell hypertrophy **[4].**

Wheat germ oil is a powerful herbal product. Consists of a high concentration of vitamin E, flavonoids, sterols, octacosanols, and glutathione, it is considered one of the most significant naturally occurring antioxidants. Unsaturated fatty acids, which are abundant in WGO, may help reduce oxidative damage **[5].** WGO is utilized in foods, biological insect control, medicine, the cosmetics sector, the manufacturing of vitamins, and the treatment of cardiac and circulatory problems and deficiencies **[2].**

This study used biochemical, histological, and PCR investigations to examine the detrimental effects of cadmium on the liver and kidneys of adult male albino rats and to test how wheat germ oil works against these harmful effects.

METHODS

Chemicals

Cadmium chloride ($CdCl_2$) was purchased from St. Louis, Missouri, USA's Sigma-Aldrich Chemical Company in the form of water-soluble, odorless, and colorless salts. It is 99.99% pure. Wheat germ oil was purchased from EMA pharm in Egypt in the form of (be active) soft gelatin capsules (330 mg of wheat germ oil/capsule). Corn oil from Gourmet Food Store Co. in Egypt. Chemicals for Real-time PCR (RT-PCR): Qiazol (Qiagen; Hilden, Germany). HPLC-grade chloroform, HPLC-grade isopropanol, and HPLC-grade 70% ethanol are all made by Sigma-Aldrich. The cDNA Kit from Applied BiosystemsTM is a high-capacity reverse transcription kit. It comes with TOPrealTM qPCR 2X PreMIX (SYBR Green with low ROX) (Cat. # P725 or P750) (Enzynomics, Korea).

Kits

Kits that use color to measure serum alkaline phosphatase, serum aspartate transaminase, serum alanine transaminase (ALP) (AST), and oxidative stress markers were purchased from Biodiagnostic Chemical Company in Egypt. We bought Colorimetric kits from Spinreact Company in Spain for serum urea, creatinine, albumin, bilirubin, total protein, and serum lactic dehydrogenase (LDH).

Animals

This study involved fifty male albino rats that are adults and each weight between 180 and 200 grams. The rats were purchased from Zagazig University's Faculty of Medicine's Animal House. For seven days, they underwent passive preliminary procedures to help them adjust to their new surroundings, and rule out any sick animals. The animals were housed in individual plastic cages free from chemical pollution sources, with an ambient temperature, relative humidity, and a 12 hr light–cycle. Softwood shavings were used for bedding and changed during the washing of cages on another day to keep animals clean. The rats received well-adjusted food which consisted of bread and barley and clean water. All of the experimental methods were given ethics approval by the Institutional Animal Care and Use Committee (IACUC) (ZU-IACUC/3/F/435/2022) **[6].**

Experimental design

Five random groups of rats (10 rats each) were created after acclimating to their new housing: **-Group I (negative control group):** For 12 weeks, each rat was given only standard food and tap water in order to test the fundamentals. **Group II (positive control group):** For a duration of 12 weeks, each rat was given 0.25 ml of corn oil (a wheat germ oil vehicle) orally once a day. **Group III (cadmium group):** For a duration of 12 weeks, each rat was given 3.5 mg/kg of body weight of CdCl2 dissolved in water every day by oral gavage. **[7].** This dose is 1/25 of LD50 of cadmium chloride in rats (Oral LD50 of CdCl2 is 88mg/kg body weight) **[8]. Group IV (wheat germ oil group):** For a period of 12 weeks, each rat was given 100 mg/kg bodyweight of WGO orally every day **[9]. Group V (cadmium + wheat germ oil group):** Every day, WGO was given orally two hours (as previous studies suggested) before the oral gavage of CdCl2 at the previously specified doses and duration.

Sample collection

Upon completion of the experiment, sodium pentobarbital injections intraperitoneally were used to anesthetize the rats in each group (50mg/kg body weight). Subsequently, blood samples, liver, and two kidneys were collected **[10].** Each rat's blood sample was taken in a sterile centrifuge tube, with 2 ml of blood being used. The tube was then incubated at a temperature of 37°C until the blood clotted. After clotting, the tube was centrifuged for a duration of 10 minutes at a speed of 3000 r.p.m. This centrifugation process was carried out to separate the serum from the blood. After the serum was separated, it went through more steps: ALT, AST, ALP, total protein, albumin, and bilirubin values are used to measure how well the liver is working. A renal function test checks the amounts of creatinine and urea in the blood. Following the sacrifice, the liver and both kidneys were promptly collected. For the histology study, a 10% neutral formalin solution has been used to keep part of the liver and one kidney using hematoxylin & eosin

staining for light microscopy examination. A portion of the liver and part of the other kidney were immersed in a 25% glutaraldehyde solution for study with electron microscopy. For PCR analysis, a piece of liver and another piece of kidney were kept in Trizol to measure gene expression of Bax, Bcl-2, Caspase-3, TNF-α, and IL-10). A portion of the liver and the remaining part of the left kidney tissues were initially rinsed with a 0.9% saline solution, followed by homogenization in a cold 7.4 pH phosphate buffer saline (PBS) solution. The homogenization process involved utilizing a tissue homogenizer at a ratio of 5-10 ml per gram of tissue. Following the process of homogenization, the resulting mixture underwent centrifugation for 15 minutes at 4 degrees Celsius, with 4000 turns per minute in speed. This was done so that the amounts of oxidative stress markers (Malondialdehyde, reduced glutathione, and superoxide dismutase enzyme activity) could be studied biochemically.

Biochemical studies

Liver enzymes assessment

A colorimetric transaminase method was used to measure blood aspartate transaminase (AST) and alanine transaminase (ALT) amounts [11]. Serum alkaline phosphatase (ALP) was measured by means of a colorimetric technique recommended by Belfield and Goldberg [12]. Serum lactic dehydrogenase (LDH)was conducted in accordance with Kaplan and Glucose[13]. Estimation of total protein was performed using a colorimetric technique method of Koller and Kaplan [14]. Estimation of albumin according to Rodkey [15]. Estimation of total bilirubin according to Malloy and Evelyn [16].

Assessment of kidney function

The serum urea and creatinine levels were colorimetrically measured following Patton and Crouch [17] and Landers et al. [18], respectively.

Tissue oxidative stress parameters:

Malondialdehyde (nmol/mg.tissue) was measured using the method of Ohkawa et al. [19]. Superoxide dismutase (SOD) (U/mg in tissue) was found using the Beauchamp and Fridovich method [20]. Reduced glutathione (ng/mg.tissue) was measured using the method of Moron et al. [21].

Real-time PCR (RT PCR)

In both liver and kidney samples, it was used to measure Bax, Bcl-2, caspase-3, TNF-α, and IL-10. We used an Agilent Stratagene Mx3005P Real-Time PCR System and TOPrealTM qPCR 2X PreMIX (SYBR Green with low ROX) (Cat. # P725 or P750) to do the real-time RT-PCR. (Enzynomics, Korea) following the manufacturer's instructions. For PCR cycling, the first step was to denaturate the DNA at 95°C for 12 minutes. This was followed by 40 cycles of denaturation at 95°C for 20 seconds, annealing at 60°C for 30 seconds, and extension at 72°C for 30 seconds. The RNA-specific primers were made by Sangon Biotech in Beijing, China.

Gene	Forward primer (5′ –3′)	Reverse primer (5′ –3′)	Size	Accession no.	Reference
BAX	CGAATTGGCGATGAACTGGA	CAAACATGTCAGCTGCCACAC	109	NM_017059.2	**[22]**
BCL-2	GACTGAGTACCTGAACCGGCATC	CTGAGCAGCGTCTTCAGAGACA	135	NM_016993.1	**[22]**
Casp-3	GAGACAGACAGTGGAACTGACGATG	GGCGCAAAGTGACTGGATGA	147	NM_012922.2	**[22]**
TNF-α	AGGGTCTGGGCCATAGAAC	CCACCACGCTCTTCTGTCTAC	103	NM_012675.3	**[22]**
IL-10	GTAGAAGTGATGCCCCAGGC	AGAAATCGATGACAGCGTCG	116	NM_012854.2	**[22]**
Gapdh	GGCACAGTCAAGGCTGAGAATG	ATGGTGGTGAAGACGCCAGTA	143	NM_017008.4	**[22]**

Relative quantification method (Relative gene expression):

GADPH is a well-known housekeeping gene that was used to normalize the transcript level of the target genes. The results are shown as fold—are different from the control group after the 2-CT method **[23].**

1- Group I was used as a standard, and group II, group III, group IV, and group V were used as test groups for both the target and reference genes.

2-The following formulae were used to compare the target gene's threshold cycle numbers (Ct) to the reference gene's threshold cycle numbers (Ct) in both the test and control groups:

ΔCt (test) =Ct (goal in test groups) - Ct (the reference value in the test groups) = Ct (the calibrator) - Ct (see control).

3- The test genes' ΔCt values were compared to the calibrator's ΔCt values to make them equal:

YΔCt = ΔCt (calibrator) - ΔCt (test) 4- To find the fold difference in relative gene expression, the following formula was used in the end: Fold shift = (2-Ct).

Histopathological studies

The kidneys and liver were promptly dissected and visually examined to evaluate any macroscopic abnormalities. The specimens were quickly prepared for examination with both optical and electron microscopes, as shown below

Light microscopy

Paraffin technique **[24].**

Hematoxylin and Eosin (H & E) **[25].**

Electron microscopy [26].

The kidney and liver specimens were first kept for 24 hours in a solution of 25% glutaraldehyde. After that, the specimens were rinsed with cacodylate buffer. Subsequently, the sample is once again immersed in a solution containing osmic acid, which is diluted in a 1:1 ratio with cacodylate buffer. Using a series of alcohol solutions with progressively higher concentrations, the samples were dehydrated (50%, 70%, 90%, and 95%), followed by immersion in absolute alcohol (100%) for one hour each. Ultimately, we employed propylene oxide to achieve thorough dehydration. The samples were immersed in a resin block and then subjected to a temperature of 60 degrees Celsius for a duration of 10 to 12 hours in an oven. The blocks are precisely trimmed using a razor blade, and a specific location is chosen for sectioning and examination.

STATISTICAL ANALYSIS

The collected data was put into a computer and statistically analyzed with Version 27.0 of the SPSS program (Statistical Package for Social Science) (IBM, 2020). Numbers were shown with the standard deviation (SD) or the mean + SD. The ANOVA and post hoc Tukey tests were used to compare the results.

(I) **Biochemical results:**

A- Liver function tests (ALT, AST, ALP, LDH, bilirubin, total proteins, and albumin):

There was a statistically significant difference ($p<0.001$) between the test groups' average amounts of ALT, AST, ALP, LDH, and total bilirubin, as shown by the ANOVA test. The post hoc test ($p>0.05$) showed that there was no statistically significant difference between the WGO, positive control, and negative control groups. Following the administration of cadmium, a large elevation in the levels of ALT, AST, ALP, LDH, and total bilirubin compared to the negative control group ($p<0.001$). The group treated with Cadmium + Wheat germ oil exhibited considerably reduced levels of ALT, AST, ALP, LDH, and total bilirubin in contrast to the group receiving cadmium alone treatment ($p<0.001$). Nevertheless, the levels in the negative control group remained greater than average ($p<0.001$) **(Table 1).**

The ANOVA test showed that there was a statistically significant difference ($p<0.001$) between the groups in terms of the average amounts of total proteins and albumin in their serum. It was found that there was no statistically significant difference ($p>0.05$) between the WGO, positive control, and negative control groups in the post hoc study. When cadmium was given, the amounts of albumin and total protein were much lower than in the negative control group ($p<0.001$). The group that was treated with Cadmium plus Wheat Germ Oil had much higher amounts of total proteins and albumin than the group that was only treated with Cadmium ($p<0.001$). Even so, these numbers were still lower than what was normal in the negative control group ($p<0.001$) **(Table 2).**

B- Kidney function tests (urea and creatinine):

The ANOVA test showed that there was a big difference ($p<0.001$) between the study groups' average levels of urea and creatinine in their blood. It was found that there was no statistically significant difference ($p>0.05$) between the WGO, positive control, and negative control groups in the post hoc study. When cadmium was given, the amounts of urea and creatinine went up a lot compared to the negative control group ($p<0.001$). The amounts of urea and creatinine were much lower in the group that was treated with cadmium than in the group that was treated with wheat germ oil plus cadmium ($p< 0.001$). However, these levels were still higher than the normal levels observed in the negative control group **(Table 3).**

C- Oxidative stress markers (MDA, SOD and GSH):

The ANOVA test showed that there was a significant difference ($p<0.001$) between the groups in the mean amounts of MDA, SOD, and GSH in the liver and kidney tissue. A post hoc test showed that there wasn't a really big difference between –ve control, +ve control & WGO groups ($p>0.05$). Cadmium administration caused a highly significant increase in MDA levels when compared with –ve

control group ($p<0.001$). The Cadmium + Wheat germ oil treated group showed significantly lower levels of MDA when compared with the Cadmium treated group ($p< 0.001$) but still more than normal levels when compared to –ve control group ($p<0.001$) while the mean values of SOD and GSH of the studied groups revealed that cadmium administration caused a high significant decrease in SOD and GSH levels when compared to the negative control group ($p<0.001$). They were much higher in the Cadmium + Wheat germ oil treated group than in the Cadmium treatment group ($p<0.001$), but they were still lower than usual in the -ve control group **(Table 4 & 5).**

(II) **RT-PCR gene expression results:**

I. Inflammatory markers in hepatic & renal tissue (TNF-α and IL-10):

The average values of The ANOVA test revealed A big difference ($p<0.001$) in the amounts of TNF-α and IL-10 in the study groups' blood. It was found that there was no statistically significant difference ($p>0.05$) between the WGO, positive control, and negative control groups in the post hoc study. The amount of TNF-α raised significantly and the amount of IL-10 decreased significantly when cadmium was given compared to the negative control group ($p<0.001$). The group treated with Cadmium + Wheat germ oil exhibited significantly decreased levels of TNF-α and elevated levels of IL-10 in contrast to the group receiving cadmium treatment ($p< 0.001$). However, the level of TNF-α was still higher, and the level of IL-10 was still lower than the normal levels observed in the negative control group **(Table 6 & 7).**

II. Bax, Bcl-2, and Caspase-3 gene expression in hepatic and renal tissue:

The ANOVA test ($p<0.001$) showed that the liver and kidney tissues from the study groups had very different levels of Bax, Bcl-2, and Caspase-3 gene expression. The negative control, positive control, and WGO groups were not statistically different from each other ($p>0.05$), according to the post hoc test. Before and after cadmium was given, there was a big difference between the negative control group and the group that got cadmium ($p<0.001$). The group that was treated with cadmium and wheat germ oil had much lower amounts of Bax and caspase-3 than the group that was only treated with cadmium ($p<0.001$). Despite that, these amounts were still higher than what was seen in the negative control group ($p<0.001$). Also, the average levels of Bcl-2 in the liver and kidneys of the groups that were studied showed that giving cadmium caused a significant drop in Bcl-2 levels ($p<0.001$) when compared to the negative control group. It was true that Bcl-2 levels were lower in the normal control group ($p<0.001$) than they were in the group that was treated with cadmium alone, but they were still higher in the group that was treated with cadmium plus wheat germ oil **(Table 8 & 9).**

III. Hepatic histopathology:

Light microscope:

Negative and positive control groups (Groups I & II) showed the normal morphological appearance of the hepatic sections; Hepatocyte plates extending they come from a central vein and are split up by blood sinusoids that are lined with Kupffer cells and endothelium. Hepatocytes have acidophilic cytoplasm and vesicular nuclei and some of them are bi-nucleated. **The cadmium group (Group III)** showed the presence of cellular infiltration surrounding a blood vessel, as well as the increased growth of bile ducts. Several hepatocytes exhibit degeneration, while others display small black nuclei. There are hepatocytes containing proteinaceous material, which is located in the spaces between them. These hepatocytes are separated by massive, crowded sinusoids. **Wheat germ oil (Group IV)** displayed pictures of normal liver cells with vesicular nuclei and acidophilic cytoplasm that were grouped in plates that extended from a central vein and were divided by blood sinusoids. There were bi-nucleated cells. **Cadmium + WGO group (Group V)** showed images of hepatocytes with cytoplasm that was acidophilic and nuclei that were vesicular arranged in a radial pattern around a congested central vein and divided by congested sinusoids that are somewhat larger. Only a small number of sinusoids exhibit the presence of single-nucleus cells infiltrating, indicating the proliferation of phagocytic Kupffer cells **(Figure 1).**

Electron microscope:

Negative and positive control groups (groups I & II): The electron microscopical examination of liver sections from control groups showed two hepatocytes separated by a sinusoid. Hepatocytes contained euchromatic nuclei, some had a prominent nucleolus and the cytoplasm showed numerous mitochondria, multiple cisternae of RER, and dense bodies**. Cadmium group (Group III):** The cadmium group's liver slices were looked at under an electron microscope and showed hepatocytes with a clogged sinusoid in some of them. Hepatocytes had small heterochromatic nuclei, a cytoplasm that was sparse and full of

mitochondria, and many cisternae of the rough endoplasmic reticulum. (RER), lysosomes, and multivesicular bodies. The nucleus exhibits clumps of heterochromatin, along with a dark cytoplasm including deformed mitochondria, vacuoles, and dense bodies. **Wheat germ oil (Group IV):** The liver slices from group IV were examined using electron microscopy. The study revealed a hepatocyte with a nucleus that had a euchromatic appearance. The hepatocyte also had a large number of mitochondria, many cisternae of rough endoplasmic reticulum (RER), and dense bodies. Additionally, lysosomes were observed. **Cadmium + WGO group (Group V):** Group V liver sections were examined and revealed hepatocytes with a euchromatic nucleus, mitochondria, several cisternae Comprising vacuoles, cisternae of smooth endoplasmic reticulum (SER), and RER stands for rough endoplasmic reticulum. In some hepatocytes, some mitochondria didn't work right and structures with many cells **(Figure 2).**

1. **Renal histopathology:**

Light microscope:

Comparable histology findings were noted in both the negative and positive control groups (Groups I & II).

Negative and positive control groups (Groups I & II) showed normal morphological appearance of the hepatic sections from negative and positive control groups (Groups I & II). It was in the form of a glomerulus surrounded by Bowman's space. Pale, spherical nuclei on simple cuboidal epithelium lined the proximal and distal convoluted tubules. **Cadmium group (Group III)** the examination revealed a sclerotic glomerulus and deformed tubules with cytoplasm that contained vacuoles. Additionally, there was cellular infiltration in the interstitium around congested blood arteries, as well as arterial hyalinosis. Some of the tubules include tiny nuclei that are dark in color, along with congested capillaries surrounding the tubules**. The wheat germ oil group (Group IV)** showed a glomerulus enclosed by the area of Bowman. The nuclei of the proximal and distal convoluted tubules were spherical and pale. The brush edges and lumen of the proximal tubules were thin. **Cadmium + WGO group (Group V) is** a glomerulus with a large Bowman's space. Several tubules with small dark nuclei, cell casts, and clogged vessels around the tubules. **(Figure 3).**

Electron microscope:

Negative and positive control (Groups I & II): renal sections from control groups revealed tubular epithelial cells with large pale nuclei, numerous mitochondria, and thin basement membrane while glomerulus sections showpodocytes surrounding glomerular capillaries with regular foot processes and thin basement membrane**. Cadmium group (Group III):** renal sections from the cadmium group showed tubular epithelial cells with a small apoptotic nucleus, irregular basement membrane with distorted mitochondria and the interstitium revealed collagen fibers and fibroblasts while the glomerulus sections showed podocytes with thick basement membrane **(Figure 4). Wheat germ oil group (Group IV):** renal sections from the WGO group showed tubular epithelial cells with large pale nuclei, and regular basal membrane infoldings with elongated mitochondria while glomerulus sections showed podocytes surrounding glomerular capillaries with regular foot processes and thin basement membrane**. Cadmium + WGO group (Group V):** renal sections from the combined group showed both normal tubular epithelial cells with large pale nuclei, rounded mitochondria, microvilli, and a thin basement membrane and another cells revealed small apoptotic nucleus while glomerulus sections showed both normal podocytes with regular foot processes and slightly-thickened basement membrane and few podocyte foot processes were distorted **(Figure 5).**

Table 1: Statistical comparison among Negative control, Positive control, Cadmium, Wheat germ oil, and Cd + WGO groups as regards ALT, AST, ALP, LDH, and total bilirubin levels in serum.

Group / ***Parameter***	**(I) Negative control N=10**	**(II) Positive control N=10**	**(III) Cadmium (Cd) N=10**	**(IV) Wheat germ oil (WGO) N=10**	**(V) Cd + WGO N=10**	**F**	**P**
ALT (*u/L*)	38.5±5.32 **C**	38.3±5.74 **C**	95.2±8.28 **ABD**	37.7±5.93 **C**	62.9±7.2 **ABCD**	**145.74**	**<0.001****

AST (*u/L*)	40.3±7.45 **C**	42.7±7.99 **C**	102.2±12.8 **ABD**	31.4±3.06 **C**	59.3±7.69 **ABCD**	**111.94**	**<0.001** **
ALP (*u/L*)	134.7±16.32 **C**	133.8±10.75 **C**	315.6±35.16 **ABD**	152±24.39 **C**	197.6±13.95 **ABCD**	**118.22**	**<0.001** **
LDH (*u/L*)	1895±17.28 **C**	1897.2±18.28 **C**	2380.7±70.1 **ABD**	1844±31.68 **C**	2006.2±43.84 **ABCD**	**263.66**	**<0.001** **
Total bilirubin *(mg/dl)*	0.76±0.26 **C**	0.75±0.24 **C**	1.84±0.22 **ABD**	0.93±0.10 **C**	1.31±0.09 **ABCD**	**55.75**	**<0.001** **

N: number of rats, Data represented as mean ± SD, F: ANOVA test, **: Highly significant (P<0.001), Post hoc: Tukey test, A: Significant versus Group (I), B: Significant versus Group (II), C: Significant versus Group (III), D: Significant versus Group (IV).

Table 2: Statistical comparison among Negative control, Positive control, Cadmium, Wheat germ oil, and Cd + WGO groups as regards total proteins and albumin levels in serum.

Group / ***Parameter***	**(I) Negative control N=10**	**(II) Positive control N=10**	**(III) Cadmium (Cd) N=10**	**(IV) Wheat germ oil (WGO) N=10**	**(V) Cd + WGO N=10**	**F**	**P**
Total protein *(g/dl)*	5.43±0.33 **C**	5.45±0.32 **C**	3.8±0.12 **ABD**	5.41±0.25 **C**	4.25±0.14 **ABCD**	**100.72**	**<0.001** **
Albumin *(mg/dl)*	3.98±0.36 **C**	3.99±0.35 **C**	2±0.23 **ABD**	3.74±0.30 **C**	2.87±0.13 **ABCD**	**90.23**	**<0.001** **

N: number of rats, Data represented as mean ± SD, F: ANOVA test, **: Highly significant (P<0.001), Post hoc: Tukey test, A: Significant versus Group (I), B: Significant versus Group (II), C: Significant versus Group (III), D: Significant versus Group (IV).

Table 3: Statistical comparison among Negative control, Positive control, Cadmium, Wheat germ oil, and Cd + WGO groups as regards urea and creatinine levels in serum.

Group / ***Parameter***	**(I) Negative control N=10**	**(II) Positive control N=10**	**(III) Cadmium (Cd) N=10**	**(IV) Wheat germ oil (WGO) N=10**	**(V) Cd + WGO N=10**	**F**	**P**
Urea *(Mg/dl)*	31.1±6.08 **C**	32.2±6.76 **C**	71.9±12.15 **ABD**	29.1±5.57 **C**	45.6±1.96 **ABCD**	**60.72**	**<0.001****
Creatinine *(Mg/dl)*	0.39±0.06 **C**	0.41±0.06 **C**	1.09±0.16 **ABD**	0.41±0.08 **C**	0.98±0.13 **ABCD**	**107.45**	**<0.001****

N: number of rats, Data represented as mean ± SD, F: ANOVA test, **: Highly significant (P<0.001), Post hoc: Tukey test, A: Significant versus Group (I), B: Significant versus Group (II), C: Significant versus Group (III), D: Significant versus Group (IV).

Table 4: Statistical comparison among Negative control, Positive control, Cadmium, Wheat germ oil, and Cd + WGO groups regarding oxidative stress markers (MDA, SOD, and GSH) level in hepatic tissue.

Group / ***Parameter***	**(I) Negative control N=10**	**(II) Positive control N=10**	**(III) Cadmium (Cd) N=10**	**(IV) Wheat germ oil (WGO) N=10**	**(V) Cd + WGO N=10**	**F**	**P**
MDA *(nmol/ mg)*	2.38±0.17 **C**	2.39±0.23 **C**	5.17±0.55 **ABD**	2.41±0.18 **C**	3.08±0.18 **ABCD**	**161.06**	**<0.001****
SOD *(u/ mg)*	142±12.88 **C**	138.5±14.71 **C**	77.6±8.25 **ABD**	128.1±2.81 **C**	101.3±7.57 **ABCD**	**72.9**	**<0.001****
GSH *(mu/ mg)*	180.2±15.41 **C**	168.0±10 **C**	84.4±10.11 **ABD**	163.6±8.85 **C**	123.5±5.30 **ABCD**	**142.9**	**<0.001****

N: number of rats, Data represented as mean ± SD, F: ANOVA test, **: Highly significant (P<0.001), Post hoc: Tukey test, A: Significant versus Group (I), B: Significant versus Group (II), C: Significant versus Group (III), D: Significant versus Group (IV).

Table 5: Statistical comparison among Negative control, Positive control, Cadmium, Wheat germ oil, and Cd + WGO groups regarding oxidative stress markers (MDA, SOD, and GSH) level in renal tissue.

Group / ***Parameter***	**(I) Negative control N=10**	**(II) Positive control N=10**	**(III) Cadmium (Cd) N=10**	**(IV) Wheat germ oil (WGO) N=10**	**(V) Cd + WGO N=10**	**F**	**P**
MDA*(nmol/ mg)*	2.29±0.23 **C**	2.45±0.28 **C**	4.86±0.55 **ABD**	2.27±0.35 **C**	3.04±0.36 **ABCD**	**86.55**	**<0.001****
SOD *(u/ mg)*	140.6±16.41 **C**	139.6±16.81 **C**	76.8±12.28 **ABD**	121.3±7.8 **C**	97.7±10.23 **ABCD**	**44.04**	**<0.001****
GSH *(mu/ mg)*	178.5±23.45 **C**	173.4±25.79 **C**	87.8±13.52 **ABD**	168.2±19.41 **C**	124.6±11.81 **ABCD**	**40.12**	**<0.001****

N: number of rats, Data represented as mean ± SD, F: ANOVA test, **: Highly significant (P<0.001), Post hoc: Tukey test, A: Significant versus Group (I), B: Significant versus Group (II), C: Significant versus Group (III), D: Significant versus Group (IV).

Table (6): Statistical comparison among Negative control, Positive control, Cadmium, Wheat germ oil, and Cd + WGO groups as regards inflammatory markers (TNF-α and IL-10) level in hepatic tissue.

Group / ***Parameter***	**(I) Negative control N=10**	**(II) Positive control N=10**	**(III) Cadmium (Cd) N=10**	**(IV) Wheat germ oil (WGO) N=10**	**(V) Cd + WGO N=10**	**F**	**P**
TNF-α	1.003±0.08 **C**	1.004±0.09 **C**	4.58±0.54 **ABD**	0.82±0.09 **C**	1.9±0.51 **ABCD**	**216.18**	**<0.001****
IL-10	1±0.07 **C**	1±0.08 **C**	0.331±0.05 **ABD**	1.25±0.03 **C**	0.83±0.08 **ABCD**	**269.28**	**<0.001****

N: number of rats, Data represented as mean ± SD, F: ANOVA test, **: Highly significant (P<0.001), Post hoc: Tukey test, A: Significant versus Group (I), B: Significant versus Group (II), C: Significant versus Group (III), D: Significant versus Group (IV).

Table 7: Statistical comparison among Negative control, Positive control, Cadmium, Wheat germ oil, and Cd + WGO groups as regards inflammatory markers (TNF-α and IL-10) level in renal tissue.

Group / ***Parameter***	**(I) Negative control N=10**	**(II) Positive control N=10**	**(III) Cadmium (Cd) N=10**	**(IV) Wheat germ oil (WGO) N=10**	**(V) Cd + WGO N=10**	**F**	**P**
TNF-α	1.004±0.14 **C**	1.003±0.15 **C**	3.62±0.46 **ABD**	1.25±0.23 **C**	1.71±0.15 **ABCD**	**182.72**	**<0.001****
IL-10	0.98±0.07 **C**	0.97±0.06 **C**	0.22±0.05 **ABD**	1.61±0.11 **C**	0.70±0.07 **ABCD**	**443.94**	**<0.001****

N: number of rats, Data represented as mean ± SD, F: ANOVA test, **: Highly significant (P<0.001), Post hoc: Tukey test, A: Significant versus Group (I), B: Significant versus Group (II), C: Significant versus Group (III), D: Significant versus Group (IV).

Table 8: Statistical comparison among Negative control, Positive control, Cadmium, Wheat germ oil and Cd + WGO groups as regard Bax, Bcl-2 and Caspase-3 level in hepatic tissue.

Group / ***Parameter***	**(I) Negative control N=10**	**(II) Positive control N=10**	**(III) Cadmium (Cd) N=10**	**(IV) Wheat germ oil (WGO) N=10**	**(V) Cd + WGO N=10**	**F**	**P**
Bax	1.02±0.1 **C**	1.02±0.1 **C**	6.98±0.69 **ABD**	2.27±0.3 **C**	3.13±0.22 **ABCD**	**605.23**	**<0.001****
Bcl-2	0.98±0.07 **C**	0.97±0.06 **C**	0.20±0.07 **ABD**	1.5±0.07 **C**	0.71±0.15 **ABCD**	**278.39**	**<0.001****
Caspase-3	0.98±0.06 **C**	0.97±0.05 **C**	8.85±0.52 **ABD**	1.05±0.04 **C**	3.93±0.55 **ABCD**	**1006.98**	**<0.001****

N: number of rats , Data represented as mean ± SD, F: ANOVA test, **: Highly significant (P<0.001), Post hoc: Tukey test, A: Significant versus Group (I), B: Significant versus Group (II), C: Significant versus Group (III), D: Significant versus Group (IV).

Table 9: Statistical comparison among Negative control, Positive control, Cadmium, Wheat germ oil and Cd + WGO groups as regard Bax, Bcl-2, and Caspase-3 levels in renal tissue.

Group / ***Parameter***	**(I) Negative control N=10**	**(II) Positive control N=10**	**(III) Cadmium (Cd) N=10**	**(IV) Wheat germ oil (WGO) N=10**	**(V) Cd + WGO N=10**	**F**	**P**
Bax	0.96±0.11 **C**	0.94±0.10 **C**	4.82±0.46 **ABD**	0.89±0.08 **C**	1.64±0.11 **ABCD**	**558.85**	**<0.001****
Bcl2	1.01±0.16 **C**	1.02±0.17 **C**	0.31±0.04 **ABD**	1.33±0.10 **C**	0.78±0.05 **ABCD**	**278.39**	**<0.001****
Caspase-3	1.007±0.07 **C**	1.009±0.08 **C**	6.08±0.39 **ABD**	0.92±0.08 **C**	3.45±0.34 **ABCD**	**888.55**	**<0.001****

N: number of rats, Data represented as mean ± SD, F: ANOVA test, **: Highly significant (P<0.001), Post hoc: Tukey test, A: Significant versus Group (I), B: Significant versus Group (II), C: Significant versus Group (III), D: Significant versus Group (IV).

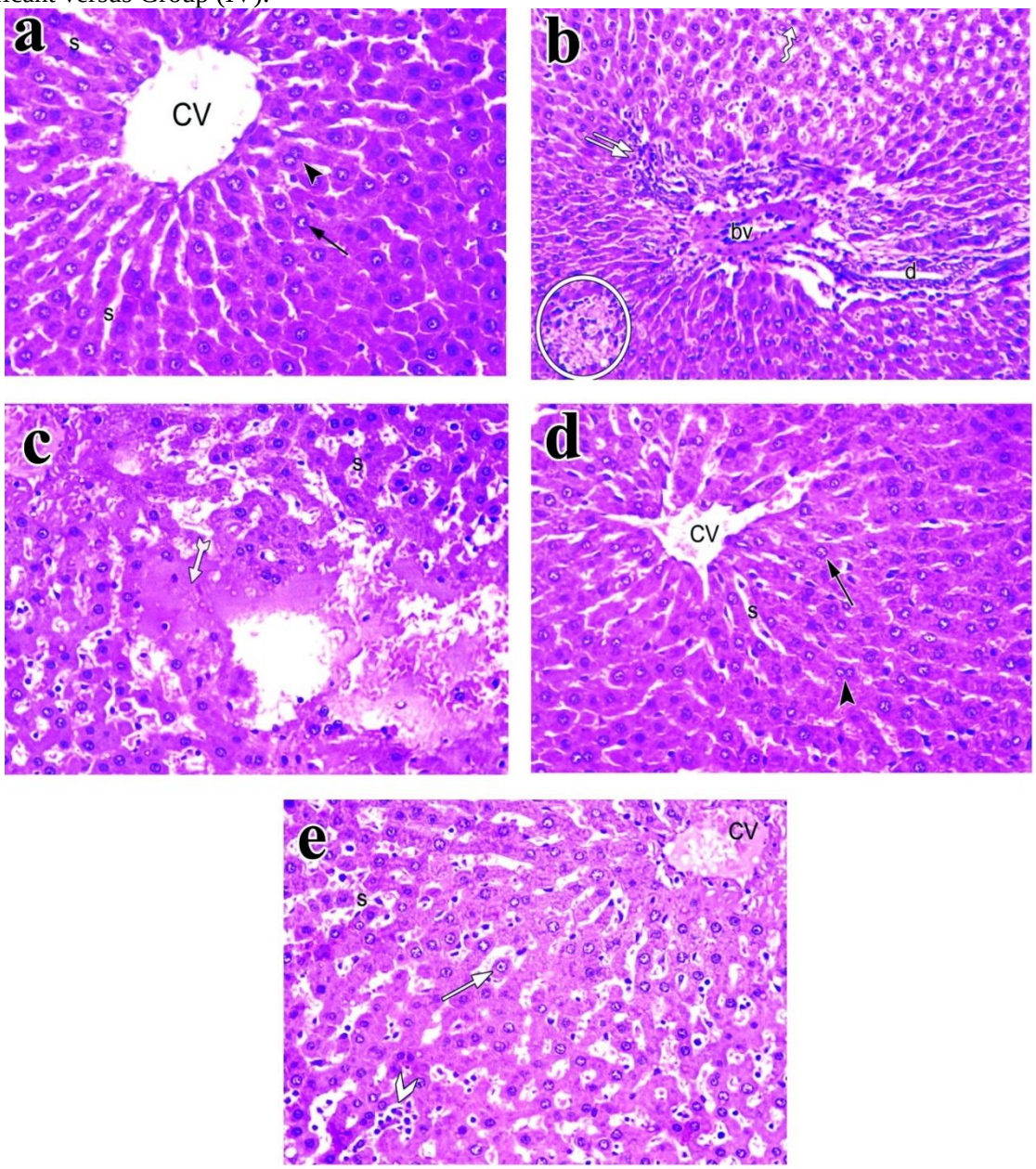

Figure (1): Representative photomicrograph (light microscope) of hepatic tissues from different groups:
a) Control group showing plates of hepatocytes radiating from a central vein (CV), and separated by blood sinusoids (s). Hepatocytes reveal acidophilic cytoplasm and vesicular nuclei (arrow). Some cells are bi-nucleated (arrowhead). Sinusoids are lined with endothelium (flat nuclei) and Kupffer cells (rounded nuclei) (H&E X 400).
b) Group III (cadmium group) showing cellular infiltration (double arrow) around a blood vessel, and proliferated bile ducts (d). Some hepatocytes are degenerated (circle). Few hepatocytes have small dark nuclei (zigzag arrow) (H&E X200).
c) Group III (cadmium group) showing hepatocytes with protinaceous material in between (bifid arrow). Hepatocytes are separated with large congested sinusoids (s) (H&E X400).
d) Group IV (wheat germ oil group) showing plates of normal hepatocytes with acidophilic cytoplasm and vesicular nuclei (arrow), radiating from a central vein (CV) and separated by blood sinusoids (s). Some cells are bi-nucleated (arrowhead) (H&E X400).

e) Group V (Cd + WGO group) showing plates of hepatocytes with acidophilic cytoplasm and vesicular nuclei (arrow), radiating from a congested central vein (cv) and separated by congested moderately-enlarged sinusoids (s). Few sinusoids show mononuclear cellular infiltration (white arrowhead) suggesting proliferation of phagocytic Kupffer cells (H&E X400).

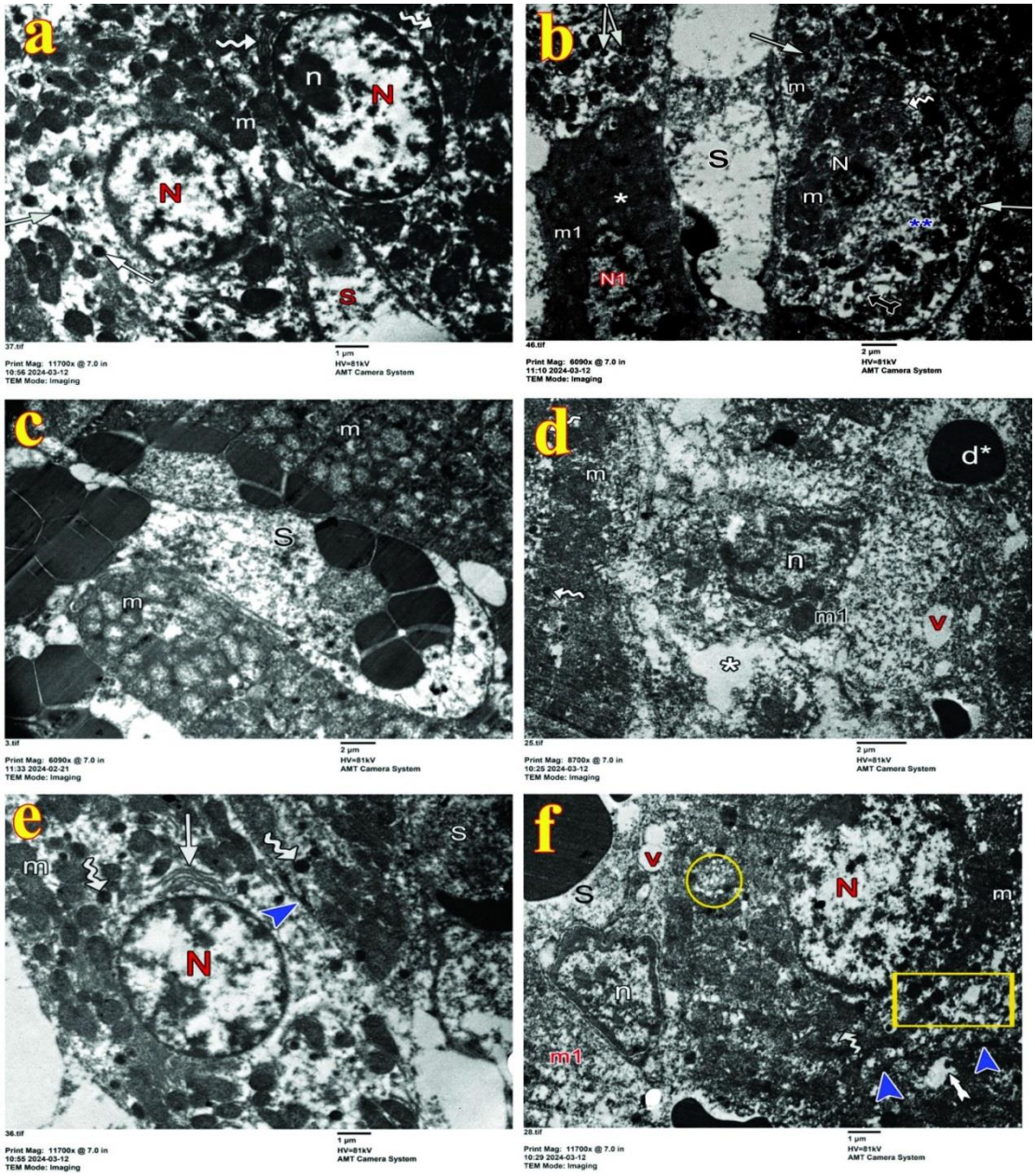

Figure (2): Representative electron photomicrograph of hepatic tissues from different groups:
a) Control group showing two hepatocytes separated by a sinusoid (S). Hepatocytes reveal euchromatic nuclei (N), some revealing a prominent nucleolus (n). The cytoplasm shows numerous mitochondria (m), multiple cisternae of RER (zigzag arrow), and dense bodies (arrow) (TEM, microscopic magnification X 11700).
b) Group III (cadmium group) showing hepatocytes with a sinusoid (S) in between. Some hepatocytes reveal a small heterochromatic nucleus (N), rarified cytoplasm (**) with mitochondria (m), multiple cisternae of RER (zigzag arrow), lysosomes (arrow), and multivesicular bodies (bifid arrow). Other hepatocytes show nuclei with heterochromatin clumps (N1) and dark cytoplasm (*) with distorted mitochondria (m1) (TEM, microscopic magnification X 6090).
c) Group III (cadmium group) showing parts of hepatocytes with a congested sinusoid (S) in between. The hepatocytes reveal numerous mitochondria (m) with distorted cristae (TEM, microscopic magnification X 6090).

d) Group III (cadmium group) showing a hepatocyte that reveals an irregular heterochromatic nucleus (n) and rarified cytoplasm (**) with few mitochondria (m1), vacuoles (v) and dense bodies (d*). Other hepatocytes show many mitochondria (m) and lysosomes (zigzag arrow)(TEM, microscopic magnification X 8700).
e) Group IV (wheat germ oil group) showing a hepatocyte with a euchromatic nucleus (N), numerous mitochondria (m), multiple cisternae of RER (arrow), and dense bodies; lysosomes (zigzag arrow). A cell junction is seen between adjacent hepatocytes (arrowhead). A sinusoid (S) is seen (TEM, microscopic magnification X 11700).
f) Group V (Cd + WGO group) showing a hepatocyte with a euchromatic nucleus (N), mitochondria (m), multiple cisternae of RER (zigzag arrow), cisternae of SER (circle), and vacuoles (v). The rectangle encloses dense bodies. Cell junctions are seen between adjacent hepatocytes (arrowhead). Other hepatocytes appear with distorted mitochondria (m1) and multivesicular bodies (bifid arrow). A sinusoid (S) is seen with its lining endothelial cell (n)(TEM, microscopic magnification X 11700)

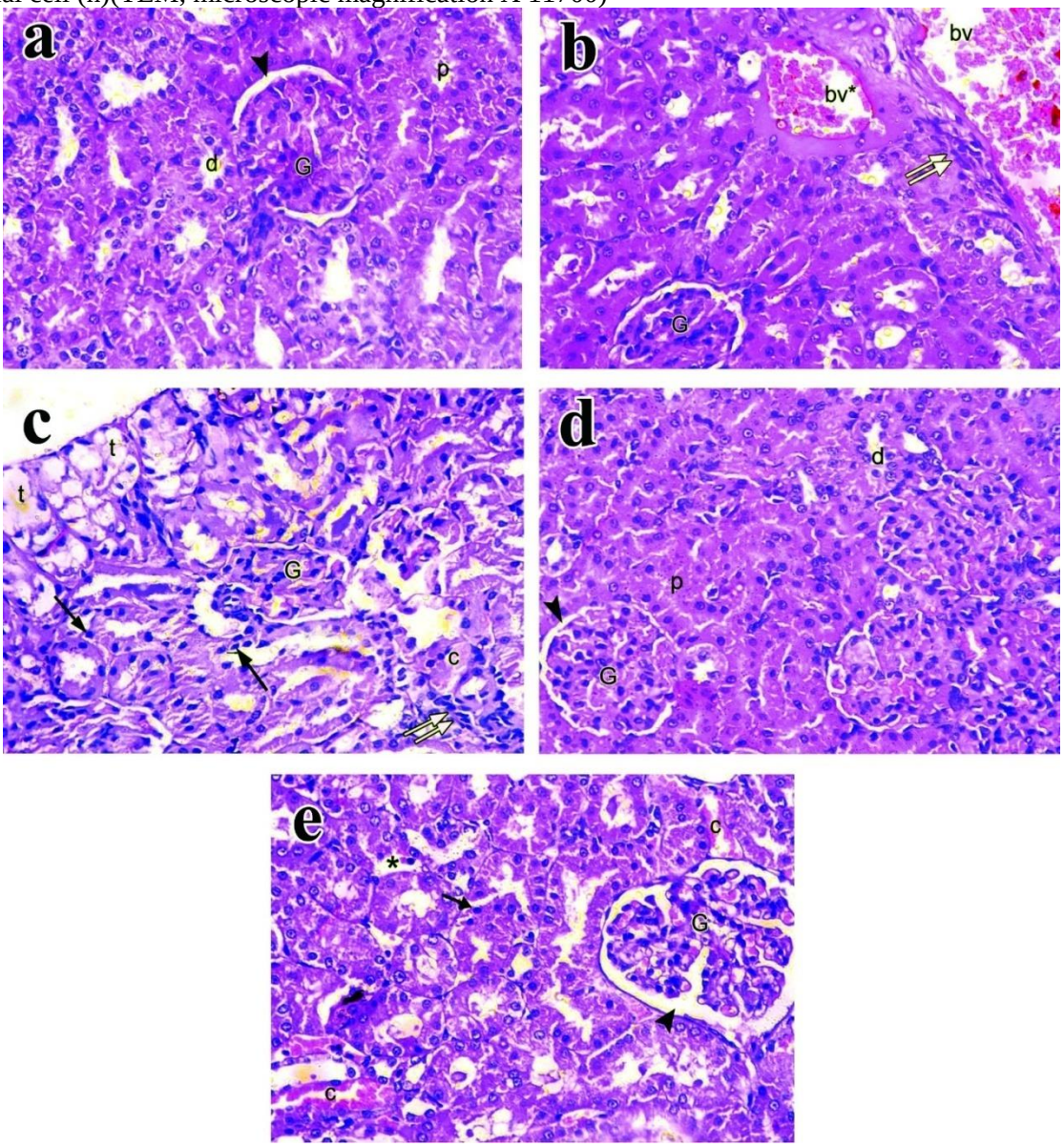

Figure (3): Representative photomicrograph (light microscope) of renal tissues from different groups:
a) Control group showing a glomerulus (G) surrounded by Bowman's space (arrowhead). Proximal (P) and distal (d) convoluted tubules are lined by simple cuboidal epithelium with pale rounded nuclei. The lumen of the proximal tubule is narrower than the distal one and exhibits a brush border (H&E X400).

b) Group III (cadmium group) showing a slightly sclerotic glomerulus (G). The interstitium reveals cellular infiltration (double arrow) around congested blood vessels (bv). Arterial hyalinosis (bv*) is also seen (H&E X400).
c) Group III (cadmium group) showing sclerotic glomerulus (G) and distorted tubules (t) with vacuolated cytoplasm. Other tubules contain small dark nuclei (arrow) with congested peri-tubular capillaries (c) (H&E X400).
d) Group IV (wheat germ oil group) showing a glomerulus (G) surrounded by Bowman's space (arrowhead). Proximal (P) and distal (d) convoluted tubules are seen with pale rounded nuclei. The proximal tubules appear with the narrow lumen and the brush borders (H&E X400).
e) Group V (Cd + WGO group) showing a glomerulus (G) with wide Bowman's space (arrowhead). Some tubules reveal small dark nuclei (arrow), cellular casts (*), and congested peri-tubular capillaries (c) (H&E X400).

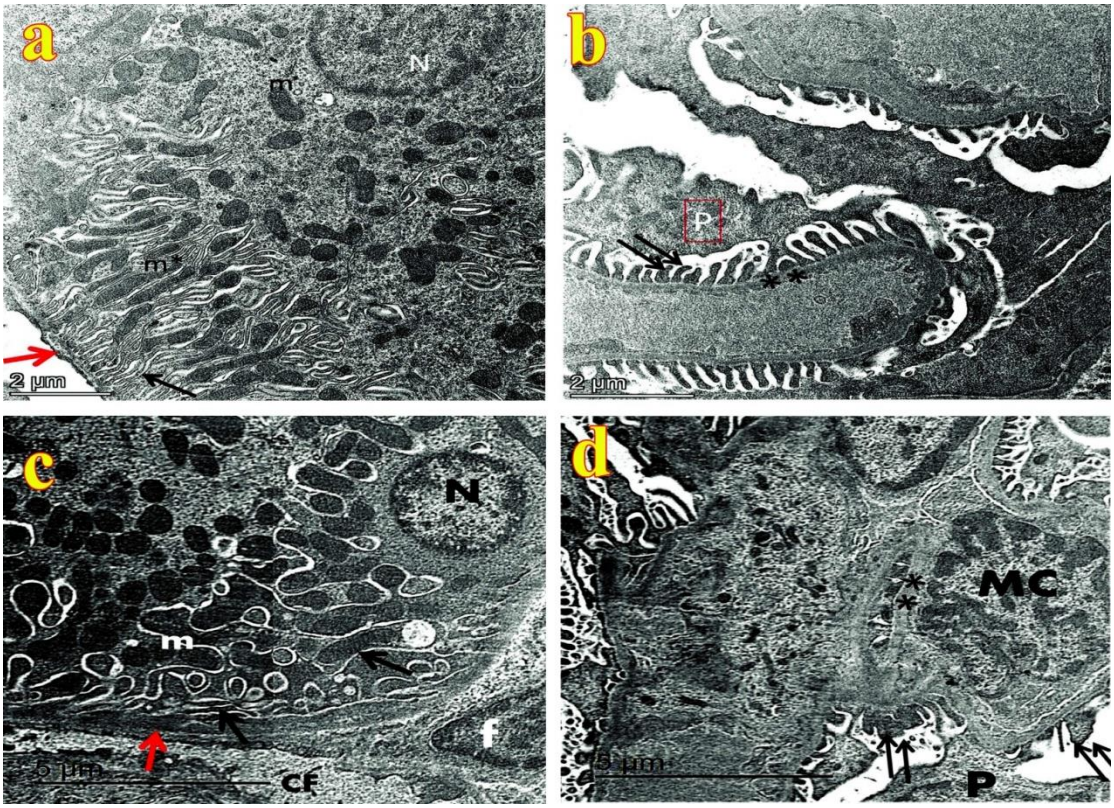

Figure (4): Representative electron photomicrograph of renal tissues from different groups:
a) Control group: tubular epithelial cell showing a large pale nucleus (N), numerous mitochondria (m), and thin basement membrane (red arrow). Regular basal membrane infoldings (black arrow) are seen with elongated mitochondria (m*) in between. (TEM, bar= 2µm)
b) Control group: glomerulus showing podocytes (P) surrounding glomerular capillaries with regular foot processes (double arrow) and thin basement membrane (**). (TEM, bar= 2µm)
c) Group III (cadmium group): tubular epithelial cell showing a small apoptotic nucleus (N), irregular basal membrane infoldings (black arrow) are seen with distorted mitochondria (m) and thickened basement membrane (red arrow). The interstitium reveals collagen fibers (cf) and a fibroblast (f). (TEM, bar= 5µm)
d) Group III (cadmium group): glomerulus showing podocytes (P) surrounding glomerular capillaries with fused foot processes (double arrow) and thick basement membrane (**). (TEM, bar= 5µm)

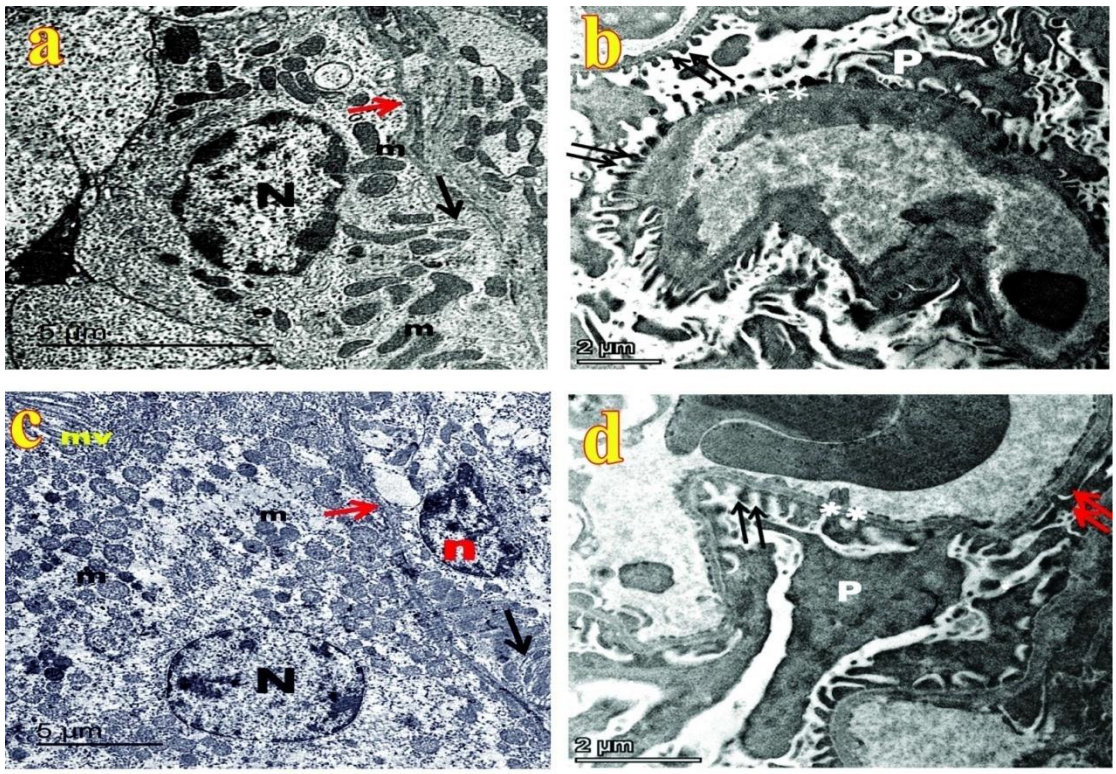

Figure (5): Representative electron photomicrograph of renal tissues from different groups:
a) Group IV (wheat germ oil group): tubular epithelial cells showing a large pale nucleus (N), regular basal membrane infoldings (black arrow) are seen with elongated mitochondria (m*) in between numerous mitochondria (m), and a thin basement membrane (red arrow). (TEM, bar= 5µm)
b) Group IV (wheat germ oil group): glomerulus showing podocytes (P) surrounding glomerular capillaries with regular foot processes (double arrow) and thin basement membrane (**). (TEM, bar= 2µm)
c) Group V (Cd + WGO group): tubular epithelial cells showing a large pale nucleus (N), rounded mitochondria (m), microvilli (mv), and a thin basement membrane (red arrow). Another cell reveals a small apoptotic nucleus (N) and regular basal membrane infoldings (black arrow). (TEM, bar= 5µm)
d) Group V (Cd + WGO group): glomerulus showing podocytes (P) surrounding glomerular capillaries with regular foot processes (double arrow) and slightly-thickened basement membrane (**). Few podocyte foot processes are distorted (red double arrow). (TEM, bar= 2µm)

DISCUSSION

The administration of cadmium in our study led to cadmium administration caused a significant increase in ALT, AST, ALP, and LDH mean values when compared to the -ve control group. The results of this study are similar to those of **Goodarzi et al. [27],** over eight days, the rats receiving treatment had higher serum levels of ALT, AST, and ALP after receiving CdCl2. Additionally, a study carried out by **Seif et al. [7],** which involved the daily administration of CdCl2 on rats resulted in increased levels of ALT, AST, and ALP. Also, in agreement with this study, **Renugadevi and Prabu [28]** found that adult male Wistar albino rats, which were treated with CdCl2 for 4 weeks had higher amounts of ALT, AST, ALP, and LDH in their serum in comparison to control group.

It has been reported that ALT is a sensitive indicator of liver injury **[29].** They are highly valuable for diagnosing and monitoring hepatocellular disease **[30].** While AST values are a useful test that is mostly used to find liver disease, they don't always show that the liver is sick. **[31].**

Alkaline phosphatases are a set of enzymes that are present in various human tissues, such as bone, gut, kidney, liver, placenta, and white blood cells [**14].** All cells contain the hardy intracellular enzyme lactate dehydrogenase (LDH) when the plasma membrane is broken, like in case of apoptosis, necrosis, or other types of cell injury; LDH is quickly released into the fluid on top of the cells **[32].**

The primary mechanism behind the elevation of these serum hepatic markers is the extensive

injury to liver cells caused by Cd, resulting in increased lipid peroxidation. This process leads to membrane damage, causing both structural and functional harm to the cell membrane. As a result, the membrane permeability rises, letting enzymes from the liver into the bloodstream. Because of this, high amounts of ALT and AST are very important for finding liver damage. The high level of ALP is due to more production because of higher biliary pressure. On the other hand, the high level of LDH shows that cells have been damaged. **[28]**.

Our investigation found a substantial and there was statistically significant rise in the amount of bilirubin in the cadmium group compared to the control groups. In a study conducted by **Novelli et al. [33],** they demonstrated a remarkable rise in the levels of total and direct bilirubin in rats when cadmium was added to their drinking water for seven days.

The current investigation demonstrates a substantial and statistically substantial decrease in albumin as well as the amount of total protein in the cadmium group compared to the negative control group. The outcome of this study agrees with what was found by **Shahriari and Moghadamnia [34],** the study involved administration of CdCl2 to adult male Wistar rats administered intraperitoneally for 35 days. Comparing the results to the control group, there was a noticeable drop in the amounts of albumin and total proteins in the serum.

Microscopic analysis of liver tissue samples from rats exposed to cadmium revealed the presence of cellular infiltration surrounding a blood vessel, as well as an increase in the number of proliferating bile ducts. Certain hepatocytes are undergoing degeneration, while others exhibit tiny nuclei with a black appearance. The hepatocytes exhibited the presence of proteinaceous material interspersed between them, and they were separated by enlarged and congested sinusoids. The presence of Cd may lead to the creation of extremely reactive radicals and consequent lipid peroxidation. Cytotoxicity can occur due to the formation of hydroperoxides, which are linked to the peroxidation of membrane phospholipids by lipid hydroperoxides. This process is responsible for causing damage to liver cells **[35].** An electron microscope analysis of liver sections revealed hepatocytes with congested sinusoids in certain areas. The hepatocytes exhibited small heterochromatic nuclei, sparse cytoplasm containing mitochondria, many cisternae of rough endoplasmic reticulum (RER), lysosomes, and structures with many compartments. The nucleus has clumps of heterochromatin and a dark cytoplasm with thick bodies, vacuoles, and mitochondria that are not shaped correctly.

Similar results were reported by **Renugadevi and Prabu, [35]** who found that administration of CdCL2 to rats for 4 weeks at a dosage of 5 mg/kg every day produced notable liver damage, characterized by sinusoidal dilatation, fatty degeneration, centrilobular vacuolization, necrosis, and infiltration of inflammatory cells.

Andjelkovic et al. [36] the study discovered that the livers of rats, that were exposed to CdCL2 at a dosage of 30 mg/kg body weight, had slightly expanded sinusoids having lymphocytes present and circulating through the liver's portal areas.

The current study found that the average amounts of creatinine and urea went up by a statistically significant amount in the cadmium-treated group relative to the control group. This outcome aligns with the findings of **Renugadevi and Prabu [35].** Who found that administration of cadmium to rats led to elevated amounts of blood urea and creatinine levels.

Based on our research and multiple studies, it has been found that all harmful processes that lead to reactive oxygen species (ROS) are made when these things happen. This shows that oxidative damage is a typical way that cadmium hurts and poisons the kidneys. Additionally, it is well known that cadmium stops amino acids from being added to proteins, which causes urea levels to rise. **[35, 37].**

Examination of kidney sections from rats treated with cadmium under a light microscope showed a somewhat sclerotic glomerulus. Cellular infiltration is observed surrounding congested blood arteries in the interstitium. Arterial hyalinosis is also observed. Certain sections exhibited sclerotic glomerulus and deformed tubules with cytoplasm including vacuoles. Some tubules contain small dark nuclei with congested peri-tubular capillaries accompanied by crowded capillaries surrounding the tubules. The tubular epithelial cells were examined using an electron microscope, revealing a small apoptotic nucleus. The basement membrane seemed uneven and had malformed mitochondria. In the interstitium, collagen fibers and fibroblasts were observed. In the sections of the glomerulus, podocytes with a thick basement membrane were observed.

These results were concomitant with the results of **Siddiqui [8]** who revealed that the daily application of CdCl2 to rats, at a dosage of 0.6

mg/kg body weight, resulted in significant harm to their kidneys. The administration of CdCl2 resulted in renal cortex damage, specifically affecting the brush border membrane, cellular membrane, proximal tubules, and distal tubules in the rat kidneys that were given medicine. But the glomeruli were not harmed as much; their walls only got thicker.

These results also go along with the results of **Liu et al. [38]** who discovered that the injection of CdCl2 at a dosage of 5 mg/kg body weight to adult male rats for 60 consecutive days resulted in renal histological alterations characterized by mitochondrial enlargement, distortion, ridge dysfunction, and vacuolar degeneration.

The results of our present study showed a highly significant increase in the mean values of MDA level and a highly significant decrease in GSH and SOD levels in both hepatic and renal tissues in Cd-treated rats when compared to the control group. This indicates the occurrence of oxidative stress in the liver and renal tissues, which significantly contributes to the development of liver and renal damage.

Goodarzi et al. [27] showed that adult male Wistar rats were given 3 mg/kg of Cd every day for seven days. When compared to the control group, the liver tissue homogenate showed a clear drop in GSH and SOD levels and a rise in MDA levels. **Newairy et al. [39]** discovered that giving adult Wister rats a daily dose of 2 mg/kg body weight of CdCl2 for 10 days caused a 3.2-fold increase in MDA levels in the liver, above the normal limit. Additionally, when compared to the control group, the introduction of CdCl2 caused GSH levels in the liver to drop.

Our obtained data were following the results obtained by **Kandemir et al. [40]** who conducted a study on adult male Sprague Dawley rats and found that administering CdCl2 orally at a dose of 25 mg/kg dissolved in distilled water resulted in an elevation of MDA levels and a significant decrease in GSH and SOD levels in both liver and kidney tissues. This phenomenon could be attributed to the increased synthesis of H2O2 and ROS, which subsequently induces oxidative stress.

Lipid peroxidation is a prominent result of oxidative damage and has been observed to have a significant impact on the toxicity of several xenobiotics**[41]**. **Demirci-Cekic et al. [42]** reported that malondialdehyde (MDA) is commonly recognized as a very sensitive lipid peroxidation indicator. It is typically thought of as a useful measure of oxidative stress.

Yasui and Baba [43] reported that superoxide dismutase (SOD) functions as an internal cellular defense mechanism to break down superoxide into oxygen and hydrogen peroxide.

Our study, along with previous studies, has demonstrated that cadmium triggers the making of reactive oxygen species, which help start lipid peroxidation and oxidative stress in many different organs. After that, these radicals attack the cell membrane, which breaks down because of lipid breakdown **[35].**

Tumor necrosis factor α is an inflammatory cytokine produced in response to acute inflammation. It is essential for starting several signaling cascades in cells that lead to necrosis or apoptosis, which is the final stage of cell death **[44]**. IL-10 is a powerful anti-inflammatory cytokine that has a critical and frequently necessary function in avoiding inflammatory and autoimmune diseases **[45]**.

The study found that in the liver and kidneys of the Cd-treated group, there was a significant and statistically significant rise in the levels of TNF-α and a significant decrease in the levels of IL-10 compared to the control group. This means that inflammation of the tissues is starting to happen. The findings of the present study are in agree with the results of **Alizadeh et al. [46].** Rats that were given Cd every other day for 4 weeks had significantly lower levels of the anti-inflammatory IL-10 and higher levels of the pro-inflammatory TNF-α in their liver tissues compared to the other groups. In a similar way, **Noor et al. [47]** found that adult male albino rats showed a significant increase in the pro-inflammatory cytokine TNF-α in their hepatic tissue when given CdCl2 orally at a dose of 5 mg/kg body weight for 30 days, relative to the control group.

In addition, **Kamel et al. [48]** discovered that when adult male Wistar albino rats were given a single intraperitoneal injection of CdCl2 at a concentration of 1.2 mg/kg on day 7. This caused the levels of TNF-α and IL-6 to rise significantly in both the liver and kidneys compared to normal rats. In any case, **Turley et al. [49]** found that administrating CdCl2 in the drinking water of adult male rats at a dose of 32 ppm for ten weeks caused the cytokine IL-10, which is normally produced during inflammation, to become activated. This activation of IL-10 is one of the mechanisms that helps regulate the inflammatory response.

In our study, we found a statistically significant rise in the average levels of cadmium. The treatment led to a big drop in the expression of the Bcl2 gene and a rise in the expression of the Bax and Caspase-3 genes compared to the control group. Based on what we found, cadmium poisoning seems to cause apoptosis in the liver and kidneys. Most likely, this is because there are more reactive oxygen species. (ROS), which raises Bax expression while lowering Bcl-2. As a result of these modifications, apoptosis terminal pathways are activated and mitochondrial Cytochrome-C is released **[48].**

These results are in accordance with the results of **Noor et al. [47]** Researchers found that giving Cd by mouth to adult male albino rats for 30 days increased the levels of Bax and caspase-3 while lowering the levels of Bcl-2 in their liver and kidneys. This means that Cd might be able to damage cells through apoptosis. In the same way, **Gelen et al. [50]** found that giving cadmium to adult male rats for 5 days in a row increased the levels of Bax mRNA expression and decreased the levels of Bcl-2 mRNA expression in liver tissue compared to the control group.

Upon administering WGO to rats treated with cadmium in the current study, there was a notable reduction in the average levels of ALT, AST, ALP, and LDH in the blood compared to the group that only got cadmium. However, the overall levels of ALT, AST, ALP, and LDH were much higher in the WGO + cadmium therapy group compared to the control groups. This showed that the patients were only partially better. The observations of the present work were in line with the results of **Elgendy et al. [51]** found that adult Wister rats, which were given a pretreatment of WGO at a dosage of 1400 mg/kg body weight orally for 15 days before ethanol treatment, showing a partial recovery in liver damage as seen by the levels of ALT, AST, and ALP returning to normal. Furthermore, **Saleh [52]** detected the beneficial impact of WGO when male mice were orally administered WGO for 8 days, along with Carbon tetrachloride and there was a notable decrease in LDH level.

According to **Anwar and Mohamed, [53],** It was shown that WGO could protect liver cells from the damage that sodium nitrate could do. It was found that giving WGO along with sodium nitrate at a dose of 900 mg/Kg body weight to female albino rats five days in a row, seven days a week, for 28 to 42 days raised the levels of ALT, AST, and ALP. The high value of WGO as a source of unsaturated fatty acids and important fatty acids like linoleic acid and alpha-linolenic acid are related to the unsaponifiable matter, certain sterols, and their ability to speed up the oxidation of fatty acids. Octacosanol and natural vitamin E are also in WGO. **[53]**.

When WGO and cadmium were administered together in this trial, the average total bilirubin levels were a lot lower than in the group that only got cadmium. Even so, the average level of total bilirubin in the WGO + cadmium group stayed much higher than in the control groups, which suggests that only a partial rebound took place. The results of the current study were consistent with the findings of **Elgendy et al. [51]** researchers found that adult Wister rats that were given WGO for 15 days before being given ethanol had a restoration of total bilirubin levels. This recovery points to a partial amelioration of liver damage.

In our present study, when we administered WGO to rats that had been treated with cadmium, we observed a noteworthy rise in the average levels of total proteins and albumin, as compared to the group that was only treated with cadmium. Nevertheless, the average values of total proteins and albumin in the WGO + cadmium-treated group remained statistically lower than those of the control groups, suggesting only a partial improvement.

Our present study results were confirmed by a study done by **Mehranjani et al. [54]** who used WGO as a preventive agent against liver damage caused by P-nonylphenol in adult male Wistar rats. WGO was administered at a dosage of 170 mg/kg body weight for a duration of 70 days, leading to a remarkable increase in blood total protein levels while serum albumin levels remained unchanged.

The administration of WGO alongside cadmium resulted in a notable enhancement of all histopathological alterations compared to the tissues of rats that had only been given cadmium. The light microscopic examination revealed hepatocytes with cytoplasm that appeared acidophilic and nuclei that were vesicular. These hepatocytes were arranged in a pattern extending from a swollen central vein and were split by swollen sinusoids. Only a small number of sinusoids exhibited cellular infiltration, indicating the proliferation of phagocytic Kupffer cells. The electron microscopy analysis of liver slices revealed hepatocytes with a typical euchromatic nucleus. Multivesicular structures and distorted mitochondria were observed in certain hepatocytes.

The preventive and therapeutic properties of wheat germ oil are responsible for its ability to prevent lipid peroxidation and oxidative stress, which in turn helps to regulate the inflammatory response **[55].**

Abdallah and Bakry, [56] observed that administering WGO to rats treated with nicotine poisoning resulted in the restoration of the liver's normal structure, along with the increased growth of kupffer cells. In the conducted study by **Elgendy et al. [51]** researchers found that pre-treating rats with a mix of wheat germ oil and ethanol caused some liver cells to break down, which showed that the shape of the liver tissue got a lot better.

In this study, the overall levels of serum urea and creatinine were much lower in the group that was treated with WGO plus cadmium than in the group that was treated with cadmium alone However, these levels were still statistically greater than those observed in the control groups, suggesting only a partial improvement.

The observations of the present work were in line with the results of **Elgendy et al. [51]** who found that rats pretreated with when taken by mouth over a period of 15 days prior to ethanol administration, led to partial improvement in kidney injury. This was indicated by the restoration of blood urea and creatinine levels.

In the same way, **Gazar et al. [57]** observed that rats who were given WGO for 7 days after being exposed to a single dose of whole body γ radiation, showed an improvement in their serum urea and creatinine levels.

Examination of renal sections from rats treated with cadmium+ WGO under a light microscope showed glomeruli with wide Bowman's space. Several tubules had small dark nuclei, cellular casts, and engorged peri-tubular capillaries.

These results are in the same line as the results of **Hafez et al. [55],** who discovered that when wheat germ oil was administered daily, compared to the group that received gentamicin alone, it caused less harm to the renal architecture when given for 15 days. The examination under a light microscope revealed minimal glomerular atrophy, tubular dilatation, swelling, desquamation, and reduced infiltration of inflammatory cells.

As regards electron microscopic examination, our results go along with the results of **El-Bana et al., [58]** who discovered that the daily oral administration of WGO effectively decreased the toxic impact of cisplatin on the kidneys. The groups treated with both cisplatin and WGO exhibited significant improvement in their pathological alterations to varying degrees. The glomeruli and renal tubules exhibited a degree of similarity to those of the control group.

Rats given WGO + cadmium in this study found that normal MDA levels went down significantly, while GSH and SOD levels went up significantly compared to the group that was only given cadmium. However, these levels have not yet fully returned to normal, suggesting only partial improvement.

Our work stands out because it measures both enzymatic and non-enzymatic antioxidant properties to evaluate the protective effect of WGO against oxidative stress generated by Cd.

The observations of the present work were in line with the results of **Elgendy et al. [51]** who found that adult Wister rats, who were given a pretreatment o of WGO for 15 days before ethanol was given, showed lower MDA levels in their liver and kidney tissues and higher GSH and SOD levels. These modifications imply less oxidative stress damage.

The results of the current study are supported by **Karabacak et al. [59]** discovered that giving WGO for 45 days helped reduce the oxidative stress effects of coumaphos. Additionally, it restored antioxidant activity by improving levels of MDA and SOD in all tissues examined, including hepatic and renal tissues.

It has been noted that tocopherols, which are a major component of WGO, have a strictly physicochemical stabilizing impact on biological membranes. They also protect these membranes against the release and activation of damaging endogenous phospholipase enzymes, which contribute to the acceleration of lipid peroxidation **[60].** Furthermore, the phenolic compounds present in WGO have antioxidant properties that can effectively reduce oxidative stress and provide a powerful antioxidant defense to many organs within the body **[52].**

Compared to the group that was only treated with cadmium, the average TNF-α level was much lower in the group that was given WGO plus cadmium. The IL-10 level also went up a lot. However, the TNF-α andIL-10 levels had not yet recovered to normal levels, indicating only partial improvement.

This result is concomitant with the results of **Elgendy et al. [51]** who found that adult Wister rats were pretreated with WGO led to a decrease in TNF-α levels and a rise in IL-10 levels in their

kidney and liver tissues for 15 days before ethanol treatment. This suggests that in comparison to the group that only got ethanol, tissue inflammation has partially improved.

Moreover, based upon the work done by **Hussein et al. [61]** discovered that administering a pre-treatment of WGO adult male rats orally for 21 days. The group that wasn't injected with endotoxin had a much lower increase in TNF-α than the group that was injected with endotoxin alone. This suggests that the anti-inflammatory properties of WGO.

Rich in both saturated and unsaturated fatty acids, WGO has anti-inflammatory properties and can lessen the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and oxygen free radicals **[52].**

Oxidative stress and inflammatory cytokines activate the intrinsic mitochondrial pathway, leading to apoptosis. The Bcl2 protein, which prevents cell death, and the Bax and caspase-3 proteins, which promote cell death, regulate apoptosis triggered by oxidative stress. Apoptosis is prevented by reducing the levels of proteins involved in apoptosis (Bax and caspase-3) and increasing the expression of Bcl2 **[62].**

The co-administration of WGO with the cadmium group in the current investigation led to a considerable rise in Bcl2 levels and a notable decrease in the average levels of Bax and Caspase-3. These modifications were noted in contrast to the group treated with cadmium alone, which has not yet returned to normal levels, indicating only partial improvement.

The observations of the present work were in line with the results of **Elgendy et al. [51]** who reported that adult Wister rats, which were given a pretreatment of WGO for 15 days prior to ethanol administration, showed a high probability of inhibiting the increase in caspase-3 caused by ethanol. Additionally, the expression of Bcl2 was mostly restored in the group that received both WGO and ethanol. This finding suggests that WGO can improve gene expression related to apoptosis in rats with liver and kidney damage induced by ethanol. Similarly, **Mohamed and Ahmed, [63]** conducted a study to investigate the impact of radiation on rat liver. They discovered that rats that were given a single oral dose of 54mg/Kg wheat germ oil led to decrease mRNA levels of Bax and caspase 3 significantly. Furthermore, compared to the rats that just got radiation, the rats that received both radiation and therapy had higher levels of bcl-2 expression.

CONCLUSION

Exposure to cadmium leads to notable biochemical, and gene expression abnormalities and histological harm in the liver and kidneys of adult male albino rats. This harm is evident through elevated indicators of liver and kidney dysfunction, oxidative stress, inflammation, and aberrant histopathology findings. The application of wheat germ oil (WGO) showed a protective effect, effectively improving the negative consequences of cadmium exposure. Although the WGO treatment did not fully restore normal biochemical and histological markers, it greatly enhanced them, suggesting its potential as a protective agent in ameliorating the toxic effects caused by cadmium. Additional investigation is necessary to investigate the processes that underlie WGO's protective qualities and prospective applications in therapeutic settings.

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Author contributions

All the authors contributed to the study concept and design, the data analysis and interpretation, wrote the manuscript and provided the clinical data. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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