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REVIEW: CARBON TETRACHLORIDE TOXICITY

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Carbon tetrachloride is a colorless liquid (b.p.76.54^{o}C) with a sweet, chloroform like odor. It is soluble in acetone, ethanol, benzene, carbon disulfide; moderately soluble in water. Since its vapour is noninflam- mable, Carbon tetrachloride is a widely used as an industrial solvent and as fire extinguisher under the commercial name PYRENE. Carbon tetrachloride is used as a solvent for the recovery of tin in tinplating waste and in the manufacture of semiconductors. It is also used in petrol additives, refrigerants, metal degreasing, and as a catalyst in the production of polymers. Carbon tetrachloride is also used as a chemical intermediate in the production of fluorocarbons and pesticides. Wide dissemination of Carbon tetrachloride in the environment represents a serious and somewhat undefined hazard for the health of mankind.

Keywords : *CCI_4, Lipid peroxidation, Cirrhosis, Oxidative stress.*

Carbon tetrachloride is one of the hydrocarbons that has a widespread use in various industries as a solvent (El- Dossouky et. al., 1978). It is also used in medicine as vermifuge in the treatment of hookworm disease. On the other hand, exposure to CCl_4 by inhalation, ingestion or absorption through the skin resulted in many cases of poisoning (Boger et. al., 1987). CCI_4 is a potent hepatotoxin in a variety of experimental animals and man. It induces necrosis, cirrhosis and hepatic carcinoma (Zimmerman and lshak, 1978). Earliest known studies on carbon tetrachloride are those of Grahm (1915) who tested its effects on liver glycogen in pups. Meyer and Pessoa (1923) also reported on its toxicity and later on Davis (1924) first of all studied the effect of diet on carbon tetrachloride toxicity. Following pathological parameters Gardner et .al. (1925), Mann et. al. (1931), Bollman and Mann (1932) and Moon (1934) reported on the nature of lesions produced by carbon tetrachloride. Cameron and Karunaratne (1936) described the histopathology of liver in details after CCI_4 poisoning.

The effects on early changes of nucleus were studied by Doljanski and Rosin (1944). Stowell and Lee (1950) made an extensive histochemical study of liver after CCI_4 treatment. Aterman (1954, 1957, 1962) also estimated the toxic effects of CCI_4 on structure and function of the liver and fibrosis. Wahi et. al. (1955) pioneered the studies on acute liver injury with special reference to histological, histochemical and aminoacid incorporation into proteins. Calvert and Brody (1958) reported rise of Na^+ and Ca^+ and fall of K^+ and Mg^{++} concentrations. Decline in cytoplasmic as well as mitochondrial enzymes was also recorded (Rees and Sinha, 1960). Recknagel and Anthony (1959) observed fatty changes and then Recknagal and Lombardi (1961) worked out the pathogenesis of fatty liver after CCI_4 treated rats. Ultrastructural studies were made by Aizawa (1962) with reference to vacuolar degeneration. Smuckler et. al. (1962) investigated intracellular defects in protein synthesis. Phenomenae like an increase in parenchymal triglycerides (Schotz and Recknagel, 1960), inhibited release of fats from the effected cells and elimination of triglycerides from the cell in the form of lipoprotein complex (Heimberg et.al.,1962) were also investigated. Recknagel and Ghosal (1966) concluded that CCI_4 damages endoplasmic reticulum by promoting the peroxidation of membranous lipids. Rana and Agarwal (1971), Rana (1976) studied the effects of CCI_4 on enzymes, lipids and connective tissue. Biochemical studies on CCI_4 induced liver injury have developed rapidly and the historical aspects have been nicely reviewed by Slater (1972). Morphological changes were reviewed by Smuckler (1976). Mechanistic studies on carbon tetrachloride hepato- toxicity have been studied by Diaz Gomez et.al. (1975). Younes et.al. (1980) reported the effects of CCI_4 on glutathione - S - transferase activity. Experimental studies have confirmed that CCI_4 to be toxic needs activation to CCI_3 and CI free radicals (Recknagel and Glende, 1973). This activation appears to occur during the reduction of cytochrome P-450complex by NADPH catalysed by the P-450reductase (D'Acosta et. al., 1973). CCI_3 radical later initiates a lipid peroxidation process. The effects of both the free radicals and the lipid peroxidation have been postulated to be involved in the process ending in necrosis (Castro et.al.,1972) and dysenzymia (Rana,1980). Noguchi et.al.,(1982) related the early loss of polypeptides in liver microsomes of CCI_4 treated rats to cytochrome P-450 content. The effect of malotilate on experimental liver fibrosis (cirrhosis) induced by carbon tetrachloride was described by Monna (1983). Studies by Davies et. al.,(1986) show that carbon tetrachloride and 2 - isopropyl - 4 - pentenamide induced activation of cytochrome P- 450 leads to heme – derived protein adducts. Igarashi et. al., (1986) reported the antifibrotic effect of malotilate on liver fibrosis induced by carbon tetrachloride in rats. Co-exposure to ethanol, acetone or isopropanol is known to potenti- ate the toxicity of carbon tetrachloride (Charbonneau et. al., 1986). Exposure to other chlorinated compounds, such as chlordecone, also potentiates the toxicity of carbon tetrachloride (Curtis et. al., 1979). Glende and Pushpendran (1986) discussed the role of phospholipase activation as a secondary mechanism of carbon tetrachloride induced hepatocyte injury. An immuno-histochemical evidence for alterations in

specific forms of rat hepatic microsomal cytochrome P- 450 during acute carbon tetrachloride intoxication was established by Moody et. al.(1986). Okuno et. al.(1986) examined the drug metabolizing activity of rat liver during long term administration of carbon tetrachloride and also, the latter's relationship with the content of hydroxyproline in the liver. Doolittle et. al., (1987) established a relationship between hepatotoxicity and induction of replicative DNA synthesis following single or multiple doses of carbon tetrachloride. The effect of alpha-naphthyl isothiocyanate and carbon tetrachloride interaction on hepatocellular calcium transport was studied by Agarwal and Zinermon (1989). Clawson (1989) attributed carbon tetrachloride hepatotoxicity to early 'metabolism dependent' effects and later 'metabolism independent' effects. Kim et. al. (1990) studied the effect of oral dosing vehicles on the acute hepatotoxicity of carbon tetrachloride in rats. It has been known for many years (Theirs et.al., 1960) that carbon tetrachloride intoxication in rats leads to an accumulation of calcium within the mitochondria. Carbon tetrachloride mediated hepatotoxicity is preceded by an increase in total liver calcium content (Recknagel,1983).

It has been known for long time that a part of the liver injury caused by carbon tetrachloride may have originated through the free radical reactions to the metabolism of CCl_4 in the liver and subsequent initiation of lipid peroxidation (Bacon et. al., 1983; Brattin et. al., 1985). This ultimately causes the body to experience oxidative stress and seems to play a major role in the pathogenesis of both acute and chronic liver damage. During the last decades, application of this compound has been further shown to be an excellent tool for the study of experimental oxidative injury due to its rapid metabolism in the liver to free radical and following deleterious effects in the liver. Recently, it has been shown that administration of CCl_4 to rats leads to distinctive formation of both non-enzymatically and enzymatically derived eicosanoids (Morrow et. al., 1990; Basu,1999).

CYP-450 activates carbon tetrachloride into its reactive intermediate trichloromethyl radical (Recknagel et. al., 1989), which is further converted to a peroxy radical (Slater,1987). CCl_4 metabolites react with polyunsaturated fatty acids to propagate a chain reaction leading to lipid peroxidation or bind covalently to lipids and proteins, resulting in destruction of cell membranes and also induced liver damage (Recknagel et. al., 1989). Many different natural compounds could alleviate the toxicity of carbon tetrachloride and other toxic agents through inhibition of lipid peroxidation, which generated from CCl_4 metabolism (Biasi et. al., 1991). For example, vitamin E, d-α-tocopherol is the most important endogenous lipid soluble antioxidant and is thought to play a major role in protecting cellular membranes against lipid peroxidation and associated loss of protein sulphydryl groups (Bjorneboe et. al., 1990). Also pretreatment of rats with α- tocopherol was found to protect the brains against the toxicity of CCl_4 (El-Demerdash et. al., 1999). It has been found that the administration of d- α-tocopherol acetate (Gallagher,1961), α-tocopherol(Biasi et.al.,1991) or liposomes containing α-tocopherol protected against CCI_4 induced liver toxicity in rats (Yao et.al.,1994). In addition,the administration of the

succinate ester form of a-T,d-α-tocopherol hemisuccinate (TS), could alleviate the hepatotoxic effects of a wide variety of toxic agents (Ray and Fariss,1994). However, in another study, d-α-tocopherol acetate administration to rats provided no protection against CCI_4 induced liver toxicity(Wolfgang et.al.,1990).

In addition to its hepatocellular toxicity, CCl_4 also has been shown to affect the immune system. Mice exposed orally to 500 mg/kg CCl_4 exhibited suppressed T-cell dependent immune responses as measured by decreased splenic antibody forming cells. These mice also had elevated plasma interleukin-2 and transforming growth factor β, measured 24 and 48 hours after exposure(Delaney et.al., 1994). However, a previous study showed that hepatotoxicity from CCl_4 occurs at much lower concentrations than does toxicity to the immune system (Smialowitz et.al.,1991).

A physiologically based pharmacokinetic model for carbon tetrachloride has been developed in the rat (Paustenbach et.al.,1988).In this model, it was estimated that 60% of inhaled CCI_4 is metabolized, and that 96% of the metabolized CCI_4 forms biological adducts which degrade slowly with a half life of 24 hours.The remaining 4% of the metabolized CCI_4 becomes CO_2.

Over the years, various evidences suggest that reactive free radical species are physiologically relevant to exert a variety of biochemical reactions that regulate many of our important physiological functions including defence against microorganisms, cell signalling , vascular control, cell generation and degeneration, control of cellular homeostasis (Bogdan,2001), and presumably many other unknown essential functions.

Very little is known about link between non-enzymatically generated free radical and cyclooxygenase(COX) catalysed reactive pathways. Indeed, induced oxidative injury and subsequent inflammatory response have recently been demonstrated following CCI_4 administration to rats (Basu,1999). It was postulated that cyclooxygenase dependent inflammatory response through PGF2α formation in CCI_4-induced hepatotoxicity may be a secondary effect to oxidative injury and might have a conceivable link between inflammatory response and oxidative injury involving both non-enzymatic and enzymatic oxidation of arachidonic acid.

Although many diseases are speculated to be associated with the disorder in free radical induced lipid peroxidation (Gutteridge, 1993), direct evidence of involvement of lipid peroxidation is limited. However, recently more reasonable evidence of isopentane formation is shown in CCl_4 induced lipid peroxidation (Basu 1998b, 1999; Sodergren et. al., 2001), atherosclerosis (Sentman et. al., 2001), liver injury (Nanji et. al., 1994), ischemic-reperfusion injury (Basu et. al., 2000; Liu et. al., 2002), chronic obstructive pulmonary disease (Pratico et. al., 1998a), septic shock (Basu et. al., 2001c), diabetes (Helmersson et. al., 2002), various

rheumatic diseases (Basu et. al., 2001a) and neurodegenerative disorders (Montine et. al., 1999). The role of free radical in the CCl_4 induced toxicity has been shown to be a mojor pathway of non-enzymatically induced lipid peroxidation, which subsequently affects various enzyme activities of the body and thereby is possibly also linked to enzymatically induced lipid peroxidation. During the initial phase of CCl_4 toxicity following its administration, a large amount of CCl_4 converts to trichloromethyl radical or other radicals, which inturn accelerate several metabolic pathways. These radicals appear to affect the adjacent lipids in the tissues to induce lipid peroxidation. Esterified arachidonic acid is an essential part of lipids *in vivo* that are found in the tissues, which can be metabolished in the liver and other tissues in different kinetics to form esterified isopentanes from arachidonic acid have previously been discussed (Lawson et. al., 1999).

Previous studies by Nishida et. al., (1996) have shown transient increases in mouse hepatic lipid peroxides with carbon tetrachloride following a single i.p. dose at 1 ml/kg upto 4 h that was followed by a greater elevation after 12 h. The transient elevation in lipid peroxides was concomitant with a decrease in hepatic GSH, however, the oxidative stress observed was accompanied by cytotoxicity. In the further study, Cabre et. al., (2000) administered rats hepatotoxic doses twice a week for 9 weeks and observed a decrease in GSH, free radical production and a correlation between GSH peroxidase activity and lipid peroxidation in the liver. These studies show a strong correlation between liver GSH depletion and lipid peroxidation in rodents.

Supporting evidence for the role of oxidative stress in carbon tetrachloride - induced liver injury was shown in a study of Sundari et. al., (1997) in which statistically significant increases in hepatic protein carbonyls were seen concomitant with a decrease in glutamine synthtase activity. Lipid peroxidation has been linked to protein binding in a study by Hartley et. al., (1999) where malondialdehyde and 4-hydroxynoneal modified proteins were observed *in vivo* . Localization of these proteins was found in zone 2 progressing to zone 3 of the liver, areas known to contain high levels of cytochrome P-450, implicating carbon tetrachloride metabolites in the oxidative responses.

Pro-inflammatory and cytotoxic cytokines are shown to be involved in liver injury and their role in inflammation of hepatotoxicity is increasing (Blazka et. al., 1995; Luster et. al., 2001). A number of enzyme systems of the body are also impaired by CCl_4 toxicity (Glende et. al., 1976). A loss of aminopyrine desmethylase, cytochrome P-450 and glucose-6-phosphatase activity was observed after CCl_4 induction (Gonzahez Padron et. al., 1996). It has also recently been shown that CCl_4 can induce prostaglandin formation through the cyclooxygenase pathway (Sodergren et. al., 2001).

Hepatic cirrhosis or liver fibrosis is known to be an irreversible distortion of the normal tissue architecture; this alteration develops during chronic liver damage (Sokol,2002). Carbon

tetrachloride under laboratory conditions is one of the most common and widely used liver intoxicators today (Lee et. al., 2001). CCl_4 action is based on membrane lipid peroxidation and induction of trichloromethyl radical (CCl_3), resulting in severe celldamage (He et. al., 2006).

REFERENCES

Agarwal, A. K. and Zinermon, W. D. (1989)- *Effect of alpha - naphthyl isothiocyanate and CCI_4 interaction on hepatocellular calcium transport.* ***Bull.Environ. Contam. toxcol. 42, 464-470.***

Aizawa,S.(1962)- *Electron microscopic cyto-histopathology (XVIII). Electron microscopic studies on vacuolar degeneration.****Acta.Patho.Japan.12,155-176.***

Aterman , K. (1954) - *Studies in fibrosis of the liver induced by carbon tetrachloride. I.Relation between hepatocellular injury and new formation of fibers tissue.A.M.A.****Arch.Pathol.54,1-11.***

Aterman , K. (1957)- *The effect of carbon tetrachloride on the structure and function of the liver of the rhesus monkey.* ***Gastroenterology. 33, 794-799.***

Aterman , K. (1962)- *Toxic effect of carbon tetrachloride on the liver cell. Brit. J.* ***Pharmacol.19,219-225.***

Bacon, B.R., Tavill,A.S., Brithenham,G.M., Park,C.M.,Recknagel,R.O.(1983)- *Hepatic lipid peroxidation in vivo in rats with chronic iron over load.* ***J.Clin. Invest. 71,429-439.***

Basu,S . (1998b) - *Radioimmunoassay of 8-iso-prostaglandin F2α- an index for oxidative injury via free radical catalyzed lipid peroxidation. Prostaglandins leukotrienes. Essent.* ***Fatty Acids. 58,319-325.***

Basu,S. (1999)- *Oxidative injury induced cyclooxygenase activation in experimental hepatotoxicity.* ***Biochem. Biophys. Res. Commun. 254, 764-767.***

Basu,S., Mutschler,D.K., Larsson ,A., Kiiski,R.,Norgren,A.,Eriksson,M .(2001c)- *Propofol (Diprivan-EDTA) counteracts oxidative injury and deterioration of the arterial oxygen tension during experimental septic shock.* ***Resuscitation. 50,341-348.***

Basu,S.,Nozari,A., Liu,X.L.,Rubertsson,S.,Wiklund,L.(2000)*-Development of a novel biomarker of free radical damage in reperfusion injury after cardiac arrest .****FEBS Lett.470,1-6.***

Basu ,S., Whiteman, M., Matty,D.L., Halliwell,B. (2001a)- *Elevated levels of F2-isoprostanes and prostaglandin F2α-in different rheumatic diseases.* ***Ann. Rheum. Dis. 60, 627-631.***

Biasi,F.,Albano,E.,Chiarpotto,E.,Corongiu,F.(1991)*-In vivo and in vitro evidence concerning the role of lipid peroxidation in the mechanism of hepatocyte death due to carbon tetrachloride.* ***Cell Biochem.Funct.9,111-118.***

Bjorneboe,A., Bjorneboe,G., Drevon,C. (1990)- *A bsorption, transport and distribution of vitamin E.* ***J. Nutr. 120, 233-242.***

Blazka,M.E. ,Wilmer,J.L., Holladay,S.D., Wilson,R.E., Luster,M.I. (1995)- *Role of pro inflammatory cytokines in acetaminophen hepatotoxicity.* ***Toxicol. Appl. Pharmacol. 133, 43-52.***

Bogdan,C .(2001)- *Nitric oxide and regulation of gene expression.* ***Trends. Cell Bio. 11, 66-75.***

Boger, M., Applemen ,L.M., Feron,V.J., Beens,R.B. and Notton,W.R . (1987)- *Effect of the exposure profile on the inhalation toxicity of carbon tetrachloride in male rats.* ***J.Appl. Toxicol. 7, 185-192.***

Bollman,J.L.and Mann,F.C.(1932)*-Experimentally produced lesions of the liver.* ***Ann.Internal Med. 5, 699-711.***

Brattin,W.J., Glande,E.A., Recknagal,R.O., (1985)- *Pathological mechanisms in carbon tetrachloride hepatotoxicity.* ***Free Radic.Biol.Med. 1, 27-28.***

Cabre,M., Camps,J., Paternain,J.L., Ferre,N., Joven,J. (2000)- *Time-course of changes in hepatic lipid peroxidation and glutathione metabolism in rats with carbon tetrachloride induced cirrhosis.* ***Clin.Exp.Pharmacol.Physiol.27,694-699.***

Calvert,D.N. and Brody, T.M. (1958)-*Biochemical alterations of liver function by the halogenated hydrocarbons.I.In vitro and in vivo changes and their modification by ethylenediamine tetraacetate.* ***J.Pharmacol. Exptl.Therap. 124, 273-281.***

Cameron, G. R. and Karunaratne, W.A.E. (1936)- *Carbon tetrachloride cirrhosis in relation to liver.* ***J.Pathol.Bacteriol. 42, 1-21.***

Castro, J.A., Cignoli, E.V., Castro,C.R.De and Fenos, O.M.De (1972)- *Prevention by cystamine of liver necrosis and early biochemical alterations induced by carbontetra chloride****. Biochem.Pharmacol. 21, 49-57.***

Charbonneau,M., Brodeur,J., Souich,P. ,Plaa,G.L .(1986)- *Correlation between acetone-potentiated CCI_4 induced liver injury and blood concentrations after son*

Clawson,G.A.(1989)-*Pathol. Immunopatho.* ***Res. 8, 104.***

Curtis,L.R., Williams, W.L., Mehendale, H.M.(1979)-*Potentiation of the hepatotoxicity of carbon tetrachloride following pre-exposure to chlordecone (Kepone) in the male rat.* ***Toxicol.Appl. Pharmacol. 51, 283-293.***

D,Acosta,N., Castro,J.A., DiazGomez,M.I.,Ferreyra,E.C.De., and Castro,C.R.De and Fenos,O.M.De. (1973)- *Role of cytochrome P450 in carbon tetrachloride activation and CCl_4 induced necrosis. Effect of inhibitors of heme synthesis. (I) 3-Amino 1,2,4 triazole.* ***Res.Commun.Chem.Pathol.Pharmacol. 6, 175-183.***

Davies,H.W., Britt,S.G. and Pohl,L.R. (1986)- *Carbon tetrachloride and 2-isopropyl-4-pentenamide-induced inactivation of cytochrome p450 leads to heme-derived protein adducts.* ***Arch.Biochem.Biophys. 244, 387-392.***

Davis,N.C. (1924)- *The influence of diet upon the liver injury produced by carbon tetrachloride.* ***J.Med.Res. 44, 601-614.***

Delaney,B., Strom, S.C., Collins, S., Kaminski,N.E. (1994)- *Carbon tetrachloride suppresses T-cell-dependent immune responses by induction of transforming growth factor-β1.* ***Toxicol.Appl.Pharmacol. 126, 98-107.***

DiazGomez,M.I., Castro,C.R.De., Ferreyra,E.C.De.,D'Acoasta,N., Fenos,O.M.De and Castro,J.A. (1975)- *Mechanistic studies on carbon tetrachloride hepatotoxicity in fasted and fed rats.* ***Toxicol.Appl.Pharmacol. 32, 101-108****.*

Doljanski,L. and Rosin,A.(1944)- *Studies on the early changes in the livers of rats treated with various toxic agents, with especial reference to the vascular lesions.I. The histology of the rat's liver in urethane poisoning.* ***Am. J. Pathol. 20, 945-959.***

Doolittle,D.J.,Muller,G.,Scribner,H.E.(1987)-*Relationship between hepatotoxicity and induction of replicative DNA synthesis following single or multiple doses of carbon tetrachloride.* ***Journal of Toxicology and environmental health. 22, 63-78.***

El-Demerdash,F.M., Yosef,M.I., Sheweita,S.A.(1999)- *Alellorating effect of some antioxidants on carbon tetrachloride-induced biochemical alterations in rats.* ***Environ. Nutr. Intract. 3(4), 245-255.***

El-Dossouky,E.A., Mikhal,T.H., Awadallah,R. and Kotlo,N.A.(1978)- *Effect of phenobarbitone and propionyl promazine on serum enzyme in carbon tetrachloride hepatotoxicity.* ***Zeitschrift fur Ermahrungswissenschaft. 17,159-168.***

Gallagher,C. (1961)- *Protection by antioxidants against lethal doses of carbon tetrachloride.* ***Nature. 192, 881-882.***

Gardner,G.H., Grove,R.C., Gustafson,R.K., Maine,E.D., Tompson,M.J., Wells,H.S. and Lamson,P.D. (1925)- *Studies on the pathological histology of experimental carbon tetrachloride poisoning.* ***Bull. Johns Hopkins hosp. 36, 107-133.***

Glende,E.A., Heruszewyez,A.M., Recknagel,R.O. (1976)- *Critical role of lipid peroxidation in carbon tetrachloride –induced loss of aminopyrine demethylase, cytochrome P450 and glucose-6-phosphatase.****Pharmacol Biochem.26,2163-2170.***

Glende,E.A.,Pushpendran,C.K. (1986)- *Activation of phospholipase A2 by carbon tetrachloride in isolated hepatocytes.* ***Biochem.Pharmacol. 35, 3301-3307.***

Gonzahez,Padron,A.De.,Toranzo,E.G.,Castro,J.A. (1996)- *Depression of liver microsomal glucose-6-phosphatase activity in carbon tetrachloride poisoned rats. Potential synergistic effects of lipid peroxidation and covalent binding of haloalkane-derived free radicals to cellular components in the process.* ***Free Radic.Biol.Med. 21, 81-87.***

Grahm,E.A. (1915)- *The resistance of pups to late chloroform poisoning in its relation to liver glycogen.* ***J.Exptl.Med. 21, 185-191.***

Gutteridge,J.M.C. (1993)- *Free radicals in disease processes: a complication of cause and consequence.* ***Free Radic. Res. Commun. 19, 141-158.***

Hartley, D.P., Kolaja, K.L., Reichard, J., Petersen, D.R. (1999)- *4- Hydroxynonenal and malondialdehyde hepatic protein adducts in rats treated with carbon tetrachloride: immunochemical detection and lobular localization.* ***Toxicol. Appl. Pharmacol. 161,23-33.***

He,S.X., Luo,J.Y., Wang,Y.P.,Wang,Y.L., Fu,H., Xu,J.L.(2006)- *Effect of extract from ginkgo biloba on carbon tetrachloride-induced liver injury in rats.* ***World J.Gastroenterol. 12(24), 3924-3928.***

Heimberg, M., Weinstein, I., Dishmon, G. and Dunkerley, A. (1962)- *The action of carbon tetrachloride on the transport and metabolism of triglycerides and fatty acids by the isolated perfused rat liver and its relationship to the etiology of fatty liver.* ***J. Biol. Chem. 237, 3623-3627.***

Helmersson,J.,Vessby,B.,Basu,S. (2002)- *Inflammation and oxidative injury in elderly men with type 2 diabetes.* ***Free Radic.Biol.Med. 33 (suppl.2) 5344.***

Igarashi,S., Hatahara,T., Nagai,Y., Hori,H., Sakakibara,K., Kotoh,M., Sakai,A. and Sugimoto,T.(1986)- *Antifibrotic effect of malotilate on liver fibrosis induced by carbon tetrachloride in rats,Japan.* ***J.Exp.Med. 56, 235-245.***

Kim,H.I., Odend'hal.S., Bruckner,J.V. (1990)- *Effect of oral dosing vehicles on the acute hepatotoxicity on carbon tetrachloride in rats.* ***Toxicol.Appl.Pharmacol. 102, 34-49.***

Lawson,J.A., Rokach,J., Fitzgerald,G.A.(1999)- *Isoprostanes: formation analysis and use of indicies of lioid peroxidation in vivo.****J.Biol.Chem. 27,24441-24444.***

Lee,K.S., Lee,S.J., Park,H.J., Chung,J.P., Han,K.H., Chon,C.Y. (2001)- *Oxidative stress effect on the activation of hepatic stellate cells. Yonsai.* ***Med. J. 42(1) 1-8.***

Liu,X.L., Nozari,A., Basu,S., Ronnquist,G., Wiklund,L. (2002)- *Neurological outcome after experimental cardiopulmonary resuscitation: a result of reperfusion injury.* ***Acta. Anaesthesiol. scand. 46, 537-546.***

Luster,L.I., Simenova,P., Gallucci,R.M., Bruccleri,A., Blazka,M.E., Yuesoy,B. (2001)- *Role of inflammation in chemical-induced hepatotoxicity.* ***Toxicol.Lett. 120, 317-321.***

Mann,F.C., Fishback,F.C., Gay,G.C., and Green,G.F. (1931)- *Experimental pathology of the liver.* ***A.M.A. Arch.Pathol. 12, 787-793.***

Meyer,J.R. and Pessoa,S.B. (1923)- *A study on the toxicity of carbon tetrachloride.* ***Am. J. Trop. Med. 3, 177-196.***

Monna,T. (1983)- *Effect of malotilate on experimental liver fibrosis (cirrhosis) induced by carbon tetrachloride or egg yolk sensitization. In: Hepatotrophic agent malotinate .* ***Ed. Oda. T. and Tygstrup, Tokyo, Excerpta. Medica .N.pp. 44-53.,***

Montine,T.J., Beal,M.F., Roberts,D., Cudkowitz,M.E., Roberts,L.J.II (1999)- *Cerebrospinal levels of F2-isoprostanes, specific markers of lipid peroxidation, are elevated in Hungington's diseases.* ***Neurology. 52, 1104-1105.***

Moody,D.E., Taylor,L.A. and Smuckler,E.A. (1986)- Drug metabolism and disposition. 14, 709.

Moon,V.H. (1934)- *Experimental cirrhosis in relation to human cirrhosis.* ***A.M.A. Arch. Pathol. 18, 381-424.***

Morrow,J.D., Hil,K.E., Bruk,R.F., Nammour,T.M., Badr,K.F., Roberts,L.J.II (1990)- *A series of prostaglandin F2-like compounds are produced in vivo in humans by a non-cyclooxygenase.Free radical catalyzed mechanism.* ***Proc.Natl.Acad.Sci.USA. 87, 9383-9387.***

Nanji,A.A., Samsuddin,K., Tahan,S.R., Sadrzadeh,S.M.J. (1994)- *Plasma levels of a novel noncyclooxygenase-derived prostanoid (8-isoprostane) correlate with severity of liver injury in experimental alcoholic disease. J.Pharmacol.Exp.Ther.* ***269, 1280-1285.***

Nishida,K., Ohta,Y., Kongo,M., Ishiguro,I. (1996)- *Response of endogenous reduced glutathione through hepatic glutathione redox cycle to enhancement of hepatic liver peroxidation with the development of acute liver injury in mice intoxicated with carbon tetrachloride .* ***Res.Commun.Mol.Pathol.Pharmacol. 93, 198-218.***

Noguchi,T., Fong,K.L., Lai,E.K., Alexander,S.S., King, M.M., Olson,L., Poyer, J.L., McCay, P.B. (1982)- *Specificity of phenobarbitol-induced cytochrome P450 for metabolism of carbon tetrachloride to the trichloromethyl radical.* ***Biochem. Pharmacol. 31, 615-624.***

Okuno,H., Hazana,H., Murase,T., Shiozaki, Y. and Sameshima,Y. (1986)- *Drug metabolizing activity in rats with chronic liver injury induced by carbon tetrachloride. Relationship with the content of hydroxyproline in the liver, Japan.* ***J. Pharmacol. 41, 363-371***

Paustenbach,D.J., Clewell,H.J., Gargas,M.L., Andersen,M.E. (1988)- *A physiologically based pharmacokinetic model for inhaled carbon tetrachloride.* ***Toxicol. Appl. Pharmacol. 96, 191-211***

Pratico,D., Basili,S., Vieri,M., Cordova,C., Violi,V., FitzGerald,G.A.(1998a)- *Chronic obstructive pulmonary disease is associated with an increase in urinary levels of isoprostane F2 alpha-11 an index of oxidant stress.* ***Am. J. Respir. Git. Care. Med. 158, 1709-1714.***

Rana,S.V.S.(1976)- *Effect of testosterone, progesterone and orchidectomy on the kidney of common ground squirrel, Funambulus pennants.* ***Anat. Anz. 140, 503-507.***

Rana,S.V.S. (1980)- *Visual evidences on reversible dysenzymia induced by Zn and a new chelating agent in carbon tetrachloride poisoned liver of squirrels* ***Mikroscopie. 36, 233-241.***

Rana,S.V.S. and Agarwal,V.P. (1971)- *Histochemical studies of few enzymes in the liver of common ground squirrel treated with carbon tetrachloride.* ***Acta. Histochem. 41, 125-130.***

Ray.S., Fariss,M. (1994)- *Role of cellular energy status in tocopheryl hemisuccinate cytoprotection against ethylmethanesulfonate-induced toxicity.* ***Arch. Biochem. Biophys. 311, 180-190.***

Recknagel,R.O. (1983)- *Carbon tetrachloride hepatotoxicity: status quo and future prospects.* ***Trends. Pharmacol. SCi. 4, 129-131.***

Recknagel,R.O. and Ghoshal,A.K. (1966)- *Lipoperoxidation as a vector in carbon tetrachloride hepatotoxicity.* ***Lab. Invest. 15,132.***

Recknagel,R.O., Anthony,D.D. (1959)- *Biochemical changes in carbon tetrachloride fatty liver: seperation of fatty changes from mitochondrial degeneration .* ***J. Biol. Chem. 234, 1052-1059.***

Recknagel,R.O., Glende,E.A.Jr. (1973)- *Carbon tetrachloride hepatotoxicity: an example of lethal cleavage.* ***CRC Crit. Rev. Toxicol. 2, 263-297.***

Recknagel,R.o., Glende,E.A.Jr., Dolak,J.A., Waller,R.L. (1989)- *Mechanisms of carbon tetrachloride toxicity.* ***Pharmacol. Ther. 43, 139-154.***

Recknagel,R.O., Lombardi,B. (1961)- *Studies of biochemical changes in subcellular particles of rat liver and their relationship to a new hypothesis regarding the pathogenesis of carbon tetrachloride fat accumulation.* ***J. Biol. Chem. 236, 564-569.***

Rees,K.R. and Sinha,K.P.(1960)- *Blood enzymes in liver injury.* ***J. Pathol. Bacteriol. 80, 297-307.***

Schotz,M.C. and Recknagel,R.O. (1960)- *Rapid increase of rat liver triglycerides following carbon tetrachloride poisoning.* ***Biochem.et.Biophys.Acta. 41, 151-153.***

Sentman,M.L., Brannstrom,T., Westerlund,S., Laukkanen,M.O., Ylaherttuala,S., Basu,S., Markund,S. (2001)- *Extracellular superoxide dismutase deficiency and atherosclerosis in mice.* ***Arterioscler.***

Slater,T.F. (1972)-*In: Free radical mechanisms in tissue injury.* ***Pion Ltd.London.85-170.***

Slater,T.F. (1987)-*In: Biochemical mechanisms of liver injury.* ***pp, 745 New Yark. Academic Press.***

Smialowitz,R.J., Simmons,J.E., Luebke,R.W., Allis,J.W. (1991)- *Immunotoxicologic assessment of subacute exposure of rats to carbon tetrachloride with comparison to hepatotoxicity and nephrotoxicity.* ***Fundam. Appl.Toxicol. 17,186-196.***

Smuckler,E.A., Iseri,O.A. and Benditt,E.P. (1962)- *An intracellular defect in protein synthesis induced by carbon tetrachloride.* ***J.Exptl.Med. 116,55-72.***

Smuckler,E.A. (1976)- *In: Recent advances in biochemical pathology:Toxic liver injury(Dianzani,M.U.,Ugazio,G.and Sena,L.M.eds).****Academic Press.New York.p.11.***

Sokol,R.J. (2002)- *Liver cell injury and fibrosis.* ***J.Pediatr.Gastroenterol.Nutr. 35(Suppl.1) S7-10.***

Sodergren,E., Cedeberg,J., Vessby,B., Basu,S. (2001)- *Reduction of non-enzymatic and enzymatic lipid peroxidation with Vitamin E supplementation in experimental hepatotoxicity.* ***Eur.J.Nutr.40, 10-16.***

Stowell,R.E. and Lee,C.S. (1950)- *Histochemical studies of mouse liver after single feeding of carbon tetrachloride.* ***A.M.A.Arch.Pathol. 50, 519-537.***

Sundari,P.N., Wilfred,G., Ramakrishna,B. (1997)- *Does oxidative protein damage play a role in the pathogenesis ofcarbon tetrachloride-induced liver injury in the rat?* ***Biochem.Biophys.Acta. 1362,169-176.***

Thiers,R.E., Reynolds,E.S. and Vallee,B.L. (1960)- *the effect of carbon tetrachloridei poisoning on subcellular metal distribution in rat liver.****J.Biol.Chem. 235, 2130-2133.***

Wahi,P.N., Tandon,H.D. and Bharadwaj,T.P. (1955)- *Acute carbon tetrachloride hepatic injury-Part 1. Histological and histochemical studies. Part 2. Free amino acid studies by paper partition chromatography with a note on the mechanism of*

Wolfgang,G., Donarski,W., Petry,T. (1990)- *Effects of novel antioxidants on carbon tetrachloride-induced lipid peroxidation and toxicity in precision cut rat liver slices.* ***Toxicol.Appl.Pharmacol. 106, 63-70.***

Yao,I., Esposti,S., Huang,L., Arnon,R. (1994)- *Inhibition of carbon tetrachloride induced liver injury by liposomes containing vitamin E.* ***Am.J.Physiol. 267, G476-e.***

Younes,M., Schlichting,R and Siegers,C.P. (1880)- *Glutathione-S-Transferase activities in rat liver: effect of some factors influencing the metabolism of xenobiotics.* ***Pharmacol.Commun. 12, 115-129.***

Zimmerman,H.J. and Ishak,K.B. (1978)- *Hepatotoxicity injury due to drugs and toxins. In: Mac Saveen,R.N.M., Anthony,P.P., Scheur,P.J. (eds).****Pathology of liver,335.pp.Churchill Livingstone,London.***