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Curative Effect of Dietary Freshwater and Marine Crustacean Extracts on Carbon Tetrachloride-induced Nephrotoxicity

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Abstract: The freshwater crustacean *Procombarus clarkii* and marine *Erugosquilla massavensis* are edible crustacean species that have a small yet growing economic importance in our markets. However, their therapeutic effects as antioxidant remain unclear. So, the present work aims to throw the light for the first time in Egypt on their antioxidant effects. Carbon tetrachloride (CCl_4) is established hepatotoxin and also induces acute and chronic renal injuries. The present study was designed to establish the curative effects of both freshwater crustacean extract (FCE) from *Procombarus clarkii* and marine crustacean extract (MCE) from *Erugosquilla massavensis* on CCl_4-induced oxidative stress and resultant dysfunction of kidney. Rats were randomly divided into 4 groups, (I) control, (II & III) administered orally FCE and MCE (250 mg/kg) respectively for 9 days and (IV) administered (CCl_4) (2.5 ml/kg b.wt. p.o) for 2 days and then subdivided into 8 subgroups, the animals of these subgroups treated for 7 days as follow, subgroup (I) distilled water, (II) sliymarin, (III, VI, V) administered 50, 100 and 250 mg/kg. FCE and (X, XI, XIII) administered 50, 100 and 250 mg/kg. MCE, respectively. CCl_4 challenge caused a significant increase in malondialdehyde (MDA) (II) and decrease in reduced glutathion (GSH) levels, catalase (CAT) activity and total antioxidant capacity (TAC) as compared to control group. Treatment with all tested doses of both FCE and MCE attenuated the CCl_4-toxicity, furthermore restore the control condition, hence the dose dependant effect study was unnecessary and the present study recommended the treatment with two studied extracts at a dose of 50 mg/kg. In conclusion, the present study demonstrated the curative effect of FCE and MCE on CCl_4 induced oxidative stress in kidney. The curative effect of FCE and MCE can be correlated to their direct antioxidant effect which may be related to their contents of sulpher-containing amino acids and taurine.

Key words: Crustacea, *Procambarus clarkii*, *Erugosquilla massavensis*, Kidney injury, Oxidative stress, CCl_4.

INTRODUCTION

Exposure to various organic compounds including a number of environmental pollutants and drugs can cause cellular damages through metabolic activation of those compounds to highly reactive substances such as reactive oxygen species (ROS). Carbon tetrachloride (CCl_4), an induistrial solvent, is a well established hepatotoxin (Szymonik-Lesiuk *et al*., 2003; Tirkey *et al*., 2005; Ye *et al*., 2009; Murugesan *et al*., 2009). Various studies demonstrated that liver is not the only target organ of CCl_4 and it causes free radical generation in other tissues such as kidney, heart, testis, brain and blood (Manjrekar *et al*., 2008; Ichi *et al*., 2009; Preethi&Kuttan, 2009). It has been reported that CCl_4 induced acute and chronic renal injuries (Ogeturk *et al*., 2005; Jaramillo-Juarez *et al*., 2008; Preethi&Kuttan, 2009).

Extensive evidence demonstrated that CCl_3 and Cl are formed as a result of the metabolic activation of CCl_4, which in turn, initiate lipid peroxidation process (Yuan *et al*., 2008; Upur *et al*., 2009; Quan *et al*., 2009). Studies also showed that certain natural extracts containing antioxidants protect against CCl_4-induced lipid peroxide levels and impairment in hepatic glutathion GSH status (Yoshikawa *et al*., 1997; Tirkey *et al*., 2005; Koyama *et al*., 2006; Quan *et al.,* 2009).

Products from freshwater and marine sources have recently become attractive as nutraceutical and functional foods and as a source material for the development of drugs and specific health foods (Koyama *et al*., 2006). Supplements derived from marine foods have been used to treat and prevent a wide variety of lifestyle-related diseases such as unsaturated fatty acids (Ikeda *et al*., 1994; Hamazaki *et al*., 2005) and

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functional peptides (Abe, 2000; Fujita *et al*., 2001). Recent attention has been focused upon supplements derived from freshwater foods and their utilization as hepatoprotective agents (Peng, 2008; Chijimatsu *et al*., 2008; Chijimatsu *et al*., 2009).

Freshwater crayfish *Procambarus clarkii* has been widely spread all over most of the River Nile (Elmossalami&Emara,1999). Marine mantis shrimp *Erugosquilla massavensis* is well established in the eastern Mediterranean, displaying and dominating the local species *Squilla mantis* (Kacatas & Katagon, 1995). *Procambarus clarkii* and *Erugosquilla massavensis* are an edible crustacean that have a small yet growing economic importance in our markets (Hamdi & Zaghloul, 2006; Hamdi & Abd El-Monem, 2006).

Consumption of these foods by humans may significantly influence their health status. It is important to know the pathological effects and mechanisms of action of these foods. In the following study, we investigated two crustacean extracts (CE), one from freshwater crayfish *Procambarus clarkii* (FCE) and the other from marine shrimp *Erugosquilla massavensis* (MCE) with a goal of determining their potential as antioxidants. Indeed, the rationale for this work based on the high taurine content found in both crustacean meat and extracts therefore (Table 1). Taurine is a sulfur containing amino acid which has been previously found to exhibit antioxidant properties (Xu *et al*., 2008; Li *et al*., 2009; Das *et al*., 2009). Because these two crustacean species are considered from the very few sources rich in taurine and since the amino acid composition of their extracts is also enriched in glutamic acid, cysteine and glycine (the amino acids component of GSH) (Table 1), we aim to throw the light for the first time in Egypt on their antioxidant activity and subsequently their curative effect against CCl_4 induced nephrotoxicity in rats.

MATERIALS AND METHODS

Preparation of Crude Freshwater and Marine Crustacean Extract (CE):

Freshwater crayfish *Procombarus clarkii* specimens were collected from the River Nile at Abu-Rawash area-Giza Governorate while marine *Erugosquilla massavensis* species were collected from Mediterranean Sea at Port-Said Governorate.

Crustacean extract powder was prepared as follows: fresh raw specimens of each species (1 kg for each) were used. All appendages were cut and the fresh whole bodies away from the carapace and stored at -20°C until needed. After thawing, the specimens were homogenized with a mixer. The homogenate was extracted with water for 3 hr. After filtration, the filtrate obtained was then concentrated and lyophilized to a brownish residue using (LABCONCO lypholizer, shell freeze system, USA). The freshwater crustacean extract (FCE) and marine crustacean extract (MCE) were analyzed by HPLC ; Beckman 6300 amino acid analyzer (Marquez *et al*., 1986 with minor modifications; Radwan *et al.,* 2007). Their components were shown in Table 1.

Chemicals:

Carbon tetrachloride was purchased from Merk Egypt. Silymarin was purchased from Sedico (Pharmaceutical Co., 6 October City, Egypt).

Experimental Animals:

The experimental animals used in this study was the adult male albino rats (*Rattus norvegicus*) weighing 100-120 g. The animals were obtained from a fixed local supplier. Animals were caged in groups of ten and given food and water ad libitum. Rats were kept under fixed appropriate conditions of housing and handling

Experimental Protocol:

Animals were divided into four main groups, the 1st group serves as control; animals of this group (6 rats/group), administered olive oil orally by gastric gavage for 2 days, and followed by distilled water for 7 consecutive days. Animals of the 2nd and 3rd groups (6 rats/group) administered orally FCE and MCE (250 mg/kg b.wt. p.o.) respectively for 9 days. Fourth group (48 rats), given CCl_4 orally (2.5 ml/kg b.wt. of 50%, dissolved in olive oil) for 2 days, this group then divided into 8 subgroups (6 rats/ subgroup), animals of these subgroups treated for 7 consecutive days as follow:

Subgroup I (CCl_4): Rats of this subgroup administered distilled water orally.

Subgroup II (Sli.): Rats treated orally with standard drug sliymarin (150 mg/kg b.wt., dissolved in distilled water).

Subgroups III, IV, V: Animals of these subgroups treated orally with FCE (50, 100 and 250 mg/kg b.wt.) respectively.

Subgroups X, XI, XII: Animals orally administered MCE (50, 100 and 250 mg/kg b.wt.) respectively.

All animals were sacrificed on the 10th day of treatment after being fasted over night; blood was collected in centrifuge tubes. Serum was prepared and was used freshly for the assessment of kidney function tests. Kidneys were quickly harvested, cleaned with saline and immediately stored at -20°C till further biochemical estimations.

Assessment of Renal Functions:

Serum samples were assayed for creatinine, uric acid, urea and blood urea nitrogen (BUN) by using standard kits (Biodiagnostic kits). Creatinine was detected by the method of (Houot, 1985), uric acid was detected by the method of (Fossati *et al*., 1980) and urea and BUN were estimated by (Patton and Crouch, 1977) method.

Assessment of Oxidative Stress:

Kidney was homogenized (10% w/v) in ice-cold 0.1 M phosphate buffer (pH 7.4). The homogenate was centrifuged at 3000 rpm for 15 min at 4°C and the resultant supernatant was used for different oxidative stress markers. The appropriate kits (Biodiagnostic) was used for the determination of lipid peroxidation which was measured by the formation of malondialdehyde [MDA] (Ohkawa *et al*., 1979), glutathion reduced [GSH] (Aykac *et al*., 1985), catalase activity [CAT] (Aebi *et al*., 1984) and total antioxidant capacity [TAC] (Koracevic *et al*., 2001).

Statistical Analysis:

Reported values represented as means + SE. Statistical analysis was evaluated by one-way ANOVA. Once a significant F test was obtained, LSD comparisons were performed to assess the significane of differences among various treated groups. Statistical Processor System Support "SPSS" for Windows soft-ware. A value of ($P<0.05$) was considered significant.

RESULTS AND DISCUSION

Effect of FCE and MCE on Kidney Function:

The levels of serum creatinine, uric acid, urea and BUN in the control, CCl_4 injured, silymarin treated , freshwater crustacean extract [FCE] and marine crustacean extract [MCE] administered rats are shown in Table 2. CCl_4 administration induced non-significant changes in the levels of the creatinine, uric acid, urea and BUN as compared to the corresponding control. Treatment with both FCE and MCE either normally or following CCl_4 intoxication was found to induce also non-significant changes, as compared to control or CCl_4-intoxicated groups respectively (Table 2).

Table 1: The ingredients of FCE and MCE extracts powder.

Amino Acids (mg/100 g)	*Procambarus clarkii extract*	*Eurgosquilla massavensis extract*
Alanine	333.81	216.17
Arginine	288.29	160.53
Aspartic acid	218.65	133.69
Cysteine	259.62	164.92
Glutamic acid	110.29	220.46
Glutamine	323.51	730.14
Glycine	206.72	217.44
Histidine	146.04	201.89
Isoleucine	392.81	227.47
Leucine	189.68	161.64
Lysine	178.51	126.64
Methionine	167.43	133.02
Phenylalanine	244.72	182.16
Proline	402.63	260.11
Serine	146.87	178.20
Threonine	416.64	261.17
Tyrosine	350.71	217.19
Valine	229.87	176.83
Taurine	126.49	133.05

Table 2: Effect of FCE, MCE and silymarin on some biochemical parameters following CCl4 –intoxication in rats.

	Group	Creatinine (mg/100 ml)	Uric acid (mg/100 ml)	Urea (mg/100 ml)	BUN (mg/100 ml)
	Control	0.51 ± 0.04	2.45 ± 0.08	43.60 ± 2.77	20.45 ± 1.34
	CCl4	0.55 ± 0.04	2.56 ± 0.06	44.93 ± 1.83	20.66 ± 0.85
	Sliymarin	0.52 ± 0.03	2.35 ± 0.08	43.75 ± 2.30	20.52 ± 1.08
FCE	Normal (250mg/Kg)	0.55 ± 0.04	2.77 ± 0.05[a]	49.08 ± 1472	22.92 ± 0.80
	CCl4 +50mg/kg	0.57 ± 0.04	2.67 ± .13	45.66 ± 2.22	21.66 ± 1.04
	CCl4+100mg/Kg	0.53 ± 0.03	2.58 ± 0.05	42.75 ± 3.56	19.64 ± 1.66
	CCl4+250mg/Kg	0.54 ± 0.02	2.48 ± 0.22	41.97 ± 0.94	19.68 ± 0.44
MCE	Normal (250mg/Kg)	0.54 ± 0.02	2.48 ± 0.05	40.64 ± 1.00	18.65 ± 0.47
	CCl4 +50mg/kg	0.50 ± 0.04	2.59 ± 0.11	43.36 ± 1.63	20.25 ± 0.76
	CCl4+100mg/Kg	0.52 ± 0.02	2.48 ± 0.78	37.41 ± 2.53	17.73 ± 1.84
	CCl4+250mg/Kg	0.53 ± 0.03	2.38 ± 0.04	39.76 ± 1.81	18.71 ±0.85

Effect of FCE and MCE on Lipid Peroxidation:

MDA levels were assessed as an indicator of lipid peroxidation, CCl_4 treatment significantly ($P<0.05$) increased the level of MDA in the kidney tissue as compared to the control (Fig. 1A). However, treatment with FCE or MCE at all tested doses and silymarin significantly ($P<0.05$) decreased the increased level of MDA as compared to the CCl_4-treated rats (Fig. 1A&B). Nine-days treatment with FCE and MCE (250 mg/kg) did not result in a significant alteration of MDA levels as compared to the control groups (Fig. 1A&B).

Effect of FCE and MCE on Reduced Glutathion Level:

CCl_4 administration significantly ($P<0.05$) decreased the level of reduced glutathion (GSH) as compared to the control group demonstring oxidative stress (Fig. 2A). Again, administration of FCE and MCE following CCl_4 treatment significantly increased the GSH level as compared to CCl_4-treated groups (Fig. 2A&B). However, FCE administration of (100 and 250 mg/kg) restore GSH level near the control value (Fig.2A). Likewise, MCE administration restore GSH level near the control value, but at (50 and 100 mg/kg) (Fig. 2B). FCE and MCE administration at (250 mg/kg) did not result in a significant alteration of GSH level as compared to the control group (Fig. 2A&B).

Effect of FCE and MCE on Catalase Activity:

Concerning the effect of CCl_4 on the catalase (CAT) activity, a significant decrease ($P<0.05$) in the CAT activity was recorded as compared to the control rats (Fig. 3A). Meanwhile, all the treatments either with FCE or MCE and silymarin caused significant increase in the CAT activity as compared to the CCl_4-treated rats (Fig.3A&B). However, the administration of FCE and MCE (250 mg/kg) to rats did not result in any significant change as compared to the control group (Fig. 3A&B).

Effect of FCE and MCE on Total Antioxidant Capacity:

As shown in Fig. 4A, CCl_4 challenge significantly decreased ($P<0.05$) the total antioxidant capacity (TAC) as compared to control rats. However, treatment with FCE or MCE and silymarin at different doses significantly increased TAC as compared to CCl_4-treated group (Fig.4A&B). Administration of FCE to CCl_4-treated groups can restore TAC near the control value at (50 and 250 mg/kg) (Fig. 4A), while administration of MCE do the same effect but at (100 and 250 mg/kg) (Fig. 4B). Regarding to the effect of FCE and MCE administration normally, the data recorded revealed that TAC did not significantly affected as compared to the control group (Fig. 4A&B).

Discussion:

There is a growing body of evidence that oxygen derived free radicals are involved in the pathogenesis of over 50 disease (Moskovitz *et al*., 2002). Antioxidant therapy aimed at reducing free radical-mediated tissue damage represents a rational approach in preventing the onset and/or progression of free radical-related tissue damage. In this connection, the measurement of antioxidant activity should form an additional basis for drug screening and selection (Zhou *et al*., 2008; Adiguzel *et al.,* 2009). In the present study, we evaluate the antioxidant potential of two crustacean extracts, freshwater *Procambarus clarkii* (FCE) and marine *Erugosquilla massavensis* (MCE) against CCl_4-induced nephrotoxicity in rats.

A number of chemicals including various environmental toxicants and clinically useful drugs can cause cellular damages in different organs of our body through metabolic activation to highly reactive substance such as free radicals. CCl_4 is one of such extensively studied environmental toxicant (Ogturk *et al*., 2005; Jaramillo-

Juarez *et al*., 2008; Preethi&Kuttan, 2009). It is well known that the toxic effects of CCl_4 stem from its metabolic transformation to trichloromethyl (CCl_3) and trichloromethyl peroxyl (CCl_3O_2) free radicals, which through peroxidation of cell membranes cause cell injury (Uskokovic-Markovic *et al*., 2007; Khan&Sultana, 2009; Miyazaki *et al*., 2009). Lipid solubility of CCl_4 allows it to cross cell membranes, distributed and deposited to organs such as liver, brain and kidney (Szymonik-Lesiuk *et al*., 2003). Kidney is especially vulnerable to xenobiotic insults due to high blood supply, high exchange rate of water, electrolytes, nutrients, metabolites, and extensive exposure to relatively high concentrations of pharmaceuticals and their metabolites (Werner *et al*., 1995). Carbon tetrachloride (CCl_4) is one of xenobiotics that have been reported to induce acute and chronic renal injuries (Ogeturk *et al*., 2005; Jaramillo-Juárez *et al*., 2008).

Any oxidative insult to a cell induces lipid peroxidation of cell membrane lipids. Studies have demonstrated that acute or chronic CCl_4 administration to experimental animals increased the formation of lipid peroxidation products, such as malondialdehyde [MDA] (Szymonik-Lesiuk *et al*., 2003; Hong *et al*., 2009; Liu *et al*., 2009). Lipid peroxidation has been postulated as the destructive process in kidney injury due to CCl_4 administration (Tirkey *et al*., 2005; Manna *et al*., 2006; Manjrekar *et al*., 2008; Jayakumar *et al*., 2008). In the present study, the significant increase in the level of MDA due to CCl_4 administration indicates enhanced lipid peroxidation leading to tissue damage and failure of antioxidant defense mechanisms in preventing the formation of excessive free indicals.

Glutathion reduced [GSH] has been to be an important cellular protectant against reactive oxygen metabolites in several cells by serving as a substrate for glutathion peroxidase (Harlan *et al*., 1984; Hiraishi *et al*., 1994). The present study confirmed the findings of earlier studies on CCl_4 toxicity in rats, Tirkey *et al*. (2005), Manna *et al*. (2006) and Ichi *et al*. (2009) by demonstrating significant decrease in GSH in the kidney tissues of CCl_4 treated rats. In accord with our results, Manna *et al*. (2006) reported that ROS generated by CCl_4 affects the antioxidant defense mechanisms, reduces intracellular GSH content. A considerable decline in GSH content in the kidney tissues following CCl_4 intoxication in the present investigation may be due to its utilization to challenge the prevailing oxidative stress under the influence of ROS generated from CCl_4.

Catalase (CAT) reduces hydrogen peroxide produced by dismutation reaction and prevents generation of hydroxyl radicals thereby protecting the cellular constituents from oxidative damage in peroxisomes. CCl_4 intoxication in the present study result in the significant decrease in CAT activity. In consonance with our results, Szymonik-Lesiuk *et al*. (2003) reported that CCl_4 intoxication would lead to damage of antioxidant enzymes or reactive intermediates formed in the course of bioactivation of CCl_4 may bind to those enzymes that are responsible for their inactivation. Escobar *et al*. (1996) indicated that enhanced free radical concentration resulting from oxidative stress conditions can cause loss of enzymatic activities. Furthermore, it was reported that regulation of the antioxidant enzymes was depressed following CCl_4 intoxication (Szymonik-Lesiuk *et al*., 2003; Manna *et al*., 2006; Jayakumar *et al*., 2008). Increased lipid peroxidation and decreased GSH level as well as the antioxidant enzyme CAT in the kidney tissues following CCl_4 administration in the present investigation was indicated by the decrease of the total antioxidant capacity.

Viewed in conjunction with the report of Tirkey *et al*. (2005), Manna *et al*. (2006) and Fahmy & Soliman (2007) data from the present investigation reflect that CCl_4 failed to induce any effect on renal function as manifested by non-significant changes in the kidney function markers, serum creatinine, uric acid, urea and BUN. This could be due one possibility which is that the time of CCl_4 exposure to the animals was not enough for the renal damage although oxidative stress could be induced by that exposure. This possibility can be confirmed from the report of Ogawa *et al*. (1992) who recorded chronic renal injury and BUN elevation in mice only after 12 weeks of CCl_4 intoxication. Furthermore, it has been reported that kidney can function normally with low grade damage, functional changes are not readily observed until a significant portion of the kidney is damaged (Price, 1992).

Antioxidant and anti-inflammatory agents play a critical role in body protection by scavenging active oxygen and free radicals and neutralizing lipid peroxides (Aniya *et al*., 2005; Maitraie *et al*., 2009). Therefore, there is need for a natural product that protects the body but cost-effective, safe and without side effects. So, the present study conducted to study the antioxidant properties of freshwater crustacean extract (FCE) and marine crustacean extract (MCE). The obtained results showed that both of two extracts at 50, 100 and 250 mg/kg b.wt. attenuate the CCl_4 toxicity as manifested by significant reduction in MDA and increase in the GSH levels, CAT activity and total antioxidant capacity, indicate their effect in quenching the reactive intermediates and radical species generated during oxidative stress. The dose dependant effect study was unnecessary in the present investigation as the three studied doses of both two extracts can attenuate CCL_4 toxicity by the same order. So, the present study recommended the treatment with FCE and MCE against CCL_4 toxicity at a dose of 50mg/kg. body weight.

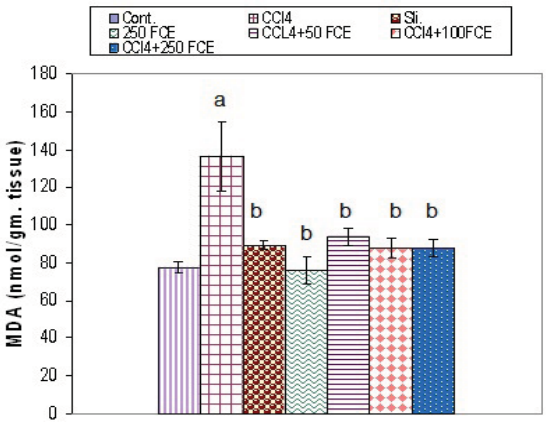

Fig. 1A: Effect of FCE and sliymarin on lipid peroxidation levels in CCl4 intoxicated rats.Values are means+SEM of five rats. a :significantly different as compared to control. b:significantly different as compared to CCl4. P<0.05

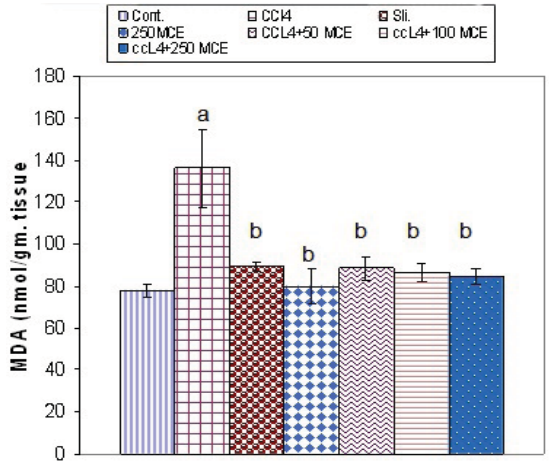

Fig. 1B: Effect of MCE and sliymarin on lipid peroxidation levels in CCl4 intoxicated rats.Values are means+SEM of five rats. a:significantly different as compared to control. b:significantly different as compared to CCl4. P<0.05

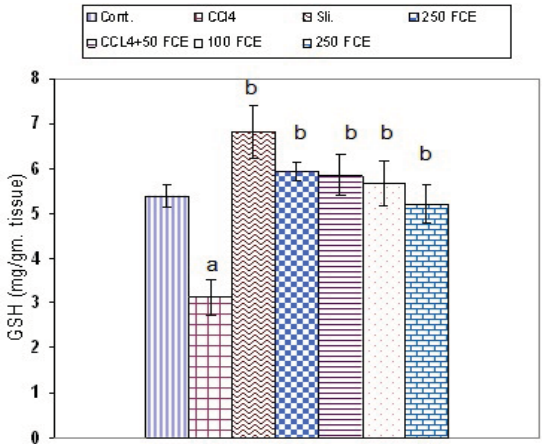

Fig. 2A: Effect of FCE and sliymarin on glutathione reduced levels in CCl4 intoxicated rats.Values are means+SEM of five rats. a:significantly different as compared to control. b:significantly different as compared to CCl4. P<0.05

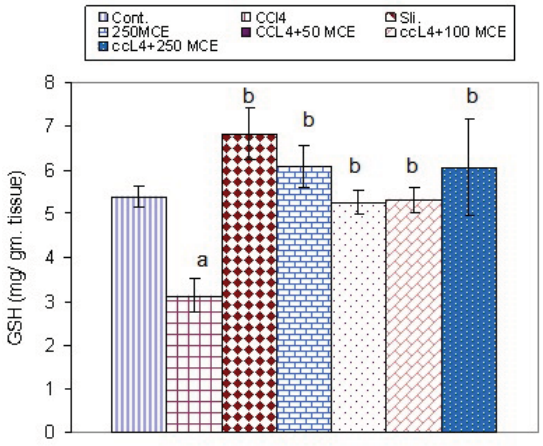

Fig. 2B: Effect of MCE and sliymarin on glutathione reduced levels in CCl4 intoxicated rats.Values are means+SEM of five rats. a:significantly different as compared to control. b:significantly different as compared to CCl4. P<0.05

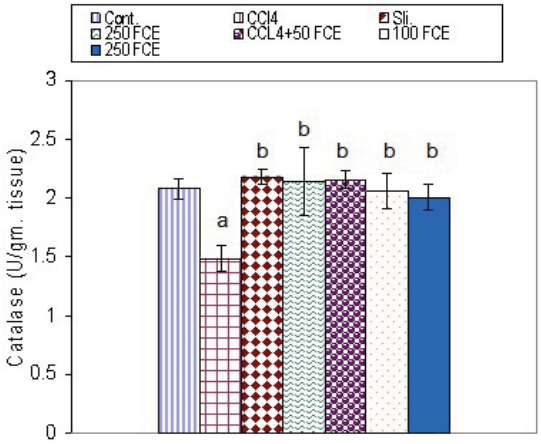

Fig. 3A: Effect of FCE and sliymarin on catalase activities in CCl4 intoxicated rats.Values are means+SEM of five rats. a:significantly different as compared to control. b:significantly different as compared to CCl4. P<0.05

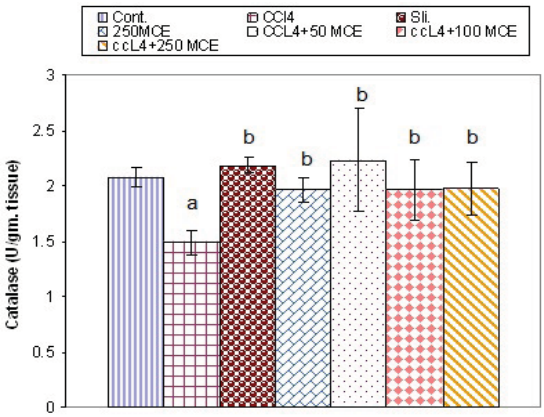

Fig. 3B: Effect of MCE and sliymarin on catalase activities in CCl4 intoxicated rats.Values are means+SEM of five rats. a:significantly different as compared to control. b:significantly different as compared to CCl4. P<0.05

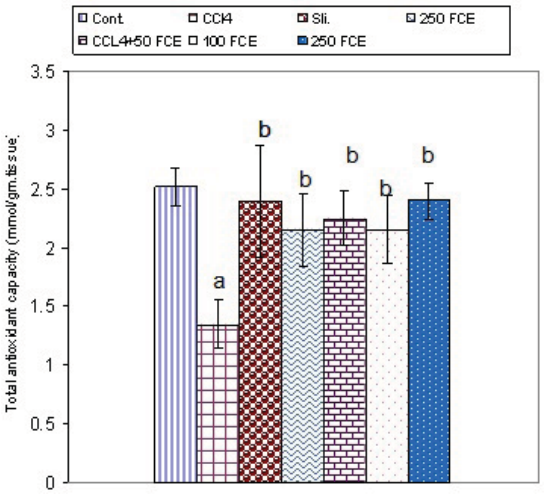

Fig. 4A: Effect of FCE and sliymarin on total antioxidant activities in CCl4 intoxicated rats.Values are means+SEM of five rats. a:significantly different as compared to control. b:significantly different as compared to CCl4. P<0.05

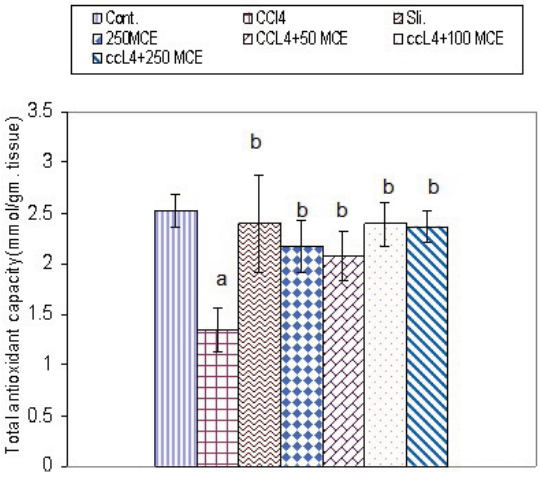

Fig. 4B: Effect of MCE and sliymarin on total antioxidant activities in CCl4 intoxicated rats.Values are means+SEM of five rats. a:significantly different as compared to control. b:significantly different as compared to CCl4. P<0.05

In recent years many studies have shown that many traditional natural products have a wide range of physiological, biochemical and pharmacological effects due to the properties of their constituents (Yoshikawa *et al*., 1997; Peng, 2008). In particular, they contain a variety of substances having antioxidant activity including thiol-containing amino acids, especially taurine. In consonance with the previous studies, the present work showed that both of FCE and MCE contain considerable level of the sulpher-containing amino acids and taurine. It was reported that, administration of such amino acids like methionine (Lieber *et al*., 1990) and cysteine (Anuradha & Vijayalakshmi, 1995) replete the levels of antioxidants and minimizes oxidative stress. However, taurine has advantages over these substances, where its antioxidant action has been demonstrated in a variety of *in vitro* (Devamanoharan *et al*., 1998) and *in vivo* systems (Li *et al*., 2009; Wojcik *et al*., 2009)

The present study can also revealed that glutamine is dominant free amino acid in MCE and found in the same time in high level in FCE. It was reported that a glutamine enriched diet increases plasma taurine in stressed rats (Boelens *et al*., 2003).

In conclusion, the results of the present study indicate that orally administration of both FCE and MCE at all tested doses attenuate disrupted renal ROS metabolism associated with kidney injury progression in rats intoxicated with CCl_4 through their antioxidant action which may be related to their contents of sulpher containing amino acids and taurine.

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