

Hepatotoxicity Implies Chemical-Driven Liver Damage Induced By Certain Medicinal and Other Chemical Agents

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Abstract:

There are increasing evidences that free radicals and reactive oxygen species play a crucial role in the various steps that initiate and regulate the progression of liver diseases. Oxidative stress in hepato-toxicity resulting from increased generation of reactive oxygen species (ROS) and other reactive intermediates as well as by decreased efficiency of antioxidant defenses actively contributes to excessive tissue remodeling. Drug-induced nephropathy is reported to be the third most common cause of acute renal failure in hospitalized patients. Excess ROS production and depressed antioxidant defence mechanism are responsible for nephrotoxicity. So, pharmacological studies in this work were done to evaluate: presence of protective effects of an antioxidant Hesperedine on carbon tetrachloride-induced hepatic toxicity and nephro-toxicity, to evaluate its effects on oxidants and antioxidants parameters and to evaluate its effect on kidney and liver functions and histo-pathological changes. Liver enzymes level AST and ALT : was increased significantly in rats treated with CCl₄ but decreased significantly in rats treated with antioxidant HDN (100 mg/ kg/ day) and in rats treated with antioxidant HDN (200 mg/ kg/ day) . in comparison between antioxidant treated rats groups liver enzymes level was decreased significantly in rats treated with antioxidant HDN (200 mg/ kg/ day) than in rats treated with antioxidant HDN (100 mg/ kg/ day) .Serum creatinine level: was increased insignificantly in rats treated with CCl₄ but decreased insignificantly in rats treated with antioxidant HDN (100 mg/ kg/ day) and in rats treated with antioxidant HDN (200 mg/ kg/ day). in comparison between antioxidant treated rats groups liver enzymes level was decreased insignificantly in rats treated with antioxidant HDN (200 mg/ kg/ day) than in rats treated with antioxidant HDN (100 mg/ kg/ day) . So, we recommend uses of antioxidant Hesperedine as it has a valuable role in improvement of liver functions and as a prophylactic of hepatic and renal tissues against toxicity achieved by free radicals.

I. INTRODUCTION

Hepato-toxicity Implies chemical-driven liver damage. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. Other chemical agents, such as those used in laboratories and industries, natural chemicals (e.g., microcystins) and herbal remedies can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins. Chemicals often cause subclinical injury to liver which manifests only as abnormal liver enzyme tests. Drug-induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures. More than 75 % of cases of idiosyncratic drug reactions result in liver transplantation or death (Ostapowicz et al., 2002; McNally and Peter, 2006).

Mitochondria are prominent targets for the hepato-toxicity of many drugs. Dysfunction of these vital cell organelles results in impairment of energy metabolism and an intracellular oxidant stress with excessive formation of reactive oxygen species and peroxy-nitrite. Induction of cytochrome P450 isoenzymes such as CYP2E1 also promotes oxidant stress and cell injury, once hepatocellular function is impaired, accumulation of bile acids causes additional stress and cytotoxicity. Cell injury, gut-derived endotoxin or a combination of both also activate Kupffer cells and recruit neutrophils into the liver. Although responsible for removal of cell debris and part of the host-defense system, under certain circumstances these inflammatory cells initiate additional liver injury (Jaeschke et al., 2002).

Drug-induced liver diseases mimic all forms of acute and chronic hepatobiliary diseases. However, the predominant clinical presentation resembles acute icteric hepatitis or cholestatic liver disease. The former is the more serious and often has a 10% mortality rate, regardless of the causative drug, (Zimmerman, 1999; and Kaplowitz, 2002).

Acute icteric hepatitis is accompanied by markedly elevated serum transaminase levels and a minimal increase in the level of alkaline phosphatase. Coagulopathy and encephalopathy are present in more severe cases. Cholestatic disease (which is also referred to as cholestatic hepatitis) is not usually life threatening; it presents with jaundice,

pruritus, and marked increases in alkaline phosphatase levels, as well as mild increases in alanine aminotransferase (ALT) levels. Mixed injury patterns with intermediate to marked increases in ALT and alkaline phosphatase levels can resemble atypical hepatitis or granulomatous hepatitis, (Kaplowitz, 2002).

Biochemical markers (e.g. alanine transferase, alkaline phosphatase and bilirubin) are often used to indicate liver damage. Liver injury is defined as a rise in either (a) ALT level more than three times of upper limit of normal (ULN), (b) ALP level more than twice ULN, or (c) total bilirubin level more than twice ULN when associated with increased ALT or ALP, (Bénichou, 1990 and Mumoli et al., 2006).

Oxidative stress in hepatotoxicity, resulting from increased generation of reactive oxygen species (ROS) and other reactive intermediates as well as by decreased efficiency of antioxidant defenses, actively contributes to excessive tissue remodeling, (Ismail and Pinzani, 2009).

Indeed, oxidative stress, presumably by favoring mitochondrial permeability transition, is able to promote hepatocyte death (necrotic and/or apoptotic). In some of clinically relevant conditions, generation of ROS within hepatocytes may represent a consequence of an altered metabolic state (like in NAFLD and NASH) or of ethanol metabolism (as in ASH), with ROS being generated mainly by mitochondrial electron transport chain or through the involvement of selected cytochrome P450 isoforms like cytochrome P2E1 (CYP2E1), (Tilg and Hotamisligil, 2006).

Glutathione (GSH) is a critical cellular antioxidant. After GSH depletion with buthionine sulfoximine (BSO), the toxicity of ethanol, iron, arachidonic acid, and acetaminophen was strikingly enhanced, (Chen et al., 1997; Chen and Cederbaum, 1998; Sakurai and Cederbaum, 1998; Wu and Cederbaum, 1999).

Cytochrome P4502E1 (CYP2E1), the ethanol-inducible form, metabolizes and activates many toxicologically important substrates, including ethanol, carbon tetrachloride, acetaminophen, and N-nitrosodimethylamine, to more toxic products, (Guengerich et al., 1990; Koop, 1992). CYP2E1-dependent ethanol metabolism produces oxidative stress through generation of reactive oxygen species (ROS), a possible mechanism by which ethanol is hepatotoxic, (Dianzani, 1985 and Bondy, 1992). Induction of cytochrome P4502E1 by ethanol is a central pathway by which ethanol generates oxidative stress, and in the intragastric model of ethanol feeding a prominent induction of CYP2E1 occurs along with significant alcohol liver injury, (Morimoto et al., 1994; Nanji et al., 1994).

Immunochemical studies indicate that the cellular site of covalent binding correlates with the toxicity, (Roberts et al., 1991 and Hart et al., 1995). Recent work shows that nitrated tyrosine occurs in hepatic centrilobular cells. These adducts colocalize in cells containing the acetaminophen-protein adducts, (Hinson et al., 2000). Peroxynitrite, a highly reactive nitrating and oxidizing species formed by the rapid reaction of nitric oxide (NO) and superoxide, produces nitrated tyrosine, (Pryor and Squadrito, 1995; Beckman, 1996).

Carbon tetrachloride is a colourless liquid, non flammable, and is heavier than air, (Etim et al., 2008). Consequently, it has been widely used as a fire extinguisher being useful for fighting fires near electrical equipment because it does not conduct electricity, (The World Book Encyclopedia, 1992). Carbon tetrachloride is very toxic and because of this, most of its uses in households and industries have been suspended, (Etim et al., 2008). Consequently, little is known about the early effects of this organic solvent in vivo, particularly on mitochondrial function. It has been shown recently in a murine model of liver fibrosis that chronic administration of CCl₄ for 6 weeks led to mitochondrial DNA (mtDNA) alterations, reduced glutathione (GSH) depletion and decreased aconitase activity (Mitchell et al, 2009), overexpression of Bcl-2 reduced liver fibrosis for the first 3 weeks of treatment by protecting hepatocytes against mitochondrial damage, but subsequently failed to prevent fibrosis with the persistence of the aggression. CCl₄ is activated by cytochrome P450 (CYP) 2E1, and very marginally by other CYPs (CYP2B and CYP3A), to form the trichloromethyl (CCl₃) free radical, which can react with oxygen to produce the trichloromethyl peroxy radical (CCl₃OO). Both radicals are highly reactive species that may covalently bind to macromolecules to form nucleic acid, protein and lipid adducts. However, the evidence for such interactions with liver DNA in vivo is limited, (Recknagel et al., 1989 and Weber et al., 2003).

In this study, we used an in vivo model to explore the very early toxic events, particularly regarding mitochondria, occurring after CCl₄ administration. Inhibition of CCl₄ activation by the CYP2E1 inhibitor diethyldithiocarbamate (DDTC) and impairment of CCl₄-induced lipid peroxidation by antioxidants allowed us to establish a direct link between lipid peroxidation and mitochondrial alterations. Antibiotics, commonly used aminoglycosides, are nephrotoxic agents. Their nephrotoxicity is mainly attributed to induction of OS and depletion of antioxidant enzyme activities in kidney. Inducible nitric oxide synthase, nuclear factor kappa-B, nitrogen-activated protein kinase (iNOS/NFκB/p38MAPK respectively) pathway, OS taking place in this axis, is involved in gentamicin-induced

nephrotoxicity, (Tugcu et al. ,2006 and Ozbek et al. ,2009). The protective effect of anti oxidants and reactive oxygen scavenger agents against gentamicin-induced nephrotoxicity. Antineoplastic agents are commonly used for the treatment of metastatic cancers. Some of these are nephrotoxic, (Ozbek et al., 2010 and Maniu et al., 2011).Excess ROS production and depressed antioxidant defence mechanism are responsible for nephrotoxicity. Cisplatin is the well-known and commonly used antineoplastic and nephrotoxic agent. Other nephrotoxic anticancer agents are carboplatin, methotrexate, doxorubicin, cyclosporine, and adriamycin. Immunosuppressant such as sirolimus and cyclosporine leads to nephrotoxicity via OS, (Giustarini et al., 2009).

In this era, analgesics, especially paracetamol and acetaminophen (APAP), and nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used throughout the world. Paracetamol and APAP are nephrotoxic drugs. Several in vitro and in vivo studies showed that analgesics nephrotoxicity is caused by increased ROS in kidney, (Zhao et al, 2011) showed the increased ROS, nitric oxide, and MDA levels, together with depleted glutathione (GSH) concentration in the kidney of rats. However, rhein, Chinese herb, can attenuate APAP-induced nephrotoxicity in a dose-dependent manner, (Zhao et al., 2011).Some studies showed a significant increase in MDA and decreases in GSHPx, CAT, and SOD activities in APAP-treated rat kidneys. These findings support the induction of OS in rat kidney by APAP. Significant beneficial changes were noted in serum and tissue OS indicators in rats treated with strong antioxidant pineal hormone melatonin and curcumin, (Ilbey et al. ,2009 ; Cekmen et al. ,2009) ,reported increased OS and TNF-alpha production in rat tissues, (Ghosh et al. ,2010) ,reported that diclofenac (NSAID) leads to nephrotoxicity by increasing intrarenal ROS in rat kidney, and antioxidant, Nacetylcysteine, prevents kidney damage, (Efrati et al. ,2007). GSH is able to regenerate the most important antioxidants, Vitamins C and E, back to their active forms; it can reduce tocopherol radical of Vitamin E directly, or indirectly, via reduction of semidehydroascorbate to ascorbate. The capacity of glutathione to regenerate the most important antioxidants is linked with the redox state of the glutathione disulphide-glutathione couple (GSSG/2GSH), (Pastore et al. , 2003). Hesperidin is a flavanone glycoside named after the term 'Hesperidium', referring to citrus fruits which are the main source of hesperidin. Hesperidin and its aglycone are common dietary flavonoids due to being large compounds of citrus fruits (alongside naringenin) and especially the peels and pericarp, (Kanes et al, 1993).

There are inhibitory effects of hesperitin on two intestinal transporters, the OATP2B1 (Organic Acid Transporting Polypeptide 2B1) transporter and MRP2 (Multidrug Resistance Protein 2). OATP2B1 appears to be acutely inhibited with supplementation of hesperidin, whereas low doses of hesperidin over a few weeks appear to downregulate the MRP2 transporter .It is notable to know that the OATPs play a fundamental role in the transport of drugs across the cell membrane, particularly in the liver and kidney. In the liver, OATPs are expressed on the basolateral membrane of hepatocytes, transporting compounds into the hepatocyte for biotransformation (Price et al, 2006).

A 0.079% hesperidin suspension given to rats for eight weeks is able to increase the overall exposure (147%) and peak concentration (138%) to the drug pravastatin, (Shirasaka et al ., 2013) which is thought to be due to inhibition of the transport protein known as Multi-drug Resistance Protein 2 (MRP2) that mediate pravastatin efflux into the intestines after absorption, (Tamai , 2012) . There appear to be antioxidant effects in the brain where hesperidin reduces the increase in lipid peroxidation during cognitive damage, but this appears to be indirect through nitric oxide signalling (inhibition) rather than a direct antioxidant effect, (Olivenza et al. , 2000; McEwen, 2001; Alexaki et al., 2004 and Takeda et al., 2008). Damage of DNA is reduced by hesperidin (Sahu et al. ,2013).Hesperidin intake in diabetic rats appears to significantly but not fully reduce levels of the (vascular endothelial growth factors)VEGF and PKC β (Protein kinase c β), and it is thought that the reduction in signalling (from VEGF towards PKC β) causes a protective effect on the retinal membrane and reduces the progression of diabetic retinopathy, (Donnelly et. al , 2004 ; Liu et al. , 2008 ; Wang et al. , 2010 and Kumar et al. , 2012).

II. MATERIALS AND METHODS

This study was conducted on Thirty two male albino rats. Animals were obtained from the animal house of faculty of medicine, Al-Azhar University. Their weight ranged between 160-200 grams each at the beginning of the experiment. Rats were housed in four groups with 8 rats each in clean capacious macrolane cages under standard laboratory conditions, including good aerated room with suitable temperature ($25\pm 5^{\circ}\text{C}$), maintained at good light, standard rodent food and water were available.

CCL₄: El-Naser Pharmaceuticals chemical company, Egypt

Hesperidine (HDN): Sigma, Aldrich.

-Saline, El-Naser Pharmaceuticals chemical company, Egypt.

- Phosphate buffered saline, Hi-media- Lab. Pvt. Inc., USA.
- SOD kit: Biochemical Enterprise, Italy
- Malon-Di-Aldehyde: Biochemical Enterprise, Italy
- Glutathione reduced determination kit: Biochemical Enterprise, Italy
- ALT and AST determination kits: Centronic_Gmbh, Germany.
- Serum Creatinine determination kits: Diamond., USA.

In the present study, the animals were divided into the following groups. Each group consisted of 8 rats:

Group I : These animals received a vehicle for HDN (i.e. CarboxyMethylCellulose) by oral route for eight days and on 8 th day, they were administered the subcutaneous injection of olive oil).Tirkey(2005 ,

Group II: These animals received vehicle for 10 days and were challenged with CCl4 2 ml/kg/s.c. (40% v/v in olive oil) on 8th day (Mandal and Sinha, 2002)

Group III: These rats received only HDN 100 mg/kg/p.o. daily for 10 days CCl4+ HDN (100): Rats received HDN continuously for 8 days. On eight day just after HDN treatment they received CCl4 2ml/kg/s.c in olive oil. HDN was further continued for 2 more days. (Tirkey, 2005)

Group IV: These rats received only HDN 200 mg/kg/p.o. daily for 10 days CCl4+ HDN (200): Rats received HDN continuously for 8 days. On eight day just after HDN treatment they received CCl4 2ml/kg/s.c in olive oil. HDN was further continued for 2 more days.((Tirkey, 2005)

Forty-eight hours after the last CCl4 injection, rats were sacrificed and blood samples were collected, centrifuged and the serum from each animal was kept in epindorff tubes in the deep freezer at (-20°C) until analyzed for liver functions.

After animals were sacrificed livers were immediately excised, rinsed from blood in ice cold saline, blotted dry by filter papers. Small piece of each liver was fixed in 10% phosphate-buffered formalin for histological examination. About 0.5 gm of each liver was homogenized by ultra sonic homogenizer in 5ml ice-cold phosphate bufferd saline (PBS) to obtain ultimately10% (w/v) whole liver homogenate (Ezz et al., 2011 ;Fahmy and Hamdi, 2011). The homogenate was centrifuged at 3000 rpm for 15 min and the resultant supernatant was stored at -20°C until used for determination of reduced glutathione (GSH), malondialdehyde (MDA), superoxide dismutase (SOD) and hydroxyproline concentration.

Determination of liver function:

Determination of alanine aminotransferase (ALT) (IU/L): (Thomas , 1998)

Determination of aspartate aminotransferase (AST) (IU/L): (Thomas , 1998).

Determination of kidney function:

Determination of Serum Creatinine (mg/dL): (Murray, 1984)

Determination of hepatic reduced glutathione mg/g tissue: (Beutler, 1963).

Determination of hepatic superoxide dismutase U/g tissue: Nishikimi et al (1972 ,.

Determination of hepatic lipid peroxide (malondialdehyde) nmol/g tissue: (Sato, 1978)

III. RESULTS

Table1. Augmented results of all biochemical parameters in all groups.

| Groups | | GROUP I CONTROL-VE NO CCL4 NO HDN 8 rats | GROUP II CONTROL+VE CCL4 NO HDN 8 rats | GROUP III HESPEREDINE (100mg/kg) 8 rats | GROUP IV HESPEREDINE (200mg/kg) 8 rats |
|--------------------------------|---------------|--|--|--|---|
| Parameters | Mean ± S.E | 49.013±1.03 | 82.763±0.91 | 81.625±0.68 | 50.2±0.38 |
| Melondialdehyde (mg/tissue) | | | | | |

| | | | | | |
|---|------------|--------------|--------------|--------------|--------------|
| Glutathione (mg/tissue) | Mean ± S.E | 5.088±0.06 | 2.88±0.048 | 3.09±0.067 | 5.025±0.072 |
| Superoxide dismutase (mg/tissue) | Mean ± S.E | 107.888±0.56 | 89.688±0.45 | 90.863±0.26 | 107.013±1.77 |
| (AST) aspartate aminotransferase (IU/L) | Mean ± S.E | 48.725±0.47 | 163.875±2.99 | 111.375±1.78 | 71.375±1.71 |
| (ALT) alanine aminotransferase (IU/L) | Mean ± S.E | 38.5±0.76 | 87.875±1.46 | 57.375±1.28 | 46.5±0.94 |
| Serum Creatinine (dL) | Mean ± S.E | 0.864±0.058 | 1.063±0.082 | 1.024±0.039 | 0.936±0.09 |

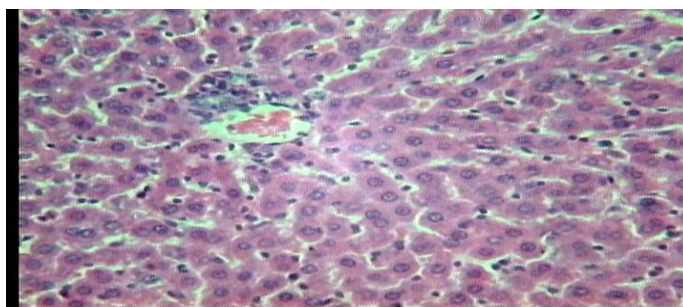


Fig1. Liver tissue of the (Group I control -ve) which were fed 5% carboxymethyl cellulose (as a vehicle) only for 10 days and were injected by olive oil S.C in the 8th day

- Normal liver tissue
- Normal architecture –normal rows
- No inflammatory cell infiltrate
- Normal cellular appearance
- Normal apparent nuclei

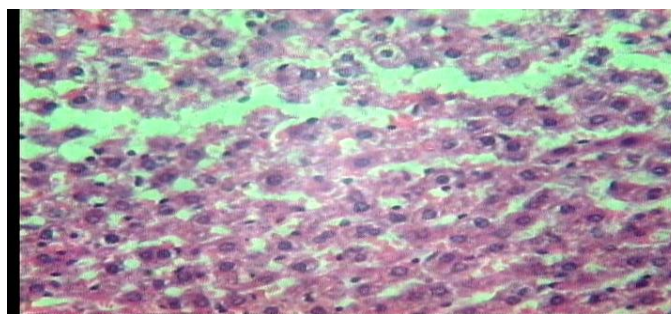


Figure2. Liver tissue of the (Group II control +ve) Which were fed 5% carboxymethyl cellulose (as a vehicle) only for 10 days and were injected by CCl₄ in olive oil(2ml/kg) S.C in the 8th day

- Extensive damage.
- Very sever vacuolation
- Inflammation cell infiltration
- Disruption of the lattice nature of hepatocytes and damaged hepatocyte cell membrane
- Irregular architecture (damaged sinusoids, rows and disintegrated central vein)
- Degenerated nuclei

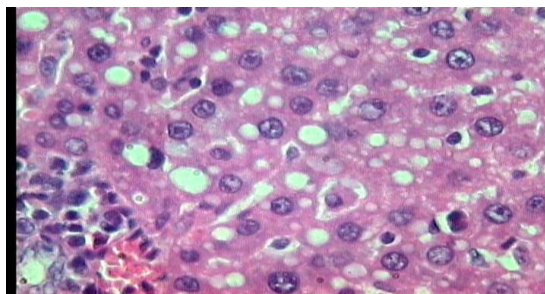


Fig3. Liver tissue of the (Group III treated with Hesperidine (HDN) as 100mg/kg in the vehicle for 10 days and were injected by CCl₄ in olive oil (2ml/kg) S.C in the 8th day .

- Presence of vacuolation but less than control positive group.
- More eosinophilic infiltration than control positive group.
- Better viability and less damage than control positive group.
- Nuclei are healthier than control positive group.
- Less disruption of the lattice nature of hepatocytes and less damaged hepatocyte cell membrane
- More regular architecture and rows than control positive.

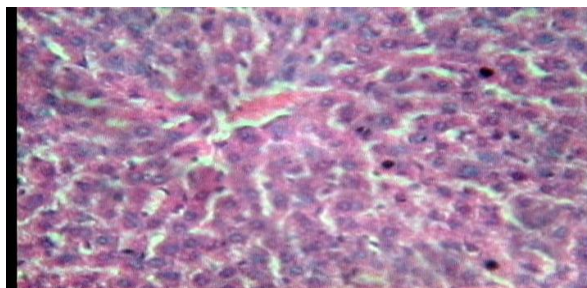


Fig4. Liver tissue of the (Group IV treated with Hesperidine (HDN) as 200mg/kg in the vehicle for 10 days and were injected by CCl₄ in olive oil (2ml/kg) S.C in the 8th day .

- Faded vacuolation (very mild)
- Architecture and rows are so close to normal.
- Normal viability
- Less infiltration by the inflammatory cells than treated groups by (HDN100)
- Normal nuclei and cell membranes
- Normal central vein and sinusoids.

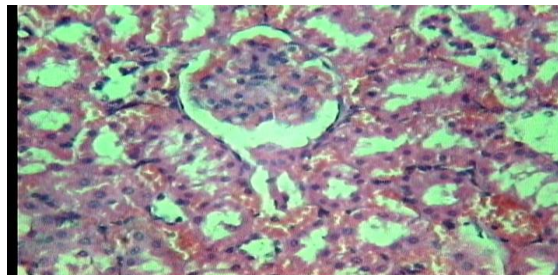


Fig5. Kidney tissue of the (Group I control –ve) which was fed 5% carboxymethyl cellulose (as a vehicle) only for 10 days and was injected by olive oil S.C in the 8th day

- Normal glomeruli and tuft of capillaries, intact Bowman capsule
- Normal tubular appearance
- Normal vasculature

- Normal viability
- No inflammatory cells infiltration

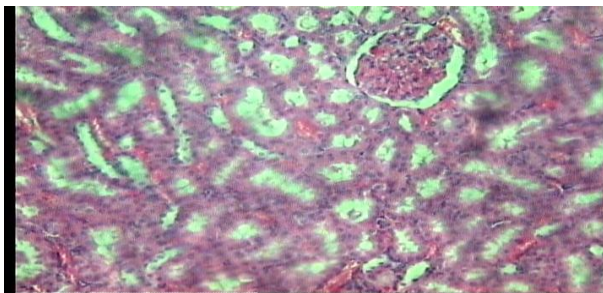


Fig6. Kidney tissue of the (Group II control +ve) which were fed 5% carboxymethyl cellulose (as a vehicle) only for 10 days and were injected by CCl_4 in olive oil (2ml/kg) S.C in the 8th day

- Marked vacuolation (extensive damage)
- Inflammatory cell infiltration (glomerular mainly)
- Disruption of the lattice nature of the cells and damaged cell membranes
- Damage is tubular more than glomerular. With slight obliteration of the tubules
- Degenerated nuclei.

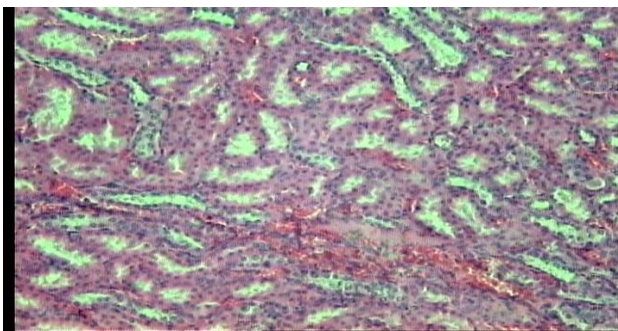


Fig7. Kidney tissue of the (Group III treated with Hesperedine (HDN) as 100mg/kg in the vehicle for 10 days and were injected by CCl_4 in olive oil (2ml/kg) S.C in the 8th day.

- Less vacuolation of the tubules than control positive group.
- Less Inflammatory cell infiltration
- More viable cells than control positive group.
- Tubules appear to be more regular than control positive group.

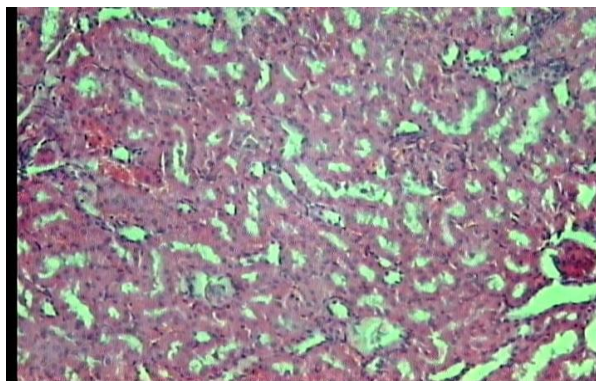


Fig8. Kidney tissue of the (Group IV treated with Hesperedine (HDN) as 200mg/kg in the vehicle for 10 days and were injected by CCl_4 in olive oil (2ml/kg) S.C in the 8th day .

- less vaculation in the tubules than in group III (HDN100)
- More viability of the cells than in group III (HDN100).
- More regular tubules than in group III (HDN100).
- Intact Bowman capsule
- It is so close to normal group

IV. DISCUSSION

In the present study, induction of acute hepatic toxicity and nephrotoxicity in Wistar male albino rats was done by s.c injection of CCl₄ 2 ml/kg/s.c. (40% v/v in olive oil) for a single dose of which is a well characterized model for acute hepatic toxicity and nephrotoxicity has been extensively performed and revealed microscopically in the liver as extensive damage, very severe vaculation, inflammatory cells infiltration, Irregular architecture (damaged sinusoids, rows and disintegrated central vein) and degenerated nuclei and in the kidney as vaculation, degenerated nuclei, obliteration of the tubules, inflammatory cell infiltration and disruption of the lattice nature of the cells and damaged cell membranes. These results are in agreement with the results obtained by Al-Qarawi et al, 2004 who reported the histopathological changes in acute hepatic toxicity, Montilla et al, 1990 who proved CCl₄ hepatotoxicity by LD₅₀ of CCl₄, the modification of Nembutal-induced sleep, the action on bile flow, serum transaminase and hepatic fatty acids levels and a histopathological study of liver tissue. Kodama and Oguchi, 1990 and Prakash et al, 2008, have also obtained similar results to our study on the effect of CCl₄ on hepatic and kidney architecture. Abdel Moneim and Mahmoud, 2013, who reported that CCl₄ induces nephrotoxicity which can be detected by estimation of oxidation and antioxidation components plus histopathological changes. Khan et al, 2009, noticed glomerular degeneration, tubular brush border loss, tubular dilatation, necrosis of epithelium and interstitial oedema in CCl₄ treated rats. The results of the present study are in disagreement with the results obtained by, Zimmerman et al, 1983 as they found an increased frequency of glomerulosclerosis, tubulointerstitial alterations and reduced renal mass only on long-term CCl₄ administration in rats. CCl₄ not only initiates lipid peroxidation but also reduces tissue GSH and SOD activities, and this depletion may result from oxidative modification of these proteins, (Augustyniak et al., 2005). CCl₄ intoxication can lead to alteration in gene expression and depletion of SOD and catalase levels in kidney and heart. Oxidative stress causes depletion of intracellular GSH, leading to serious consequences. CCl₄-induced early signs of hepatotoxicity could be mediated through two different mechanisms involving or not lipid peroxidation. Lipid peroxidation triggered mtDNA degradation and mitochondrial dysfunction but not other CCl₄-induced deleterious events such as hepatocyte swelling, abnormal expression of heme oxygenase 1(HO-1) and heat shock protein (Hsp70), and reduction of CYP2E1 mRNA levels, (Szymonik-Lesiuk et al., 2003). Kidney tissue has great affinity for CCl₄ because of the predominant presence of the cytochrome p450 in the cortex. Previous reports suggest that CCl₄ generates free radicals with the implication of pathological environment by damaging the integrity of cell membranes, elevating thiobarbituric acid reactive substances (TBARS) level with subsequent necrosis and affecting physical parameters of kidney such as urinary and serum profile (Sahreem et al., 2011).

In the present study, CCl₄ induces a severe hepatic damage as represented by markedly elevated levels of ALT and AST. These results are in agreement with the studies Alam et al, 2000; Mousa et al, 2004 and Prakash et al, 2008 who proved that administration of CCl₄ causes hepatotoxicity detected by increased levels of ALT and AST.

Usually, the extent of hepatic damage is assessed by the increased level of cytoplasmic enzymes (ALT and AST), thus leads to leakage of large quantities of enzymes into the blood circulation. This was associated by massive centrilobular necrosis, ballooning degeneration and cellular infiltration of the liver, (Shankar et al., 2008). In response to hepatocellular injury initiated by the biotransformation of CCl₄ to reactive radicals, "activated" Kupffer cells in liver respond by releasing increased amounts of active oxygen species and other bioactive agents, (El-Sisi et al, 1993) these products include conjugated dienes, lipid hydroperoxides, malonaldehyde-like substances, and other short-chain hydrocarbons, (Tom et al, 1984).

Reduced glutathione (GSH) is a major endogenous antioxidant which counterbalances free radical mediated damage. It is well known that GSH is involved in the protection of normal cell structure and function by maintaining the redox homeostasis, quenching of free radicals and by participating in detoxification reactions, (Pushpakiran et al., 2004).

Superoxide dismutase (SOD) an enzyme that catalyzes the dismutation of superoxide (O₂⁻) into oxygen and hydrogen peroxide. Thus, it is an important antioxidant defense in nearly all cells exposed to oxygen, (Shahid et al., 2012).

The results of the present study showed that, subcutaneous injection of CCl₄ lead to decreased hepatic reduced glutathione (GSH) level, superoxide dismutase (SOD) level and increased Malondialdehyde (MDA) level. These results are in agreement with the studies of Kang et al, 2001 who noticed that CCl₄ causes decreased hepatic reduced glutathione (GSH) level, superoxide dismutase (SOD) level. Manjrekar et al, 2008 who noticed that CCl₄ causes decreased hepatic reduced glutathione (GSH) level and increased Malondialdehyde (MDA) level. Siu-Po and Kam-Ming, 1996 who noticed that CCl₄ causes decreased hepatic reduced glutathione (GSH) level.

Pereira-Filho et al, 2008 claimed that hepatic malondialdehyde (MDA) levels were also highly significantly increased in CCl₄ treated group, showing an increased oxidative stress compared to control group. The increased MDA level suggests enhanced lipid peroxidation leading to tissue damage and failure of antioxidant defense mechanisms to prevent formation of excessive free radicals as described above and confirmed by, (George et al, 2002; Loki and Rajamohan, 2003 and Rajesh and Latha, 2004 and Kim et al 2010). The results of this present study are in disagreement with Stryjecka-Zimmer. et al , 2003 who claimed that change in antioxidant enzyme activities may be relevant to the ability of the liver and other investigated organs to cope with oxidative stress during CCl₄ poisoning No statistically significant changes in SOD and glutathione peroxidase (GPX) activities were observed in the liver after CCl₄ administration.

Oxidative stress in hepatotoxicity, resulting from increased generation of reactive oxygen species (ROS) and other reactive intermediates as well as by decreased efficiency of antioxidant defenses, actively contributes to excessive tissue remodeling (Ismail and Pinzani, 2009). ROS and other reactive mediators such as 4-hydroxynonenal (HNE) can be generated outside PMNLs, being released either by activated inflammatory cells or deriving from hepatocytes damaged by the specific etiological agent or conditions (Duffield et al., 2005). Indeed, oxidative stress, presumably by favoring mitochondrial permeability transition, is able to promote hepatocyte death (necrotic and/or apoptotic). In some of clinically relevant conditions, generation of ROS within hepatocytes may represent a consequence of an altered metabolic state (like in NAFLD and NASH), with ROS being generated mainly by mitochondrial electron transport chain or through the involvement of selected cytochrome P450 isoforms like cytochrome P2E1 (CYP2E1), (Tilg and Hotamisligil, 2006). Case control studies and various documented case reports increasingly establish that hydrocarbon solvents produce renal diseases in humans, (Ruprah et al, 1985).

To assess renal affection by detection of renal functions: Serum samples were assayed for serum creatinine, (Bhattacharya et al, 2005). The results of the present study showed that insignificant increase of Serum Creatinine in CCl₄ intoxicated group. The results of the present study are in agreement with the studies of Zimmerman et al , 1983 who did not report any rise in kidney functions levels even after chronic treatment of CCl₄ in nephrectomized rats , Ogawa et al ,1992 found an increased frequency of glomerulosclerosis and tubulointerstitial alterations in rats with reduced renal mass on CCl₄ administration thereby indicating nephrotoxicity only on long-term CCl₄ administration in rats. The results of the present study are in disagreement with Olagunjua et al, 2009 who noticed increase in kidney function in CCl₄-induced nephrotoxicity and Stephen et al, 2007 who reported that the nephrotoxicity can be detected by kidney functions tests. Renal sources for ROS are activated macrophages, vascular cells, and various glomerular cells. ROS may affect cells of the host organism, especially at sites of inflammation in addition to playing a role in the defense system against other agents. This effect plays a role in a variety of renal diseases such as glomerulonephritis and tubulointerstitial nephritis which can contribute to proteinuria and other conditions (Ichikawa et al., 1994).

The presence of inflammation is well documented factor influencing the development of oxidative stress in dialysis patients (Samouilidou and Grapsa, 2003). However the pathology related with renal function failure that is stimulated by CCl₄ remains controversial. As kidneys have an affinity against CCl₄, and as they contain predominantly, cytochrome p450 in the cortex, it is very possible that CCl₄ contributes a lot to nephrotoxicity, (Ogeturk et al., 2005).

The results of the present study showed that oral administration of hesperidine (100mg/kg) and (200mg/kg) significantly decrease the ALT and AST in CCl₄-treated rat and in the group of the dose 200mg/kg produces more decrease in ALT and AST. The results of the present study are in agreement with the study done by Ahmad et al, 2012 who proved that hesperidine ameliorates the hepatotoxicity-induced by acetaminophen, and this was detected by decrease in ALT and AST not only that but also he noticed that the acuity of toxicity is decreased gradually by increasing the dose of hesperidine similar to our results.

Balakrishnan and Menon, 2007 reported that administration of hesperidine to nicotine treated rats at different doses decreases these enzymes significantly but in dose-dependent manner. Anandan and Ramaswamy, 2012 reported protective effects of hesperidin (HDN 100 mg/kg) for 14 days against gentamicin (GEN 100 mg/kg) induced

hepatotoxicity for 8 days detected by decrease in ALT and AST. Park et al, 2012 reported that protective effects of hesperidin+ Curdlan (HDN+CDN 100 mg/kg) for 7 days against γ -radiation induced hepatotoxicity.

AST and ALT are the aminotransferase in liver cells. They are cytoplasmic in nature, but upon liver injury large quantities of these enzymes enter into the circulatory system due to altered permeability of membrane, centrilobular necrosis, degeneration, and reduced performance status of the liver. So the elevated serum ALT and AST are the most sensitive biomarkers used in the diagnosis of liver diseases (Pari and Kumar, 2002 and Gao et al., 2012).

CCl₄ induced a severe hepatic damage as represented by markedly elevated levels of ALT and AST coupled with a marked hepatic oxidative stress. (Tirkey. et al, 2005). Oxidative stress in hepatotoxicity, resulting from increased generation of reactive oxygen species (ROS) and other reactive intermediates as well as by decreased efficiency of antioxidant defenses, actively contributes to excessive tissue remodelling (Ismail and Pinzani, 2009). Hesperidin in combination with diosmin, shows a marked protective effect against inflammatory disorders, both in vivo and in vitro, possibly through a mechanism involving an inhibition of eicosanoid synthesis and/or antioxidant free radical scavenger activity (Jean and Bodinier, 1994).

The results of the present study showed that oral administration of Hesperidine (100mg/kg) causes insignificant decrease in Malondialdehyde (MDA) and insignificant increased hepatic reduced glutathione (GSH) and superoxide dismutase (SOD) levels.

These results of the present study are in agreement with the study done by Tirkey et al, 2005 who proved that oral administration of Hesperidine (100mg/kg) causes insignificant decrease in Malondialdehyde (MDA) and insignificant increased hepatic reduced glutathione (GSH) level and superoxide dismutase (SOD) level.

The results of the present study are in disagreement with the study done by Park et al, 2010 who observed protective effects of hesperidin+ Curdlan (HDN+CDN 100 mg/kg) for 7 days against γ -radiation induced hepatotoxicity, through significant decrease in Malondialdehyde (MDA) and significant increased hepatic reduced glutathione (GSH) level and superoxide dismutase (SOD) level. Anandan and Ramaswamy, 2012 observed protective effects of hesperidin but in gentamycin-induced hepatotoxicity, this was detected by significant decrease in Malondialdehyde (MDA) and significant increased hepatic reduced glutathione (GSH) level and superoxide dismutase (SOD) level.

The present study showed that oral administration of Hesperidine (200mg/kg) causes significant decrease in Malondialdehyde (MDA) and significant increase hepatic reduced glutathione (GSH) level and superoxide dismutase (SOD) level. These results are in agreement with the study done by (Xiao-min et al, 2011) who reported significant decrease in Malondialdehyde (MDA) and significant increased hepatic reduced glutathione (GSH) level and superoxide dismutase (SOD) level by studying the protective effect of Hesperidin on hepatotoxicity induced by cisplatin. **Wei and Jun, 2010** posted that HDN had protective effects on CCl₄-induced chemical liver injury. It was possibly related to removal of free radicals and inhibition of lipid peroxidation. HDN(250 and 500 mg/kg) could reduce the levels of MDA and significant increased hepatic superoxide dismutase (SOD) level. **Wei and Jun, 2010** also observed certain cytokines as IL-1 and TNF are inhibited by HDN (250 and 500 mg/kg) through decreasing mRNA expression. **Xiao-min et al, 2011 reported** that administration of hesperidin (300mg/kg p.o.) for 7 consecutive days had a remarkable protective effect on hepatotoxicity induced by cisplatin (5mg/kg, intraperitoneally for 5 consecutive days from the third day of hesperidine administration). The protective effect of hesperidin was possibly related to removal of free radicals and inhibition of lipid peroxidation produced by cisplatin intoxication. HDN (300mg/kg) could reduce the levels of MDA, significant increased hepatic superoxide dismutase (SOD) level and significant increased GSH.

Shrivastava, 2011 noticed that administration of hesperidin (HDN) (100mg/kg p.o.), for 7 days had a remarkable protective effect on Cardiotoxicity induced by single intraperitoneal injection of cyclophosphamide CP (200mg/kg body weight). The protective effect of hesperidin was possibly related to removal of free radicals and inhibition of lipid peroxidation produced by cyclophosphamide intoxication. HDN (100mg/kg) could reduce the levels of MDA, significant decreased LDH, CPK, ALT and AST. Also **(Tirkey et al, 2005 and Pradeep et al, 2008)** obtained similar results to our study on the effect of hesperidine on oxidants and antioxidants parameters.

Ko et al, 1995 reported that certain natural extracts containing antioxidants protect against the CCl₄-induced increased lipid peroxide levels and impairment in hepatic GSH status. Hepatic malondialdehyde (MDA) levels were also highly significantly increased in CCl₄ treated group, showing an increased oxidative stress compared to control group. The increased MDA level suggests enhanced lipid peroxidation leading to tissue damage and failure of

antioxidant defense mechanisms to prevent formation of excessive free radicals as described by (Pereira-Filho et al, 2008) and confirmed by (Kim et al, 2010).

Glutathione is an important intracellular antioxidant that also plays a role in the detoxification and elimination of potential carcinogens and toxins. Studies in animals have found that glutathione synthesis and tissue glutathione levels are significantly lower in aged animals than in younger animals, leading to decreased ability of aged animals to respond to oxidative stress or toxin exposure (Hagen et al., 2000).

Superoxide dismutase (SOD) catalyzes the destruction of the O₂⁻ free radical. ($2O_2^{\cdot-} + 2H^+ \longrightarrow O_2 + H_2O_2$). It protects oxygen-metabolizing cells against harmful effects of superoxide free-radicals (Petkau et al., 1975).

CCl₄ challenge significantly decreased the levels of SOD and catalase in liver, by alteration in gene expression and depletion of SOD and catalase levels (Stryjecka-Zimmer et al, 2003). Antioxidants are agents that inhibit or neutralize potentially harmful elements known as free radicals (Zielinska et al., 2001; Galati and O'Brien, 2004).

Flavonoids are naturally occurring polyphenolic compounds in plants that are thought to have positive effects on human health (Wahsha and Al-Jassabi, 2009). HDN administration ameliorates the increased level of lipid peroxidation after CCl₄ treatment, able to show improvement in the levels of endogenous antioxidant enzymes SOD and Improvement of hepatic GSH levels in HDN-treated rats in comparison to CCl₄ intoxicated rats, thereby this demonstrates the antioxidant effect of HDN (Turkey et al, 2005). Flavonoids are known to operate via direct scavenging of Reactive Oxygen Species (ROS), chelation of redox active transition metal ions, inhibition of enzymes involved in ROS production, regeneration of endogenous antioxidants (Fitzgeorge et al., 1994 ; Zielinska et al.,2001). It was found that Hesperidin has an important antioxidant activity in humans, it enhances the integrity of the blood vessels and it is found in great quantity in citrus fruits (lemons and oranges) (Tripoli et al., 2007).

Hesperidin and Silymarin are polyphenolic compounds which play an important role as antioxidants; they can directly quench free radicals, inhibit the enzymes of oxygen reduction pathways and also prevent the sequestration of transient metal actions (Chatterjee et al., 1999; Berker et al., 2007). The radical scavenging power of flavonoids is thought to be related to their structure. Flavonoids in general, scavenge oxidizing radicals preferentially via their B-ring catechol; in particular the ortho-dihydroxy structure in the B ring gives a higher stability during the formation of aroxyl radicals and participation in electron dislocation. The presence of the 3' and 5' OH functions together give a maximum radical scavenging potential: this property is found in both Silymarin and Hesperidin, (Markham, 1982; Joshi et al., 2005; Andersen and Markham, 2006).

The results of the present study showed that oral administration of hesperidine (100mg/kg) and (200mg/kg) significantly improves hepatic architecture microscopically in dose-dependent manner as the group of hesperidine administration (100mg/kg) shows slight improvement while the group of hesperidine administration (200mg/kg) shows no difference with control normal group. This result is in agreement with the study done by (Balakrishan et al ,2007) who observed that administration of hesperidine to nicotine treated rats at different doses improves hepatic architecture significantly in dose-dependent manner even in high doses ,he doesnot observe any morphological changes compared to normal. Ahmad et al, 2012 observed that Hesperidin alleviates acetaminophen induced toxicity in dose-dependent manner and in high doses he doesnot observe any morphological changes compared to normal. Also Bentli et al, 2013 obtained similar results to our study on the effect of hesperidine on hepatic architecture.

Our data showed that oral administration of hesperidine (100mg/kg) and (200mg/kg) significantly improves renal architecture microscopically in dose-dependent manner as the group of hesperidine administration (100mg/kg) showed slight improvement while the group of hesperidine administration (200mg/kg) showed no difference with control normal group. This result is in agreement with the histopathological study done by Anandan and Subramanian, 2012, who proved renal protective effect of hesperidin on gentamicin-induced acute nephrotoxicity. Balakrishan et al, 2006 administration of hesperidine to nicotine treated rats at different doses improves renal architecture significantly but in dose-dependent manner, and in high doses he doesnot observe any morphological changes compared to normal. Ahmad et al, 2012 observed that Hesperidin alleviates acetaminophen induced toxicity in dose-dependent manner and in high doses he doesnot observe any morphological changes compared to normal. Sahu et al, 2013 who reported that Hesperidin attenuates cisplatin-induced acute renal injury by decreasing oxidative stress, inflammation and DNA damage.

V. CONCLUSION

The present study suggested that the antioxidant properties of Hesperedine might be the main factor responsible for its strong protective action on CCl₄-induced hepatotoxicity and nephrotoxicity.

VI. REFERENCES

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