**Hepatotoxicity Implies chemical-driven liver damage induced by certain medicinal and other chemical agents**

Mohamad Sayyed Bakheet\(^1\)*, Haredy Hassan Haredy\(^2\), Ali Abdesalam\(^2\), Hoda Khalifa Abd alhaday sayed\(^3\)

\(^1\)Department of Biochemistry, Faculty of Medicine, Al-Azhar University, Assuit, Egypt,
\(^2\)Department of pharmacology, Faculty of Medicine, Al-Azhar University, Assuit, Egypt,
\(^3\)Department of physiology, Faculty of Medicine, Al-Azhar University, Assuit, Egypt.

**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 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. 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 Hesperidin 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 CCl\(_4\) 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 CCl\(_4\) but decreased insignificantly in rats treated with antioxidant HDN (200 mg/ kg/ day) and in rats treated with antioxidant HDN (100 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 Hesperidin 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.

**Keywords:** Hepatotoxicity, CCl\(_4\), HDN, Antioxidant, Hesperidin.

**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).

*Corresponding Author Email: sayyed_2006@yahoo.com*
Mitochondria are prominent targets for the hepatotoxicity 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 peroxynitrite. 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). 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).

Immunohistochemical 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 CCI4 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. CCI4 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, nitorgen-activated protein kinase (iNOS/NFxB/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 metastastic 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 through 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, (Taiami, 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 PKCβ (Protein kinase cβ), and it is thought that the reduction in signalling (from VEGF towards PKCβ) 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).

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±5°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 1: 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 buffered saline (PBS) to obtain ultimately 10% (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: (Satoh, 1978)

RESULTS AND 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. (Table 1 and figure 1 to 8) 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
Table 1. Augmented results of all biochemical parameters in all groups

| Parameters                  | GROUP I CONTROL-VE NO CCL4 NO HDN | GROUP II CONTROL+VE CCL4 NO HDN | GROUP III HESPEREDINE (100mg/kg) | GROUP IV HESPEREDINE (200mg/kg) |
|-----------------------------|-----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Melondialdehyde (mg/tissue) | Mean ± S.E 49.013±1.03             | Mean ± S.E 82.763±0.91            | Mean ± S.E 81.625±0.68            | Mean ± S.E 50.2±0.38             |
| Glutathione (mg/tissue)     | Mean ± S.E 5.088±0.06              | Mean ± S.E 2.88±0.048             | Mean ± S.E 3.09±0.067             | Mean ± S.E 5.025±0.072            |
| Superoxide dismutase (mg/tissue) (AST) | Mean ± S.E 107.888±0.56 | Mean ± S.E 89.688±0.45             | Mean ± S.E 90.863±0.26            | Mean ± S.E 107.013±1.77           |
| aspartate aminotransferase (IU/L) (ALT) | Mean ± S.E 48.725±0.47 | Mean ± S.E 163.875±2.99            | Mean ± S.E 111.375±1.78           | Mean ± S.E 71.375±1.71            |
| alanine aminotransferase (IU/L) | Mean ± S.E 38.5±0.76              | Mean ± S.E 87.875±1.46             | Mean ± S.E 57.375±1.28            | Mean ± S.E 46.5±0.94              |
| Serum Creatinine (mg/dL)    | Mean ± S.E 0.864±0.058             | Mean ± S.E 1.063±0.082             | Mean ± S.E 1.024±0.039            | Mean ± S.E 0.936±0.09             |

Figure 1. 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
Figure 2. 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 severe vaculation
- Inflammatory 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

Figure 3. 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 vaculation 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.
Figure 4. 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 vaculation (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.

Figure 5. 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
Figure 6. 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 CCl₄ in olive oil (2ml/kg) S.C in the 8th day
- Marked vaculation (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

Figure 7. Kidney 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.
- Less vaculation 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.
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 (Sahreen 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 and increased Malondialdehyde (MDA) 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 decreased efficiency of antioxidant defenses, actively contributes to excessive tissue remodeling (Ismail and Pinzani, 2009).ROS and other reactive mediators such as 4-hydroxyynonalen (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 Olagunja 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 hesperedine (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 hesperedine 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 hesperedine similar to our results.

Balakrishnan and Menon, 2007 reported that administration of hesperedine 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+ Curdian (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 hesperedine 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 Cardiototoxicity 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 hesperedine 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 $\text{O}_{2}^{-}$ free radical. 

\[ 2\text{O}_{2}^{-} + 2\text{H}^{+} \rightarrow \text{O}_{2} + \text{H}_{2}\text{O}_{2} \]  

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 (Tirkey 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 hesperedine (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 histopathological study done by Anandan and Subramanian, 2012, who proved renal protective effect of hesperidine on gentamicin-induced acute nephrotoxicity. Balakrishan et al, 2006 administration of hespredened 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.Als0 Bentli et al. 2013 obtained similar results to our study on the effect of hespredened on hepatic architecture.

Our data showed that oral administration of hesperedine (100mg/kg) and (200mg/kg) significantly improves renal architecture microscopically in dose-dependent manner as the group of hesperedine administration (100mg/kg) showed slight improvement while the group of hesperedine 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 hesperidine on gentamicin-induced acute nephrotoxicity. Balakrishan et al, 2006 administration of hesperedine 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. Sahu et al. 2013 who reported that Hesperidin attenuates cisplatin-induced acute renal injury by decreasing oxidative stress, inflammation and DNA damage.

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

REFERENCES
Abajo FJ, Montero D, Madurga M, Garcia Rodriguez LA (2004). “Acute and clinically relevant drug-induced liver injury: a population basedcase–control study”. Br J Clin Pharmacol. 58: 71–80.
Abdel Moneim AE, Mahmoud SM (2013). “The Protective Effect of Pomegranate (Punica granatum) Juice against Carbon Tetrachloride-Induced Oxidative Stress in Brain Tissue of Adult Male Albino Rats”. Life Sci J,10(1):151-158.
Abdel-Raheem IT and Abdel-Ghany AA (2009). “Hesperidin alleviates doxorubicin-induced cardio toxicity in rats”. J Egypt Natl Canc Inst. 21(2):175-84.
Abraham P, Wilfred G, Cathrine (1999). “Oxidative damage to the lipids and proteins of the lungs, testis and kidney of rats during carbon tetrachloride intoxication”. Clin Chim Acta, 289:177-179.
Agency for Toxic Substances and Disease Registry (ATSDR) , 2003 Aguilaniu H, Gustafsson L, Rigoulet M, Nyström T (2003). “Asymmetric inheritance of oxidatively damaged proteins during cytokinesis”. Science, 299.: 1751–1753.
Ahmad ST, Arjumand W, Nafoes S, Seth A, Ali N, Rashid S, Sultana S (2012). “Hesperidin alleviates acetaminophen induced toxicity in Wistar rats by abrogation of oxidative stress, apoptosis and inflammation”. Toxicol Lett. Jan 25;208(2):149-61.
The Quality of Efficacy of hesperidin against Synthetic LX. Br J Pharmacol. 1998, 155-165.

Hesperidin inhibits ovariectomized Angioloy. 45, 554, McKillip 2008.

Phenolic factors and liver histology in Hesperedin promotes MyoD 2012.

H-12, 55–80, 20th Edition, W.B. Saunders Company, 2008.

Ilbey YO, Ozbek E, Cekmen M (2009). "Melatonin prevents Huerta 2009.

Horst D, Grace N, Le Compte P (1980). "Prolonged cholestasis and Horcajada MN, Habauzit V, Trzeciakiewicz A, Morand C, Gil Henry J, John B (2001). "Clinical Diagnosis and Management by

Henry J (1974). "Clinical Diagnosis and Management by Laboratory Methods". W.B. Saunders and Co, Philadelphia, PA. p 361

Henry J, John B (2001). "Clinical Diagnosis and Management by Laboratory Methods", 20th Edition, W.B. Saunders Company, Philadelphia.

Hinson JA, Michael SL, Ault SG, Pumford NR (2000). "Western blot analysis for nitrotyrosine protein adducts in livers of saline-treated and acetylated-menadione-treated mice". Toxicol. Sci. 53: 467-476

Hollingsworth, B. (1974). "Clinical Diagnosis and Management by Laboratory Methods". W.B. Saunders and Co, Philadelphia, PA. p 361

Hart SG, Cartun RW, Wyand DS, Khairallah EA, Cohen SD (1995). "Hepatotoxicity associated with sulfasalazine in inflammatory arthritis: a case series from a local surveillance of serious adverse events". BMC Musculoskelet Disord. 9:48

Johnson S, Chan J, Bennett C (2002). "Hepatotoxicity after prophylaxis with a nevirapine-containing antiretroviral regimen". Ann Intern Med. 137: 146-147.

Jones DP, Carlson JL, Mody VC, Cai JY., Lynn MJ, Sternberg P (2000). "Redox state of glutathione in human plasma". Free Radic. Biol. Med. 28, 625-632

Joseph SB, McKilligen E, Pei L, Watson MA, Collins AR, Lafitte B, Chen M, Noh G, Goodman J, Haggen GN, Tran J, Tippin TK, Wang X, Lusis AJ, Hseuh WA, Law RE, Collins JL, Willson TM, Tontonoz P (2002). "Synthetic LXR ligand inhibits the development of atherosclerosis in mice". Proc Natl Acad Sci USA. 99(11):7604-9.

Joshi G, Sultana R, Tangpong J, Cole MP, St Clair DK, Vore M, Estus S, Butterfield DA (2005). "Free radical mediated oxidative stress and toxic side effects in brain induced by the anti cancer drug adriamycin: Insight into chemobrain". Free Radical Research. 39(11): 1147-1154.

Kadiska MB, Gladen BC, Baird DD, Geroile D, Graham LB (2005). "Biomarkers of oxidative stress study II: are oxidation products of lipids, proteins, and DNA markers of CCI4 poisoning" Free Radical Biology & Medicine.38: 698–710

Kalpana KB, Devipriya N, Srinivasan M, Menon VP (2009). "Investigation of the antiallergic and antiproliferative efficacy of hesperidin against gamma-radiation induced cellular damage in cultured human peripheral blood lymphocytes". Mutat Res. 676(1-2):54-61.

Kanda M, Ibara Y, Murata H (2006)."Glutaredoxin modulates platelet-derived growth factor-dependent cell signaling by regulating the redox status of low molecular weight protein- tyrosine phosphatase". Journal of Biological Chemistry, 281: 28518–28528.

Kanes K, Tisselat B, Berow H, M. Vandercook C (1993). "Phenolic composition of various tissues of rutaceae species" Phytochemistry 1993 //, 32: 967–974

Kang JO, Kim SJ, Kim H (2001). "Effect of astaxanthin on the hepatotoxicity, lipid peroxidation and antioxidative enzymes in the liver of CCI4 treated rats" Methods Find Exp Clin Pharmacol. Mar;23(2):79-84.

Kaplowitz N (2000). "Mechanisms of liver cell injury". J Hepatol. 32:39–47.

Kaplowitz N (2002). "Biochemical and cellular mechanisms of toxic liver injury". Semin Liver Dis.22:137–144.

Kaplowitz N (2002). "Drug-induced liver disorders: introduction and overview".In: Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. NewYork: Marcel Dekker. 1–13.

Kaplowitz N. (2004). "Drug-induced Liver Injury" Clinical Infectious Diseases, 38(Suppl 2):S44–8

Kaplowitz N, DeLeve LD (2002). "Mechanisms of cell death and relevance to drug hepatotoxicity". In: Drug-induced liver disease, eds. New York: Marcel Dekker, p85–95.
Kaster MP, Budni J, Santos AR, Rodrigues AL (2007). "Pharmacological evidence for the involvement of the opioid system in the antiedgpressant-like effect of adenosine in the mouse forced swimming test." Eur J Pharmacol. 576(1-3):91-8.

Katsoinos P, Vasilidou T, Xiarchos P (2000). "Ursodeoxycholic acid (UDCA) for the treatment of amoxyclim-clavulanate pneumonia (Augmentin) -induced intra-hepatic cholestasis: Report of two cases". Eur. J. Gastroenterol. Hepatol. 2000, 12: 365-368.

Kawaguchi K, Mizuno T, Aida K, Uchino K (1997). "Hesperidine as an inhibitor of lipase form porcine pancreas and Pseudomonas". Biocat Biotechnol Biochem. 61:102-104.

Kawai Y, Nakao T, Kunimura N, Kohda Y, Gembia M (2006). "Relationship of intracellular calcium and oxygen radicals to cisplatin-related renal cell injury". Journal of Pharmacological Sciences. 100: 65 – 72.

Khan MR, Rizvi W, Khan GN, Khan RA, Shaheen S (2009). "Carbon tetrachloride-induced nephrotoxicity in rats: protective role of Digera muricata". J Ethnopharmacol. Feb 25;122(1):91-9.

Kinh RA, Khan MR, Sahleen S (2012). "CCl4-induced hepatotoxicity: protective effect of rutin on p53, CYP2E1 and the antioxidative status in rat" BMC Complementary and Alternative Medicine. 12:178.

Kim HY, Kim JK, Choi JH, Jung JY, Oh WY, Kim DC, Lee HS, Kim YS, Kang SS, Lee SH, Lee SM (2010). "Hepatoprotective effect of pinosylvin on carbon tetrachloride-induced hepatic damage in mice". J. Pharmacol. Sci. 112(1):105-112.

Kinteringham NM, Centenery Int. 60:266-71.

Klasesen CD, Liu J, Diwan BA (2009). "Metallothionein protection of cadmium toxicity". Toxicol Appl Pharm. 2009 ; 238:215-20.

Knobies S, Uetrecht J, Shear N (2000). "Idiosyncratic drug reactions: the reactive metabolite syndrome". Lancet.356:1587–91.

Ko KM, Ip SP, Poon MK, Wu SS, Che CT, Ng KH, Kong YC (1995). "Effects of S lignan from Fructus indirubus extract on hepatic glutathione status in rats: protection against carbon tetrachloride toxicity". Planta Med. 61: 134 - 7.

Ko WC, Shih CM, Lai YH, Chen JH, Huang HL (2004). "Inhibitory effects of flavonoids on phosphodiesterase isoforms from guinea pig and their structure-activity relationships". Biochem Pharmacol. 68(10):2087-94.

Kodama K, S5Guchi K, 5Tsuji M (1990). "Protective effect of S-adenosyl-l-methionine against CCl4-induced hepatotoxicity in cultured hepatocytes". Jpn J Pharmacol.52(2):209-14.

Kodner CM, Kudrimoti A (2003). "Diagnosis and management of acute intestinal ischemia". Am Fam Physician. 67(12):2527-2534.

Koo DR (1992). "Oxidative and reductive metabolism by cytochrome P4502E1". FASEB J. 1992; 6: 724–730.

Kramer JM, Furst DE, Weintel MB, Blotner SD (1996). "Significant changes in serum markers across human histological biopsy grades: Prospective analysis of 3 cohorts receiving metotrexate therapy for rheumatoid arthritis". J. Rheumatol. 23: 459-461.

Krogholms KB, Bredsford L, Knuthsen P (2010). "Relative bioavailability of the flavonoids quercetin, hesperitin and naringenin given simultaneously through diet". Eur J Clin Nutr. 64:432-435.

Kucuktu E, Kaster MP, Budni J, Santos AR, Rodrigues AL (2007). "Postulated carbon tetrachloride mode of action: a review". J Environ Sci Health C 25: 185.

Kuo AL, Rajamohan T (2003). "Hepatoprotective and antioxidant effect of tender coconut water on Carbon tetrachloride induced hepatotoxicity in rat". Indian J Biochem Biophys. 40(5):354-7.

Loscalzo LM, Loscalzo LM, Wasowski C, Paladini AC, Marder M (2008). "Oxidative stress in human populations: a study of oxidative stress and its contribution to the development of cancer and cardiovascular disease". J. Pharmacol. Sci. 112(1):105-112.

Luo GL, Luo W, Wu SS, Che CT, Ng KH, Kong YC (1995). "Effects of s lignan from Fructus indirubus extract on hepatic glutathione status in rats: protection against carbon tetrachloride toxicity". Planta Med. 61: 134 - 7.

Liu J, Yu CC, Lin-Tan D and Ho HH (2001). "Lead chelation therapy and urea excretion in patients with chronic renal diseases and gout". Kidney International. 59:259-61.

Liu L, Shan S, Zhang K, Ning ZQ, Lu XP, Cheng YY (2008). "Naringenin and hesperetin, two flavonoids derived from Citrus aurantium up-regulate transcription of adiponectin". Phytother Res. 22(10):1400-3.

Loeper J, Descatoire V, Maurice M (1990). "Presence of functional cytochromeP450 on isolated rat hepatocyte plasma membrane". Biochem Pharmacol. 40: 2203-2207.

Loki AL, Rajamohan T (2003). "Hepatoprotective and antioxidant effect of tender coconut water on Carbon tetrachloride induced hepatotoxicity in rat". Indian J Biochem Biophys. 40(5):354-7.

Loscalzo LM, Wasowski C, Paladini AC, Marder M (2008). "Oxidative stress in human populations: a study of oxidative stress and its contribution to the development of cancer and cardiovascular disease". J. Pharmacol. Sci. 112(1):105-112.

Loscalzo LM, Yow TF, Wasowski C, Chebib M, Marder M (2011). "Hesperidin induces antioxidant effects in mice and its aglycone, hesperitin, binds to μ-opioid receptor and inhibits GIRK1/2 currents". PharmacoB Pharm Biol. 99(3):333-41.

Luciani P, Deledda C, Rosati F, Benvenuti S, Cellai I, Dichiara F, Morello M, Vannelli GB, Danza G, Serio M, Peri A (2008). "Seladine-1 is a fundamental mediator of the neuroprotective effects of estrogen in human neuroblast long-term cell cultures". Endocrinology. 149(9):4256-66.

Mehmood-Rahman R, Ng JC, Naidu R (2009). "Chronic exposure of arsenic via drinking water and its adverse health impacts on humans". Environ Geochem Health 2009, 31:189-200.

Manach C, Manach C, Williamson G, Morand C, Scalbert A, Rémésy C (2005). "Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies". Am J Clin Nutr. 2005 , 81:230S–42S.

Manach C, Morand C, Gil-Izquierdo A, Bouteloup-Demange C, Re’mey’s C (2003). "Bioavailability in humans of the flavonones hesperidin and narirutin after the ingestion of two doses of orange juice". Eur J Clin Nutr. 2003.57: 235–242.

Mandal AK, Sinha J, Mandal S, Mukhopadhyay S, Das N (2002). "Targeting of liposomal flavonoid to liver in combating hepatocellular oxidative damage". Drug Deliv 9:181-185.

Manibasun MK, Odin M, Eastmond DA (2007). "Postulated carbon tetrachloride mode of action: a review". J Environ Sci Health C 25: 185.

Markrejak AP, Jisha V, Bag PP, Adhikari B, Pai MM, Hegde A, Nandini M (2008). "Effect of Phyllanthus niruri Linn. treatment on liver, kidney, and brain in rat against CCl4 induced hepatotoxic rats". Indian J Exp Biol. 46(7):514-20.

Mark B, Brent T, Katherine K, Carl V (1996). "Survey of phenolic compounds produced in citrus" In Technical Bulletin, 158: no 1856.

Markham KR (1982). "Techniques of Flavonoid identification".
Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davron JT, Steven HB, Timothy M, Reisch J (2002). “Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States”. Ann Intern Med 137, 1954.

Ozbek E, Ilibey YO, Ozbek M, Simsek A, Cekmen M, Somay A (2009). “Melatonin attenuates unilateral ureteral obstruction-induced renal injury by reducing oxidative stress, iNOS, MAPK, and NF-kB expression”. Journal of Endourology 2009, 23:1165–1173.

Ozbek E, Ilibey YO, Simsek A, Cekmen M, Mete F, Somay A (2010). “Rosiglitazone, peroxisome proliferator receptor gamma agonist, ameliorates gentamicin-induced nephrotoxicity in rats”. International Urology and Nephrology. 2010, 42:579–587.

Padma VV, Suja V, Shyamala DCS (1998). “Hepatoprotective effect of Liv-52 on antidepressic drug-induced hepatotoxicity in rats”. Fitoterapia 69(6):520-522

Palmer BF (2002). “Renal dysfunction complicating the treatment of hypertension”. N Engl J Med 2002, 347(16):1256-1261.

Pari L, Kumar NA (2002). “Hepatoprotective activity of Moringa oleifera on carbon tetrachloride induced liver damage in rats”. J. Med. Food. 5 (3), 171–177.

Park SH, Pradeep K, Ko KC, Choi MH, Kang JA, Chung YJ (2012). “Hesperidin and Curdian treatment ameliorates γ-radiation induced cellular damage and oxidative stress in the liver of Sprague-Dawley rats”. Journal of Medicinal Food 2012, 15(5):419-27.

Pastore A, Federici G, Bertini E, Piemonte F (2003). “Analysis of glutathione:implication in redox and detoxification”. Clin. Chim. Acta. 333:19–39.

Perazella MA (1999). “Crystal-induced acute renal failure”. Am J Med. 106(4):459-465.

Perazella MA (2003). “Drug-induced renal failure: update on new medications and unique mechanisms of nephrotoxicity”. Am J Med Sci. 325(6):349-362.

Perazella MA (2003). “Drug-induced nephropathy: an update”. Expert Opin Drug Saf. 4(4):689-706.

Perche O, Vergnaud-Gauduchon J, Morand C, Dubray C, Mazur A and Vasson MP (2013). “Orange juice and its major polyphenol hesperidin consumption do not induce immunomodulation in healthy well-nourished humans”. Clin Nutr. pii: (13)S0261-S614.

Pereira-Filho G, Ferreira C, Schwengber A, Marroni C, Zettler C and Marroni N (2008). “Role of N-acetylcysteine on fibrosis and oxidative stress in cirrhotic rats”. Arg Gastroenterol. 45(2):156-62.

Petersen JJ, Dwyer JT, Beecher GR, Bhagwat SA, Gebhardt SE, Haytowitz DB, Holdenc SE, Williams & Wilkins p371

Petrčuk A, Chelack A, Pleskach S, Meeker B, Brady C (1975). “Radiation protection of endothelial cells from Superoxide Dismutase”. Biochemistry 19: S66

Pham PT, Peng AW, Wilkinson AH (2000). “Cycloporsine and tacrolimus associated thormbotic microangiopathy”. Am J Kidney Dis. 36:844–850.

Pham T-V, Lu S, Kaplowitz N (1997). “Acetaminophen hepatotoxicity”. In: Taylor MB, ed. Gastrointestinal emergencies. 2nd ed. Baltimore: Williams & Wilkins p371-88

Pisoni R, Ruggenenti P, Remuzzi G (2001). “Drug-induced thrombotic microangiopathy: incidence, prevention and management”. Drug Saf. 24(7):491-501.

Pizzol F, Morera JC (2007). “Protective effects of Passiflora alata against carbon tetrachloride induced oxidative liver damage in rats”. Int. J. Pharma. 26(6):559-66.

Pommereau F, Moreira JC, Bessière J, Bessière M (2007). “Kidney injury markers in patients with multi-organ failure at 17 tertiary care centers in the United States”. Ann Intern Med. 147(4):290-4.

Porzialek WC, Vaidya VS, Liu J, Waalkes MP, Edwards JR, Lamar PC, Bernard AM, Dumont X, Bonventre JV (2007). “Kidney injury molecule-1 is an early biomarker of cadmium nephrotoxicity”. Kidney Int. 72:985-93.

Pryor WA, Squadrato GL (1995). “The chemistry of peroxynitrite: A product from the reaction of nitric oxide with superoxide”. Am. J. Physiol. 1995, 268: L699–L722

Pushpakiran G, Mahalakshmi K, Anuradha CV (2004). “Protective effects of taurine on glutathione and glutathione-dependent enzymes in ethanol-fed rats. Pharmacie. 59(11):869-872

Quintieri L, Palatini P, Moro S, Florenani M (2011). “Inhibition of cytochrome P450 2C8-mediated drug metabolism by the flavonoid diosmetin”. Drug Metab Pharmacokinet. 26(5):569-65.

Raghavendra M, Vidya MJ (2013). “Functions of kidney & artificial kidneys” International Journal Of Innovative Research In Electronics, Electrical, Instrumentations And Control Engineering 2013. Vol. 1, Issue 1

Rajesh M G and Latha M S (2004). “Protective activity of Glycyrrhiza glabra Linn. on carbon tetrachloride-induced peroxidative damage: " Indian J Pharmacol. 36:284-7.

Recknagel RO, Glendek EA Jr, Dolakka JA, Waller RL (1989). “Mechanisms of carbon tetrachloride toxicity Pharmacol”. Ther. 1989, 43:139–154

Reichie FM, Conzen PF (2003). “Halogenated inhalational anesthetics”.Best Practice & Research Clinical Anaesthesiol.2003, 17: 29-46.

Reimund E, Ramos A (1994). “Niacin-induced hepatitis and thrombocytopenia after 10 years of niacin use”. J Clin Gastroenterol. 18: 270–271

Reynolds ES, Fariish HH, Moslen MT (1984). “Relationship between the pharmacokinetics of Carbon tetrachloride conversion to Carbon dioxide and chloroform and liver injury” Arch.Toxicol. 1984 7(Suppl):303-306.

Rhoden EL, Pereira-Lima L, Kailil AN, Lucas ML, Mauri M, Menti E, Rhoden CR, Pereira-Lima J, Zettler CG, Belló-Klein A (2000). “Effects of ischemia and reperfusion on oxidative stress in hepatic cirrhosis induced by carbon tetrachloride in rats”. Kobe J Med Sci. Aug;46(4):171-80.

Richter C, Gogvadze V, Laffranchi R (1995). “Oxidants in mitochondria: from physiology to diseases”. Biochimica et Biophysica Acta 1271; 67–74

Rizza S, Muniyappa R, Iantorno M, Kim JA, Chen H, Pullikotil P, Senese N, Tesauro M, Lauro D, Cardillo C, Quon MJ (2011). “Citrus polyphenol hesperidin stimulates production of nitric oxide in endothelial cells while improving endothelial function and reducing inflammatory markers in patients with metabolic syndrome”. J Clin Endocrinol Metab. 96(5):E782-92.

Robert BM, Wu TJ, Bucci J, Lister RW, Warbritton AR, McAra TE, Pumford NR, Hinson JA (1991). “Immunochemical localization and quantification of the 3-(cystein-S-yl)-acetaminophen protein adduct in acetaminophen hepatotoxicity”. Am. J. Pathol. 138, 359–371.

Robin MA, Le Roy M, Descauteux V (1997). “Plasma membrane cytochromeP450 as neuroantigens and autoimmune targets in drug-induced hepatitis”. J Hepatol 26(1Suppl):23–30.

Rodicio, R, Prodi G, Grilli S (1973). “In vivo and in vitro binding of carbon tetrachloride with nucleic acids and proteins in rats and mouse liver”. Int J Cancer. 11:419–425

Rodman JS, Deutsch DJ, Gutman SI (1976). “Myelid dopa hepatitis. A mechanism and management”. Postgrad Med J. 69(811):333-336.

Roppert J (2001). “Drug-induced acute interstitial nephritis”. Kidney Int. 60(2):804-817

Rudnicky MA, Schnegelsberg PN, Stead RA, Braun T, Arnold HH, Jaenisch R (1993). “Moxy or Myl-5 is required for the formation of skeletal muscle”. Cell, 75(7):1351-9.

Rudnicky M, Silveira MM, Pereira TV, Oliveira MR, Regnato FH, Dal-Pizzol F, Moreira JC (2007). “Protective effects of Passiflora alata extract pretreatment on carbon tetrachloride induced oxidative damage in rats”. Food Chem. Toxicol. 45: 565–661.

Ruprah H, Mant TGR, Flanagan RJ (1995). “Acute carbon tetrachloride poisoning in 19 patients:implications for diagnosis and treatment”. Lancet.1995, 1: 1027-1029.

Coneard AM, Dumont X, Bonventre JV (1993). "Journal of Medicine. Churchill & form and liver injury" Arch,Toxicol. 1984
Russo J, Hasan Laraeef M, Balogh G, Guo S, Russo IH (2003). "Estarogens and its metabolites are carcinogenic agents in human breast epithelial cells". J Steroid Biochem Mol Biol. 87(1):1-25.

Ryter SW, Kim HP, Hoetzl A, Park JW, Nakahira K, Wang X, Choi AM (2007). "Mechanisms of cell death in oxidative stress". Antioxid. Redox Signal. (9): 49-89.

Sahreen S, Siddiq P, Shah NA, Khan MR, Khan RA (2013). "Modulation of carbon tetrachloride-induced nephrotoxicity in rats by n-hexane extract of Sonchus asper". Toxicol Ind Health 2013 P80-90 doi: 10.1177/0748237313485885

Sahu BD, Kuncha M, Sindhura GJ and Sistla R (2013). "Hesperidin attenuates cisplatin-induced acute renal injury by decreasing oxidative stress, inflammation and DNA damage". Phytomedicine. 20(5):453-60.

Sakurai K, Cederbaum AI (1998). "Oxidative stress and cytotoxicity induced by ferric-nitroliotriacetate in HepG2 cells expressing CYP 2E1". Mol. Pharmacol. 54: 1024–1035.

Samoulidou EC, Grabpa EJ (2003). "Oxidative stress markers and creatinine protein in end-stage renal failure patients on dialysis". Urol Nephrol (35): 393–7.

Sato N, Seiwa C, Uruse M, Yamamoto M, Tanaka K, Kawatika T, Komatsu Y, Yasukawa A, Takao M, Kudo C, Hasegawa A, Ishige A, Watanabe K, Asou H (2011). "Administration of chini, a component of the herbal medicine ninjin-youi-to, reverses age-induced demyelination". Evid Based Complement Alternat Med. Article ID 616029.

Satoh K (1978). "Serum lipid peroxide in cerebrovascular disorders determined by a new colorimetric method". Clinical Chemical Acta. 90,37.

Scarborough H (1940). "Deficiency of Vitamin C and Vitamin P in Man". The Lancet. -%-%.: 634 – 647.

Schetz M, Dasta J, Goldstein S and Golper T (2005). "Drug interactions of the angiotensin-converting enzyme inhibitors: a review of mechanisms of action and clinical implications". Curr Opin Crit Care. 11(6):555-665.

Schmitz G, Kelly KJ (2007). "Pathophysiology of nephrotic syndrome". Pathobiology. 67(5-6):236-40.

Schneick R, Kelly KJ (2007). "Pathophysiology of nephrotic acute renal failure". In: Beri T, Bonventre JV, eds. Acute Renal Failure. Philadelphia, Pa.: Blackwell Science 1999, Schier RW, ed. Atlas of Diseases of the Kidney,vol.1.1.http://www.kidneyatlas.org/book1/ adk115.pdf. Accessed August 8, 2007.

Schoolwerth AC, Sica DA, Ballermann BJ, Wilcox CS (2001). "Renal considerations in angiotensin converting enzyme inhibitor therapy": a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. Circulation. 104(16):1985-1991.

Schumann G, Bonora R, Ceriotti F, Férard G, Ferrero CA, Franch PF, Gelia FJ, Hoelzel W, Jørgensen PJ, Kanno T, Kessler A, Klauke R, Kristiansen N, Lessinger JM, Linsinger TP, Misaki H, Pantechni M, Pauwels J, Schiele F, Schimmel HG, Weidemann G, Siekmann L (2002). "IFC primary reference procedure for the measurement of catalytic activity concentrations of enzymes at 37 °C. Part 5: Reference procedure for the measurement of catalytic concentration of aspartate aminotransferase". Clin Chem Lab Med;40:725-33.

Seiwa C, Yamamoto M, Tanaka K, Fukutake T, Ueki T, Takeda S, Sakai R, Ishige A, Watanabe K, Akita M, Yagi T, Tanaka K, Asou H (2007). "Restoration of FcRGamma/Fyn signaling repairs central nervous system demyelination". J Neurosci Res. 85(5):954-66.

Selim K, Kaplowitz N (2003). "Hepatotoxicity of Psychotropic Drugs". Hepatology, 29: 1348-1350.

Selvaraj P and Pugalendi KV (2012). "Efficacy of hesperidin on plasma, heart and liver tissue lipids in rats subjected to isoproterenol-induced cardiotoxicity". Exp Toxicol Pathol. 64(5):449-52.

Seo BM, Muira M, Gronthos S, Bartold PM, Batoulis S, Brahml H, Young M, Robey PG, Wang CY, Shi S (2004). "Investigation of multipotent progenitor stem cells from human periodontal ligament". Lancet. 364(9429):149-55.

Sesink AL, Aloys L, Sesink A, Ilja CW (2003). "Intestinal uptake of quercetin-3-glucoside in rats involves hydrolysis by lactase phlorizin hydrolase". J Nutr. 133:773-776.

Shahid M, Dumat C, Silvestre J and Pinelli (2012c). "Effect of fulvic acids on lead-induced oxidative stress to metal sensitive Vicia faba L. plant". Biol Fert Soils. 10.1007/s00374-012-0662-9.

Shankar M, Gowrishankar NL, David Raj C, Ansar MD, Pranathi P, Raju GV (2012). "Screening of Methanolic Extract of Eugenia Jambolana Leaves for its Hepatoprotective Activity in Carbon Tetrachloride Induced Rats" International Journal of Applied Research in Natural Products. 5 (2):14-18.

Shear N, Spielberg S (1988). "Anticonvulsant hypersensitivity syndrome: invitro assessment of risk". J Clin Invest 1988, 82:1826–32.

Shirasaki Y, Shichiri M, Mori T, Nakanishi T, Tamai I (2013). "Major active components in grapefruit, orange, and apple juices responsible for OATP2B1-mediated drug interactions". J Pharm Sci. 2013, 102(9):3418-26.

Shrivastava M, Kar V, Shrivastava S (2013). "Cyclophosphamide alters myocardial marker enzymes: protection provoked by hesperidin in rats". J App Pharm. 4(03): 407-415.

Singh C, Bishop P, Wilson R (1996). "Extreme hyperbilirubinemia associated with the use of anabolic steroids, health/nutritional supplements and ethanol: Response to ursodeoxycholic acid treatment". Am. J. Gastroenterol. 91: 783-785.

Siu-Po I, Kam-Ming K (1996). "The crucial antioxidant action of quercetin in B in protecting against carbon tetrachloride hepatotoxicity in mice: A comparative study with butylated hydroxytoluene" Biochimie Biomol. Pharmacol Biol Psychiatry. 13:52(11):1687-93.

Smythe MA, Umstead JS (1989). "Phenotoin hepatotoxicity: a review of the literature". Ann Pharmacotherapy. 23: 13-18.

Souza LC, de Gomes MG, Goes AT, Del Fabbro L, Filho CB, Boeira SP, Jeeza CR (2013). "Evidence for the involvement of the serotonin 5-HT(1A) receptor in the antidepressant-like effect caused by hesperidin in mice". Prog Neuropsychopharmac Biol Psychiatry. 40:103-9.

Stephen OA, Salako AA, Doherty OW, Naicker T (2007). "Effect of Melatonin on Carbon Tetrachloride- Induced Kidney Injury in Wistar Rats" African Journal of Biomedical Research, Vol. 10.153 – 164.

St-Pierre J, Drori S, Ultry M, Silvaghi JM, Rhee J, Jäger S, Handschin C, Zheng K, Lin J, Yang W, Simon DK, Bachoow R, Spiegelman BM (2006). "Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators". Cell. 127(2):397-408.

Strijzek-Jimmer M, Szymonik-Lesiku S, Cezhowska G, Stomka M, Madro A, Celinski K (2003). "Catalase, superoxide dismutase, and glutathione peroxidase activities in various rat tissues after carbon tetrachloride intoxication". Journal of Hepato-Biliary-Pancreatic Surgery 10(4):309-15.

Sulkowski M, Thomas D, Chaissong R, Moore R (2000). "Hepatotoxicity associated with antiretroviral therapy in adults infected with HIV and the role of hepatitis C or B virus infection". J Am Med Assoc. 283: 74–80.

Szymonik-Lesiku S, Cezhowska G, Steyrek-Jimmer M, Stomka M, Madro A, Celinski K, Wielosz M (2003b). "Catalase, superoxide dismutase, and glutathione peroxidase activities in various rat tissues after carbon tetrachloride intoxication". J Hepatobiliary Pancreat. Surg. 10: 309–315.

Takeda H, Sadakane C, Hattori T, Katsurada T, Ohkawara T, Nagai K, Asaka M (2008). Rikkunshito, an herbal medicine, suppresses cisplatin-induced anorexia in rats via 5-HT2 receptor antagonism". Gastroenterology. 134(7):2004-13.

Takumi H, Nakamura H, Simizu T, Harada R, Kometani T, N adamoto T, Mukai R, Murota K, Kawai Y, Terao J (2012). "Bioavailability of orally administered water-dispersible hesperidin and its effect on peripheral vasodilation in human subjects: implication of endothelial functions of plasma conjugated metabolites". Food Funct. 3(4):389-98.

Tamai I (2012). "Oral drug delivery utilizing intestinal OATP transporters". Adv Drug Deliv Rev. 64(6):508-14.

Tanaka T, Makita H, Kawabata K, Mori H, Kukamoto M, Satoh K, Hara A, Sumida T, Tanaka T, Ogawa H (1997). "Chemoprevention of azoxymethane-induced rat colon carcinogenesis by the naturally
occuring flavonoids, diasmin and hesperidin”. Carcinogenesis. 18(5):957-65.

Tarazi EM, Harter JG, Zimmerman H (1993). “Sulindac-associated hepatic injury: analysis of 91 cases reported to the Food and Drug Administration”. Gastroenterology 104:569-74.

Taylor PC (2001). “Anti-tumor necrosis factor therapies”. Curr Opin Rheumatol. 13(3):164-9.

The World Book Encyclopedia. Volume 3. 1992. Chicago: World Book Inc. 1992, pp. 366-7.

Thomas L (1998). “Alanine aminotransferase (ALT), A sparte aminotransferase (AST)”. In: Thomas L, editor. Clinical Laboratory Diagnosis, 1st ed. Frankfurt: TH-Books veriaggesellschaft,p.55-65.

Thompson N, Caplin M, Hamilton M (1995). “Anti-tuberculosis medication and the liver: dangers and recommendations in management”. Eur Respir J. 8:1384–8

Tietz, N. W., ed., “Clinical Guide to Laboratory Tests”, 2nd Edition, W.B. Saunders Company, Philadelphia (1994)

Tilg H, Hotamisligil GS (2006). “Nonalcoholic fatty liver disease: Cytokine-adipokine interplay and regulation of insulin resistance”. Gastroenterology, 131: 934–945.

Tirkey N, Pilkhwal S, Kuhad A, Chopra K (2005). “Hesperidin, a citrus bioflavonoid, decreases the oxidative stress produced by carbon tetrachloride in rat liver and kidney”. BMC Pharmacology. 5:2

Tom WM, Fong D, Woo B, Prasongwatana V, Boyde TR (1984). “Microsomal lipid peroxidation and oxidative metabolism in rat liver”. Chemical and Pharmaceutical Interactions. 13: 351 – 363.

Tostmann A, Boeree MJ, Aarnoutse RE, Lange WCM,Vander Ven AJ, Tom WM, Fong D, Woo B, Prasongwatana V, Boyde TR (1984). “Protection of mice liver damage against Microcytomato toxicities caused by acetaminophen”. Jap J Nephrol, 42:66

Tveit S, Furu M, Alice K, Asikainen E, Svinhufvud K (2013). “Hesperidin metabolite go: World Book”. The citrus flavonone hesperidin, Nature. 50: 361

Wang Q, Zhang HM, Zhang GC, Tao WH (2007). “Interaction of the flavonoid hesperidin with bovine serum albumin: A fluorescence quenching study” Journal of Luminescence. 126: 211–218.

Wasowski C, Loscalzo LM, Higgs J, Marder M (2012). “Chronic intraperitoneal and oral treatments with hesperidin induce central nervous system effects in mice”. Phytother Res. 26(2):308-12.

Weber LW, Boll M, Stampf A (2003). “Hepatotoxicity and mechanism of action of halokalenes: carbon tetrachloride as a toxicological model”. Crit Rev Toxicol. 33:105–36

Wei D, Ci X, Chu X, Wei M, Hua S, Deng X (2012). “Hesperidin suppresses ovalbumin-induced airway inflammation in a mouse asthma model”. Inflammation. 35(1):114-21

Wei L, Jun L (2010). “Protective Effects and Mechanisms of Hesperidin Against Acute Chemical Liver Injuries in Mice”. China Papers June 29, http://mt.china-papers.com/2/?p=50550

Wellman PJ, Clifford PS, Rodriguez JA (2013). “Ghrelin and ghrelin receptor modulation of psychostimulant action”. Front Neurosci. p 7:171.

Williamson G, Manach C (2005). “Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies”. Am J Clin Nutr. 81 : 243S-255S.

Willis D, Moore AR, Frederick R, Willoughby DA (1996). “Heme oxygenase: a novel target for the modulation of the inflammatory response”. Nat Med. 2 : 87 – 93.

Wit F, Weverling G, Weel J, Jurrians S, Lange J (2002). “Incidence and risk factors for hepatotoxicity associated with antiretroviral combination therapy”. J Infect Dis. 186: 23–31.

Wu D, Cederbaum AI (1999). Ethanol-induced apoptosis to HepG2 cell lines expressing human cytochrome P4502E1. Alcohol”. Clin. Exp. Res. 23: 67–76.

Xiao-min Y, Jun-ge Q, Qing-zhi L,Hong-wei L, Guo-kang W, Quan- yi J, Ye (2011). “Comparative Effects of Baicalin and Hesperidin on Hepatotoxicity Induced by Cisplatin in Mice”. Journal of Liaoning University of Traditional Chinese Medicine, 2011-06

Yachi R , OsamuI , garashi O, Kiyose C (2010). “Protective effect of hesperetin inhibits growth of aromatase xenoBiotic interplay and regulation of insulin resistance”. British Journal of Urology International. 98: 680–686.

Uetrecht J (1999). “New concepts in immunology relevant to idiopathic drug reactions: the “danger” hypothesis and innate immunity”. ChemRes Toxicol. 12:97–95.

Valko M, Leibfritz D, Moncola J, Cronin M, Mazura M, Telser I (2007). “Free radicals and antioxidants in normal physiological functions and human disease”. Int J Biochem Cell Biol. 39(4):53-60.

Valko M, Leibfritz D, Moncola J, Cronin M, Mazura M, Telser I (2007). “Free radicals and antioxidants in normal physiological functions and human disease”. Int J Biochem Cell Biol. 39(4):53-60.

Vitagliano P, Morisco F, Caporaso N and Fogliano V (2004). “Dietary antioxidant compounds and liver health”. Crit Rev Food Sci Nutr. 44: 575–586.

Von Oettingen WF (1959). “The Halogenated, Aliphatic, Olefinic, Cyclic Arocaromatic, and Aliphatic-aromatic hydrocarbons Including the Halogenated Nictisidices.” U.S. Public Health Service Publ. 414:15-30.

Vulimiri SV, Berger A, Sonawane B (2011). “The potential of metabolomic approaches for investigating mode(s) of action of xenobiotics. Case study with carbon tetrachloride”. Mutat. Res. 722, 147–153.

Walsh DL, Al-Jassabi S (2009). “The role of Silymarin in the protection of mice liver damage against Microcystin-LR toxicity”. Journal of Biological Sciences, 2 (2): 63–68.

Walker AM (1997). “Quantitative studies of the risk of serious hepatic injury in persons using nonsteroidal anti-inflammatory drugs”. Arthritis Rheum 40: 201–208

Walker U, Setzer W, Venhoff N (2002). “Increased long-term mitochondrial toxicity in combinations of nucleoside analogue reverterstranscriptase inhibitors”. AIDS. 16: 2165–2173.

Wang J, Xu X, Elliott MH, Zhu M, Le YZ (2010). “Müller cell-derived VEGF is essential for diabetes-induced retinal inflammation and vascular leakage”. Diabetes. 59(9):2297-305.

Wang L, Wang H, Hu M, Cao J, Chen D, Liu Z (2009). “Oxidative stress and apoptotic changes in primary cultures of rat proximal tubular cells exposed to lead”. Arch Toxicol 83:417-27.

Wang X, Sakurai T, Chen X (2008). “Hydrolysis of flavanone glycosides and degradation of the corresponding aglycones from dried immature Citrus fruit by human fecal flora in vitro”. Planta Med. 74(14) .1751-5.

Wang YQ, Zhang HM, Zhang GC, Tao WH (2007). “Interaction of the flavonoid hesperidin with bovine serum albumin: A fluorescence quenching study” Journal of Luminescence. 126: 211–218.

Wang YQ, Zhang HM, Zhang GC, Tao WH (2007). “Interaction of the flavonoid hesperidin with bovine serum albumin: A fluorescence quenching study” Journal of Luminescence. 126: 211–218.

Yang YL, Hsu HT, Wang KH, Wang CS, Chen CM and Ko WC (2012). “Hesperidin-3-o-methyl ether is more potent than hesperidin in phosphodiesterase inhibition and suppression of ovalbumin-induced airway hyperresponsiveness”. Evid Based Complement Alternat Med. 908562.

Ye L, Chan FL, Chen S, Leung LK (2012). “The citrus flavonone hesperitin inhibits growth of aromatase-expressing MCF-7 tumor in ovariectomized athymic mice”. J Nutr Biochem. 23(10):1250-7.

Yoshimura E, Fujii M, Koide S (2000). “A case of Chinese herbs nephropathy in which the progression of renal dysfunction was slowed by steroid therapy”. Jap J Nephrol, 42:66-72.

Yue L, Ye F, Gui C, Luo H, Cai J, Shen J, Chen K, Shen X, Jiang H (2005). “Ligand-binding regulation of LXR/RXR and LXR/PPAR heterodimerizations: SPR technology-based kinetic analysis correlated with molecular dynamics simulation”. Protein Sci. 14(3):812-22.

Zager RA (1997). “Pathogenic mechanisms in nephrotic acute renal failure”. Semin Nephrol. 17(1):3

Zhang W, Yuan J, Yang Y, Xu L, Wang Q, Zuo W, Fang X, Shen YG
(2010). "Monomeric type I and type III transforming growth factor-β receptors and their dimerization revealed by single-molecule imaging". Cell Res. 20(11):1216-23.
Zhao YL, Zhou GD, Yang HB (2011). “Rhein protects against acetaminophen-induced hepatic and renal toxicity”. Food and Chemical Toxicology, 49:1705–1710.
Zielińska M, Kostrzewa A, Ignatowicz E and Budzianowski J (2001). “The flavonoids, quercetin and isorhamnetin 3-O-acylglucosides diminish neutrophil oxidative metabolism and lipid peroxidation”. Acta Biochimica Polonica. 48(1):183–189.
Zimmerman H (1999). "Drug-induced liver disease". In: Schiff E, Sorell M, Madding W, eds. Schiff's diseases of the liver. 8th ed. Philadelphia: Lippencourt Raven 1999, p 973–1064
Zimmerman H (1999). "Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver". 2nd ed. Philadelphia: Lippincott, Williams &Wilkins, p483-498
Zimmerman HJ (1978). "Drug-induced liver disease". Drugs. 16 (1): 25–45

Zimmerman SW, Norback DH, Powers K (1983). "Carbon tetrachloride nephrotoxicity in rats with reduced renal mass". Arch Pathol Lab Med. 107:264-269.

How to cite this article: Bakheet MS, Haredy HH, Abdesalam A, Abd alhady sayed HK (2015). Hepatotoxicity Implies chemical-driven liver damage induced by certain medicinal and other chemical agents. Int. Inv. J. Med. Med. Sci. Vol. 2(10): 144-164