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Research Article

THE ROLE OF SESAME OIL IN PROTECTION AGAINST TOXICITY OF CARBON TETRACHLORIDE

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Abstract

The effect of carbontetrachloride (CCl4) with or without sesame oil on liver and kidney functions parameters and some biochemical indices of male rabbits were investigated.Levels of total protein and albumin showed a significant decrease after treatment with carbon tetrachloride.But their levels increased significantly after treatment with the combination of CCl_4 and sesame oil. Levels of bilirubin increased significantly but decreased after treatment with the combination of CCL4 and sesame oil. Levels of ALT, AST, ALK, ACP and LDH increased significantly after treatment with carbon tetrachloride.Their levels decreased significantly after treatment with the combination of CCl4 and sesame oil compared to control. Glucose in serum of male rabbits decreased significantly after treatment with CCl4 compared to control.

Keywords: Carbontetrachloride, Liver Functions, Kidney Functions, Carbon Tetrachloride.

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INTRODUCTION

CCl4 is a xenobiotic known to induce chemical liver injury. CCl4 is metabolized by hepatic microsomal cytochrome P450 to free radicals such as trichloromethyl radical (CCl3) and proxytrichloromethyl radical (OOCCl3) [1]. Trichloromethyl is hepatotoxic metaboliteof CCl4, can react with sulfhydryl groups and may deplete glutathione and protein thiols and affect enzymes such as catalaseand superoxide dismutase. The hepatic injury isassociated with distortion of of some liver functions.Liver,therefore, is susceptible to diseases including hepatitis,cirrhosis, alcohol-related disorders, and liver cancer [2].

The liver plays an important role in metabolism ofendo-and exo-genous substances. A major cause of these disorders isdue to exposure to different environmental pollutantsand xenobiotics i.e., carbon tetrachloride (CCl4),thioacetamide, paracetamol, and alcohol. These toxicants mainly damage the liver by producing reactiveoxygen species (ROS) [3]. Reactive oxygen speciesmay produce tissue injury through covalent bindingand lipid oxidation.They augmentfibrosis byincreasing collagen synthesis(Adesanoye [4] and Farombi, 2010). Carbon tetrachloride is used primarily as a chemical intermediate in the production of the refrigerants Freon 11 and 12. Freon 11 and 12 are also used as solvents, in plastic and resin production, as foam blowing agents, and previously as aerosol propellants(HSDB [5], 2000).

In the first stage of CCl_4 metabolism, trichloromethyl radicals ($CCl{\cdot}_3$) are generated by theliver microsomal cytochrome P450 oxygenase system. This radical rapidly oxidizes to form trichloromethylperoxy radical ($CCl_3OO{\cdot}$) [1],which is even more reactive than $CCl{\cdot}_3$, $CCl_3OO{\cdot}$ more readily abstracts hydrogen from polyunsaturated fatty acids (PUFA), leading to lipid peroxidation despite having a shorter half-life than $CCl_{3{\cdot}}$ Increased lipid peroxidation on the cell membrane alters enzyme activity, thereby inducing hepatic injury and necrosis [6].

Sesame seeds and sesame oil have long been used as health foods and display multiple physiological functions against different pathological factors and symptoms [7,8]. Sesame seeds are not only rich in oil (about 50%) and protein (about 20%). Sesame seed provides highly stable oil and nutritious protein and meals [9].

Recently, clinical and animal studies have shown that extract of the black seeds have many therapeutic effects [10]. Some nutraceutical characteristics of sesame seeds have been identified, including antioxidant, hypocholesterolemic, and hepatoprotective effects, as well as prevention of hypertension [11]. Two types of antioxidants have been isolated and identified from sesame seeds: fat soluble and water soluble. The fat-soluble antioxidants are tocopherols, sesaminol, sesamolinol, and pinoresinol. During the industrial bleaching process of unroasted sesame oil, sesamolinis chemically converted to sesaminol. Sesaminolglucosides are the main water-soluble antioxidants in sesame seed and include sesaminolmonoglucoside, sesaminoldiglucoside, and sesaminoltriglucoside [12].

MATERIALS AND METHODS

TESTED COMPOUNDS

In this study, the effect of carbontetrachloride (CCl4) with or without sesame oil on liver and kidney functions parameters and some biochemical indices of male rabbits were investigated. CCl4 was brought fromchemistry department, faculty of science 1mg/ml (CCL4). Sesame oil was purchased from public market for medicinal herbs.

ANIMALS AND TREATMENTS

Twenty eight male white rabbits weighing 550-600 g were obtained from the Public market. Animals were housed 7 per cage and kept on commercial diet and tap water was provided *ad libitum*. All animals received human care and our study complies with the instruction's guidelines. After two weeks of acclimation, animals were divided into four equal groups, 7 animals in each group. The first group was used as control. While, second group was treated with CCl4 1 mg/kg BW in olive oil by gavage twice a week, group 3 was treated with sesame oil 1ml/kg BW daily, group 4 was treated with the combination of CCl4 and sesame oil. Rabbits were orally administered their respective doses by gavage for twenty one days.

CCL4 and sesame oil doses and way of administration were established according to previous studies. Rats were orally administered with 1 ml/kg BW of CCl_4 twice a week according to Ryoji[13]*et al.* (2007). While, sesame oil was given orally by gavages at a volume of 5 ml/kg body weight according to the previous study of Shakoori[14]*et al.* (1990). Animals were weighed daily while receiving treatment for 21 days. On the 22th day of theexperiment all animals were anesthetized with methyl alcohol and blood samples were obtained for biochemical analysis.

BLOOD BIOCHEMICAL PARAMETERS AND ENZYME ACTIVITIES

Plasma was obtained by centrifugation of samples at 860 xg for 20 min, and was stored at -20°C until used for analyses.Stored plasma samples were analyzed for total protein (TP) by the Biuret method according toArmstrong[15] and Carr (1964). Albumin (A) concentration was determined by the method ofDoumas[16]*et al.,* (1977). Plasma glucose, urea and creatinine concentrations were measured by the method of Trinder[17] (1969), Patton and Crouch[18] (1977) and Henry[19]*et al.,* (1974), respectively. Plasma total bilirubin was measured using the method of Pearlman[20] and Lee (1974).

The activities of plasma aspartate transaminase (AST; EC 2.6.1.1) and alanine transaminase (ALT; EC 2.6.1.2) were assayed by the method of Reitman and Frankel[21] (1975). Alkaline phosphatase (AlP; EC 3.1.3.1) activity was determined in plasma according to the method of (Principato[22]*et al.*, 1985). Acid phosphatase (AcP; EC 3.1.3.2) activity was determined according to the method of Moss[23] (1984).

STATISTICAL ANALYSIS

Statistical analysis was carried out by Minitab software statistics. Significance was assessed using two samples T-test analysis. P<0.05 is considered significant (Paulson[24], 2008).

BIOCHEMICAL PARAMETERS

Table (1) show levels of total protein, albumin and bilirubin in the serum of male rabbits. Levels of total protein and albumin showed a significant decrease after treatment with carbon tetrachloride compared to the control.Levels of total protein and albumin increased significantly after treatment with the combination of CCl_4 and sesame oil compared to the CCL4 alone group.Levels of bilirubin increased significantly after treatment with CCl_4. Levels of bilirubin decreased after treatment with the combination of a CCL4 and sesame oil, but still significant difference compared to CCL4alone.

Table 01 : Mean ± SE of serum of male rabbits treated with carbon tetrachloride (CCl_4), sesame oil and their combination (CCl_4 and So).

Parameter	Control	CCL_4	So	CCL_4 + S o
Total Protein	$9^b \pm 0.2$	$6.5^a \pm 0.14$	$8.5^b \pm 0.14$	$7.8^b \pm 0.12$
Albumin	$6.1^b \pm 0.16$	$4.5^a \pm 0.10$	$5.7^b \pm 0.09$	$5.6^b \pm 0.19$
Bilirubin	$0.85^b \pm 0.04$	$1.4^a \pm 0.07$	$0.92^b \pm 0.0$	$0.89^b \pm 0.01$

Values are expressed as mean ± SE. Mean values within a row not sharing a common superscript letter were significantly different (P < 0.05).

Table (2)shows that levels of ALT and AST increased significantly after treatment with carbon tetrachloride compared to the control.Levels of ALT and AST decreased significantly after treatment with the combination of CCl4 and sesame oil compared to CCl4 group.

Table 02: Mean ± SE of alanine transminase and aspartate transaminase in serum of male rabbits treated with carbon tetrachloride , sesame oil and their combination (CCl_4 and So).

Parameter	Control	CCl_4	So	CCl_4 + S oil
ALT (U/L)	**$13.4^b \pm 2.2$**	**$19.2^a \pm 0.21$**	**$13^b \pm 0.19$**	**$11.9^b \pm 0.16$**
AST (U/L)	**$22.8^b \pm 0.17$**	**$33.2^a \pm 0.29$**	**$22.7^b \pm 0.27$**	**$29.4^c \pm 0.23$**

Values are expressed as mean ± SE. Mean values within a row not sharing a common superscript letter were significantly different (P < 0.05).

Table 03 shows that levels of alkaline phosphatase and acid phosphatase increased significantly after treatment with carbon tetrachloride compared to control.Levels of ALK and ACP decreased significantly after treatment with the combination CCl4 and sesame oil compared to control.

Table 03 : Mean ± SE of alkaline phosphatase and acid phosphatase in serum of male rabbits treated with carbon tetrachloride , sesame oil and their combination (CCl_4 and So).

Parameter	Control	CCl_4	So	CCl_4 + S oil
ALP	69.6^b ± 0.37	81^a ± 0.3	68.5^b ± 0.39	78.6^b ±0.32
ACP	10.64^b ± 0.37	19.9^a ± 0.27	11.7^b ± 0.33	15.1^b ± 0.18

Values are expressed as mean ± SE. Mean values within a row not sharing a common superscript letter were significantly different ($P < 0.05$).

Table 04 show that levels of lactate dehydrogenase and glucose in serum of male rabbits. Levels of LDH increased significantly after treatment with carbon tetrachloride compared to control. Levels of LDH increased significantly after treatment with the combination of CCl4 and sesame oil compared with the control. Glucose in serum of male rabbits decreased significantly after treatment with CCl4 compared to control. There was a significant difference between group treated with CCl4 and group treated with the combination of CCl4 and sesame oil.

Table 04 : Mean ± SE of lactate dehydrogenase (LDH) and glucose levels in serum of male rabbits treated with carbon tetrachloride (CCl_4) , sesame oil and their combination (CCl_4 and So).

Paramete r	Contro l	CCl_4	So	CCl_4 + S oil
LDH	852.4^b ± 1.6	973^a ± 1.27	859^b ± 2.9	855.4 ^{b} ±1.9
Glucose	91.6^b ± 1.07	123.4 ^{a} ± 1.3	89.4 ^{b} ± 1.4	107^b ± 1.41

Values are expressed as mean ± SE. Mean values within a row not sharing a common superscript letter were significantly different ($P < 0.05$).

Table 05 shows levels of urea and creatinine in serum of male rabbits. Levels of urea increased significantly after treatment with carbon tetrachloride compared to control.There is a significant difference between groups treated with the combination of CCl4 and sesame oil and group treated with CCl4 alone.Levels of creatinine increased significantly after treatment with carbon tetrachloride compared to the control.There is a significant difference between groups treated with the combination of CCl4 and sesame oil and group treated with CCl4 alone.

Table 05: Mean ± SE of urea and creatinine levels in serum of male rabbits treated with carbon tetrachloride (CCl_4) , sesame oil and their combination (CCl_4 and So).

Parameter	Control	CCl_4	So	CCl_4 + S oil
Urea	44.3^b ± 0.33	50.8^a ± 0.43	42.6^b ± 0.23	39.6^b ±0.23
Creatinine	0.91^b ± 0.03	1.5^a ± 0.1	0.9^b ± 0.06	0.89^b ± 0.04

Values are expressed as mean ± SE. Mean values within a row not sharing a common superscript letter were significantly different ($P < 0.05$).

DISCUSSION AND CONCLUSSION

Our results were in agreement with the results obtained by Nevin [25] and Vijayammal (2005), who reported that decrease in total protein in CCl_4 treated groups is due the damage caused to the liver by CCl_4. protein is done as a routine test to evaluate the toxicological nature of various chemicals [25].

In the present study, the results were in agreement with results obtained by Shahat (2011) [26], where the blood serum enzymes, bilirubin, were significantly increased while the total protein and albumin were significantly decreased in CCl4 treated group. These results were in agreements with Kanter et al [27]. (2005) who reported that, after treatment of rats with CCl4, an increase in the serum activities of ALT, AST, ALP, and bilirubin were observed. This increase was probably due to hepatic damage, oxidative stress, and loss of the liver functions.

The results of the current work also showed treatment with sesame oil only caused no significant changes in TP and albumin, while decrease glucose, bilirubin, urea and creatinine in male rats. Sesame oil minimized the toxic effect of CCl4 in the combination group and this means that it alleviated the harmful effect of CCl4. These results are in accordance with Hussien et al [28]. (2013) who reported that rats treated with sesame oil and cypermethrin exhibited a significant ($p < 0.05$) increase in the levels of total protein and albumin and decrease in the levels of cholesterol and triacylglycerol compared to cypermethrin group. Sesame oil ameliorated the reduction in plasma total protein and albumin. Also, the observed decrease in plasma proteins could be attributed in part to the damaging effect of CCl4 on liver cells as confirmed by the increase in the activities of plasma AST and ALT.

The increase in bilirubin is in agreement with Sahare et al [29]. (2006) who reported that the using the model of CCl_4-induced hepatotoxicity in the rats demonstrated that ethanol and aqueous extracts caused significant increase in bilirubin levels. Increase in serum bilirubinis related to the function of hepatic cell.

Treatment with sesame oil alone caused a significant ($p<0.05$) decrease in plasma and increase in liver AST, ALT, AlP, AcP and LDH activities. While, treatment with CCl_4 significantly ($p<0.05$) increased plasma and liver AST, ALT, AlP and AcP activities compared to control. The presence of sesame oil with CCl_4 minimized its toxic effect on plasma and liver enzymes to reach the control levels.

In liver injury, the transport function of the hepatocytes is disturbed, resulting in the leakage of plasma membrane, thereby causing an increased enzyme level in serum, and soluble enzymes like AST will also be similarly released. The elevated activities of AST and ALT in serum are indicative of cellular leakage and loss of functional integrity of cell membranes in liver (Rajesh [30] and Latha, 2004). Jeong [31]et al. (2006) reported that CCl_4 is known to cause hepatic damage with a marked elevation in serum levels of transaminase enzymes (AST and ALT), because these enzymes are cytoplasmic in location and are released into the blood after cellular damage. Additionally, AST is found in every tissue of the body, and the amount of AST is particularly high in the cardiac muscle. In contrast, ALT is present in moderately high concentration in liver and low in cardiac. After a single injection of CCl_4, serum activities of ALT and AST enzymes in the hepatotoxic model group were significantly increased. The hepatotoxicity induced by CCl_4 is due to its activation by cytochrome P-450 to form a trichloromethyl radical, $CCl3^-$.The trichloromethyl radical leads to liver damage by alkylating cellular proteins and other macromolecules with a simultaneous attack on polyunsaturated fatty acids to produce lipid peroxides [1]. This radical can bind to cellular molecules (nucleic acid, protein, lipid), impairing crucial cellular processes such as lipid metabolism, with the potential outcome of fatty degeneration. The covalent binding of trichloromethyl radicals to cellular macromolecules is considered to function as the initiator of membrane lipid peroxidation and cell necrosis [6]. Hepatocellular necrosis leads to elevations of serum AST and ALT activities and an increased incidence and severity of histopathological hepatic lesions in rats. It has been hypothesized that one of the principal causes of CCl_4-induced liver injury is formation of lipid peroxides by free radical derivatives of CCl_4 [23]

An increase in serum lactate dehydrogenase (LDH) activity is one of important biomarkers to evaluate myocardial injuries due to various pathological causes, such as drug toxicity, myocardial ischemia-induced acute or chronic cardiac inflammation. Sharma et al [33]. (2012) conducted a research to determine the role of sesamol in chronic high-cholesterol/high-fat diet in rats. Rats on sesamol diet had decreased levels of glucose, hepatic alanine transaminase and aspartate transaminase and alkaline phosphatase.

Mokuda et al [34]. (1995)reported that in the CCl_4-injured liver, net glucose output was less suppressed at high glucose levels than in the normal liver. Deposition of the carbon from [14C] glucose into glycogen was stimulated at high glucose levels and was markedly reduced in the CCl_4-injured liver compared to the normal liver. Ikeda et al [35]. (1986) reported that carbon tetrachloride-induced liver injury in rats, hyperinsulinemia and hyperglucagonemiamay be dependent on decreased insulin and glucagon extraction by the liver. The increases in urea and creatinine in the present study due to CCl_4 treatment are in agreement with the results of Karima [36] (2007)who reported that CCl_4 injection induced significant increase in serum urea and creatinine concentrations. Our results were in agreement with the results of Liu et al [3]. (2015), who studied chronic kidney disease induced by subcutaneously injecting uni-nephrectomized rats with deoxycorticosterone acetate (DOCA) and 1% NaCl [DOCA/salt] in drinking water. Four weeks later, the rats were gavaged with sesame oil (0.5 or 1 mL/kg per day) for 7 days. Blood urea nitrogen, creatinine, urine volume were significantly higher in the DOCA/salt treated rats than in control rats. Sesame oil significantly decreased these parameters in DOCA/salt treated rats, compared to control rats. Exposure to CCl_4 also induces acute and chronic renal injuries (Tirkey et al. [31], 2005**)**. Gavin [38]

(1995) reported that CCl_4 injection induced significant increase in serum urea and creatinine concentrations. These changes in urea and creatinine levels may indicate a reduction in the glomerular filtration rate (GFR) as a result of ccl_4 intoxication, since the serum concentration of these two parameters depends largely on the glomerular filtration.

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