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PROTECTIVE ROLE OF GREEN TEA ON CARBONTETRACHLORIDE-INDUCED ACUTE HEPATOTOXICITY

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ABSTRACT

Carbon tetrachloride (CCl_4) is largely used as solvent in chemical industries. CCl_4 is also well known for hepatic and renal toxic actions. The in vivo metabolism of carbon tetrachloride to trichloromethyl ($CCl_3^{\cdot}$) and peroxy trichloromethyl ($CCl_3O_2^{\cdot}$) radicals has been extensively reported to cause acute liver damage like cirrhosis, steatosis and necrosis. Recently, considerable attention has been focused on dietary and medicinal phytochemicals that inhibit, reverse, or retard diseases caused by oxidative and inflammatory processes. Green tea polyphenols have both antioxidant and antiinflammatory properties. We have evaluated protective action of green tea extract on CCl_4-induced acute hepatictoxicity in male rats. Fifty male Albino rats were divided into five groups, 10 rats each: normal control, green tea extract group, green tea-protected for 15 days and then received an acute dose of CCl_4 (i.p.), CCl_4-intoxicated and the last 10 rats was the sham group (corn oil). Results demonstrated that protection with green tea ameliorates CCl_4-toxicity by significantly decreasing ($P<0.001$) liver weight, aminotransferases concentrations, bilirubin and alkaline phosphatase with rise in total protein and albumin. Liver homogenate showed a significant decline ($P<0.001$) in the level of lipid peroxidation (MDA) with rise in superoxide dismutase (SOD), catalase, glutathione S-transferase (GST) and reduced glutathione (GSH) levels. At the same time, green tea-protected animals augmented the level of immunoglobulin, total lymphocytes and neutrophils phagocytic activity. The results of DNA electrophoresis demonstrated that DNA damage observed in animals intoxicated with CCl_4 has been recovered with green tea protection. Overall results indicate that the aqueous extract of green tea possesses hepatoprotective effects on CCl_4-induced acute hepatotoxicity in rats.

KEY WOEDS: GREEN TEA – HEPATOPROTECTIVE - ANTIOXIDANTS

INTRODUCTION

Carbon tetrachloride is a manufactured chemical that does not occur naturally. Most of the carbon tetrachloride produced is used in the production of chlorofluorocarbons (CFCs) and other chlorinated hydrocarbons. Various substances are known to cause liver and kidney damage, and one of them is carbon tetrachloride (CCl_4), which is a well-known hepato- and nephrotoxin (Ogeturk et al., 2005). Within the body, CCl_4 breaks down to highly toxic trichloromethyl ($CCl_3^{\cdot}$) and trichloromethyl peroxyl ($CCl_3O_2^{\cdot}$) free radicals by cytochrome P450 enzyme and causes damage to hepatocytes (Ohta et al., 2000). Short and long-term exposure to CCl_4 also causes damage to the skin, brain and blood and in some cases results in death.

There has been a great deal of interest recently in the role of complementary and alternative medicines for the treatment of various acute and chronic diseases (Seef et al., 2001). Of the various herbal and botanical agents available, interest has focused on the antiinflammatory and antioxidant properties of polyphenols found in green tea. The green tea polyphenols include (–)-epigallocatechin gallate (EGCG), (–)-epigallocatechin, (–)-epicatechin gallate, and (–)- epicatechin (Varilek et al., 2001). Of these polyphenolic components of green tea, EGCG is the major constituent and is also the component with the highest antioxidant properties (Guo et al., 1996). Because oxidative stress plays a major role in several liver diseases, it was of interest to evaluate the role of green tea polyphenols in protecting against liver injury. One study, for example, showed that green tea suppresses D-galactosamine–induced liver injury in rats. The mechanism of the protective effect of the crude green tea extract used in the study was thought to be through inhibition of tumor necrosis factor –induced apoptosis (He et al., 2001). Other studies have generally used isolated cells to evaluate the effects of green tea polyphenols (Pam et al., 2000). This study aims to evaluate the protective effect of green tea on acute hepatotoxicity induced by CCl_4 in male Albino rats.

MATERIALS AND METHODS

ANIMALS AND GROUPS OF STUDY

Adult male Albino rats, weighing about 140-150 g, were purchased and maintained at the animal house of zoology department, faculty of science, Minufiya University. Ten animals were given only standard pellet diet and tap water and served as normal controls. Another ten rats were given standard pellet diet and aqueous green tea extract (1.5%; w:v.) as the sole drinking fluid during the 15 days (El-Beshbishy, 2005). Group 3 included of ten rats given standard

pellet diet and aqueous green tea extract as the sole drinking fluid during the 15 days. On the last day, CCl_4 / corn oil (v:v) (2 mL/kg of b.w.) was administrated intraperitoneally (Lee et al., 2007). More ten rats were given only standard pellet diet and tap water for 15 days. On the last day, rats were intraperitoneally injected with CCl_4 (2 mL/kg of b.w.). The fifth group included ten animals that were given only standard pellet diet and tap water for 15 days. On the last day, 2 ml/kg (b.w.) of corn oil (vehicle) was injected intraperitoneally. All groups of rats were sacrificed 24 h post-injection.

BLOOD AND TISSUES COLLECTION

Blood, liver and spleen tissues samples were tacked for analysis during rats sacrificed at the end of experiments. Serum samples were prepared for biochemical analysis. Livers were weighted, washed with ice cold PBS and used to prepare liver homogenate (5% w:v) and stored at -80°C. The spleens were harvested and kept in RPMI-1640 complete medium for immunological studies.

BIOCHEMICAL ASSAYS

Liver enzymes, alanine transaminase (ALT) and aspartate transaminase (AST) were determined in serum according to the method of Reitman and Frankel (1957). Total bilirubin (Bil) was also determined in serum using the method of Jendrassik (1938). Total protein (TP) in serum was determined by the method of Gornall et al. (1949). Level of serum albumin (Alb) was estimated according to Doumas (1971). The activity of alkaline phosphatase (AlkP) in the serum was assayed by the method described by EL-Aaser and EL-Merzabani, (1975).

MEASUREMENT OF LIPID PEROXIDATION

The degree of lipid peroxidation in liver homogenate was determined by measuring malodialdehyde (MDA), the end product of oxidation according to the method of Okhawa (1979).

Estimation of hepatic antioxidant level

The reduced glutathione (GSH) level in the liver tissue was determined according to the method of Ellman (1959). The glutathione S-transferase (GST) activity was estimated by the method of Surapaneni and Venkataramana (2007). Hepatic superoxide dismutase (SOD) activity was estimated by the method of Kakkar et al. (1984). The catalase activity was estimated by the method of Aebi (1984).

IMMUNOLOGICAL STUDIES

Spleen lymphocytic was isolated according to the method of Boyum (1984) and counted. Moreover, T-lymphocytes were separated by using Dynall®

magnetic beads. The neutrophils phagocytic activity was assessed against bakery yeast according to the method of Yamamoto et al. (2008) and phagocytic index was calculated. The level of total IgG in serum was estimated using radial immunodiffusion procedure.

DNA EXTRACTION AND ELECTROPHORESIS

DNA was extracted from liver tissue by using Qiagene® purification kit (cat. no. 69504). Comparison of DNA from different animal groups was done after electrophoresis on 1.2% agarose gel.

STATISTICAL ANALYSIS

The statistical analyses were performed by one-way ANOVA, followed by *t*-test according to Snedecor and Cochran (1967). The results were expressed as the mean ± SD to show variations in a group. Differences are considered significant when ($P < 0.05$).

RESULTS

Administration of acute dose of carbon tetrachloride (CCl_4) intraperitoneally to normal male Albino rats caused a highly significant elevation ($P<0.001$) the levels of AST, ALT, AlkP and Bil as compared to those of normal controls. Whereas, decrease in the levels of TP and Alb were significantly observed indicating acute hepatocellular damage. The protected rats with aqueous extract of green tea (1.5%) for 15 constitutive days prior to CCl_4-intoxication showed a significant decrease ($P<0.001$) in all the elevated AST, ALT, AlkP and Bil levels and significant increase in TP and Alb levels (Table 1).

The administration of CCl_4 to the control animals caused a significant decrease in the level of CAT, SOD, GSH and GST together with a significant increase in the level of lipid peroxidation in liver homogenate ($P< 0.001$), when compared to normal rats (Tables 2 & 3). A highly significant reversal of these changes towards the normal group was observed by the protection with green tea for 15 days prior to CCl_4-intoxication. Animals maintained on green tea extract before CCl_4-intoxication exhibited a significant decrease in the level of lipid peroxidation and rise in the level of CAT, SOD, GSH and GST, when compared to CCl_4 treated control.

Table 1: Effect of green tea on CCl_4-induced toxicity in rats

	Normal Control	Green Tea	Green Tea / CCl_4	CCl_4-intoxicated	Corn Oil (Vehicle)
AST (IU/L)	120.1 ± 9.35	116.9[b] ± 3.11	123.9[b] ± 5.55	373.5[a,c] ● 15.57	126.2[b] ± 11.72
ALT (IU/L)	49.5 ± 1.58	45.7[b] ± 134	47.9[b] ± 1.2	142.7[a,c] ± 6.9	49.1[b] ± 1.2
AlkP (IU/L)	312.4 ± 12.59	303.8[b] ± 5.35	305.5[b] ± 8.57	418.6[a,c] ± 9.09	315.1[b] ± 7.71
Bil (mg/dL)	0.33 ± 0.08	0.28[b] ± 0.11	0.33[b] ± 0.04	1.28[a,c] ± 0.28	0.31[b] ± 0.10
Albumin (g/dL)	3.61 ± 0.26	3.79[b] ± 0.23	3.85[b] ± 0.20	1.14[a,c] ± 0.21	3.86[b] ± 0.46
Tot. Prot. (g/dL)	6.31 ± 0.25	6.69[b] ± 0.20	6.3[b] ± 0.34	3.02[a,c] ± 0.44	6.44[b] ± 0.28

([a]): Significant as compared to normal control group.
([b]): Significant compared to CCl_4-intoxicated group.
([c]): Significant as compared to vehicle group

Table 2: Effect of green tea on lipid peroxidation level in CCl_4-intoxicated rats.

	Normal Control	Green Tea	Green Tea / CCl_4	CCl_4-intoxicated	Corn Oil (Vehicle)
MDA (nmol/g tissue)	52.1 ± 1.79	45.5[b] ± 2.68	49.0[b] ± 1.63	122.6[a,c] ± 1.71	51.5[b] ± 1.08

([a]): Significant as compared to normal control group.
([b]): Significant compared to CCl_4-intoxicated group.
([c]): Significant as compared to vehicle group

As shown in table (4), the immunological investigations demonstrated that intoxication of normal rats with CCL_4 resulted in a significant depletion ($P < 0.001$) in total lymphocytic count, T-cells as well as level of IgG as compared to normal controls. Also, phagocytic activity of neutrophils was diminished significantly ($P < 0.001$) comparing to that of control group. Results showed a

significant increase ($P < 0.001$) in these parameters in rats maintained on green tea extract prior to CCl_4-intoxication as compared to CCl_4 treated control.

Table 3: Effect of green tea on antioxidant status in CCl_4-intoxicated rats.

	Normal Control	Green Tea	Green Tea / CCl_4	CCl_4-intoxicated	Corn Oil (Vehicle)
SOD (U/mg protein)	223.7 ± 8.08	$288.5^{a,b,c}$ ± 19.85	$265.7^{a,b,c}$ ± 9.32	$77.5^{a,c}$ ± 8.83	225.5^{b} ± 15.46
Catalase (kU/mg protein)	3.3 ± 0.25	$4.22^{a,b,c}$ ± 0.32	3.11^{b} ± 0.36	$1.14^{a,c}$ ± 0.14	3.53^{b} ± 0.09
GST (M/min/g tissue)	20.5 ± 0.85	21.61 ± 0.65	21.02 ± 0.92	32.22 ± 0.84	21.2 ±1.32
GSH (nmol/mg protein)	19.3 ± 1.25	$23.9^{a,b,c}$ ± 1.60	18.8^{b} ± 1.69	$10.26^{a,c}$ ± 0.79	18.8^{b} ± 1.23

(^{a}): Significant as compared to normal control group.
(^{b}): Significant compared to CCl_4-intoxicated group.
(^{c}): Significant as compared to vehicle group

Table 4: Effect of green tea on immunological parameters in CCl_4-intoxicated rats.

	Normal Control	Green Tea	Green Tea / CCl_4	CCl_4-intoxicated	Corn Oil (Vehicle)
IgG (mg/dL)	1707.8 ± 19.16	1778.4^{b} ± 21.51	1730.9^{b} ± 31.09	$364.8^{a,c}$ ± 7.76	1699.6^{b} ± 54.42
Lymphocytes (10^6/ml)	26.2 ± 1.75	$32.4^{a,b,c}$ ± 1.84	28.6^{b} ± 2.72	$12.1^{a,c}$ ± 1.52	27.6^{b} ± 1.26
T-lymphocytes (10^6/ml)	20.1 ± 1.20	$24.7^{a,b,c}$ ± 1.06	23.7^{b} ± 1.57	$7.2^{a,c}$ ± 1.40	21.4^{b} ± 0.84
Neutrophil P.I.	82.5 ± 2.42	$89.3^{a,b,c}$ ± 2.11	83.7^{b} ± 2.26	$48.6^{a,c}$ ± 2.50	80.5^{b} ± 1.78

(^{a}): Significant as compared to normal control group.
(^{b}): Significant compared to CCl_4-intoxicated group.
(^{c}): Significant as compared to vehicle group

Figure (1) shows the effect of green tea on hepatic DNA extracted from CCl_4-intoxicated rats. CCl_4-Intoxication resulted in DNA fragmentation indicating the damage induced in DNA. While, protection with green tea for 15 days prior to CCl_4-intoxication prevented the DNA damage.

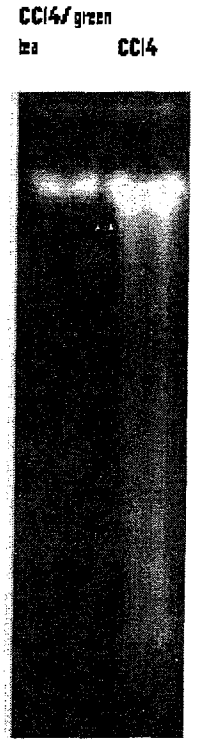

Figure 1: Effect of green tea on hepatic DNA damage induced with CCl_4.

DISCUSSION

Carbon tetrachloride is a widely used as a solvent in many modern industries. Many studies have implicated its severe hepato- and nephrotoxicity. The principal objective of the present study was to assess the oxidative damage sustained by the liver following acute exposure to CCl_4 and to investigate the protective potential of aqueous green tea extract supplementation. Liver plays a central role in detoxification and is chronically exposed to xenobiotics and their toxic derivatives. It has been previously reported that acute exposure to CCl_4 induces oxidative stress in rats (Sharma et al., 1994). Our result strengthens this hypothesis and suggests that induction of oxidative stress is perhaps the central

mechanism by which CCl_4 exerts their cellular damage. Oxidative damage primarily occurs through production of reactive oxygen species, including $CCl_3^{\cdot}$ and $CCl_3O_2^{\cdot}$ radicals that subsequently react with biological molecules as well as causing damage to membranes and other tissues (Singh et al., 1998). A significant decrease in the level antioxidant enzymes and a concomitant increase in lipid peroxidation level following administration of CCl_4 were observed in the present study. The decrease in GSH level leads to a net suppression in the total antioxidant capacity since it plays a key role as a substrate for the enzyme glutathione S-transferase (GST). Also, GSH depletion has been shown to intensify lipid peroxidation and predispose cells to further oxidant damage (Kaszkin et al., 2004). The increase in lipid peroxidation in the liver following exposure to CCl_4 may lead to membrane damage resulting in gross damage of liver cells and eventually loss of membrane integrity. The increase in serum activities of transaminases, AST and ALT and alkaline phosphatase and a decrease in biosynthetic function of the liver as shown by decreased levels of total protein and albumin is the end result of this phenomenon. It has been reported previously that during liver damage there is an observed decrease in antioxidant defenses in the liver (Khan and Kour, 2007). The by-products of oxygen metabolism initiate different subcellular outcomes. The superoxide radical has been shown to directly inhibit the activities of enzyme catalase (Kono and Fridovich, 1982); likewise, singlet oxygen and peroxyl radicals have been shown to inhibit SOD and CAT activities (Escobar et al., 1996). These observations explain the significant inhibition of SOD and CAT activity in animal group treated with CCl_4. The results are in agreement with previous studies of Ostrowska et al. (2004) where alterations in reduced glutathione, lipid peroxidation and changes in the activity of SOD and CAT in liver have been noted following exposure to xenobiotics. GSH in conjunction with GST comprises the GSH redox cycle that maintains the redox status of tissues and protects structural and regulatory proteins against ROS-induced damage (Lu, 1999). Elevation of free radicals and depletion of antioxidants status have an inhibitory effect on the production of lymphocytes. Also, phagocytic activity of neutrophils was deteriorated as a result of increased level of free radicals accompanied with CCl_4-intoxication.

Green tea contains polyphenols that have been shown to selectively induce metabolic enzymes which increase the formation and excretion of detoxified metabolites resulting from xenobiotic metabolism (Leung et al., 2001). It appears that supplementation with 1.5% crude green tea extract in rats prior to CCl_4 exposure leads to a partial reversal of oxidative damage. This is shown by a marked recovery in terms of oxidative stress parameters e.g., a significant

reduction in level of lipid peroxidation and enhancement in levels of GSH, highlighting their protective role against CCl_4-induced hepatotoxicity. Similarly, green tea supplementation resulted in significant amelioration in the activities of enzymes CAT, SOD and GST.

Green tea treatment may either replenish the levels of antioxidant directly or spare the endogenous pool of GSH from being exhausted by the free radicals generated. Interestingly, a few recent studies suggest that the protective effect rendered by green tea on the liver may not be specific to the xenobiotic involved (Erba et al., 1999). Hence, the normalization of lipid peroxidation, restoration of reduced glutathione concentration and GST activity may indeed occur via the same underlying biochemical cytoprotective mechanism irrespective of liver injury induced by CCl_4, ethanol or pesticides.

Also, the results of the present study indicated that green tea has a stimulatory action on the components of immune system. Highly significant increase was observed in the count of total lymphocytic count, T- and B-cells as well as level of IgG as compared to CCl_4 treated group. These findings run in parallel with the previous results of Vanessa and Gary (2004), who reported that green tea catechins could act as immune modulators in immunodysfunction. On the other hand, green tea administration for 15 days prior to CCl_4-intoxication resulted in augmentation of phagocytic activity of neutrophils as compared to the CCl4 control group. This observation revealed the activity of green tea as anti-inflammatory agent through the augmentation of innate immunity. Santosh et al. (2001) reported that green tea has immunregulatory action resulting in elevation of neutrophils count and function.

As shown in our results, hepatic DNA damage induced by CCl4-toxicity is prevented by protection with green tea. This finding supports the biomarker assays as hepatoprotective effect of green tea is observed. It is suggested that scavenging of free radicals due to green tea protection resulted in inhibition of DNA damage.

In summary, our results demonstrate that acute exposure to CCl_4 leads to significant oxidative damage and a compromised antioxidant status as shown by increase in lipid peroxidation and decrease in the activity of key antioxidant enzymes like CAT, SOD and GST as well as GSH. Administration of crude aqueous green tea extract exerts significant protective role against the oxidative stress in rat liver. Further, immunological and molecular studies unraveled the detailed role played by the green tea.

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التأثير الوقائي للشاي الأخضر للتسمم الكبدى الحاد المستحدث بواسطة رباعي كلوريد الكربون.

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يتم استخدام مركب رباعي كلوريد الكربون علي نطاق واسع في الصناعة. و لقد تم التعرف علي تأثيره السام علي الكبد و الكلي حيث ينتج مركبات الأكسجين النشطة في الجسم والتي تؤدي الي تدمير الكبد و تليفه.
وفي الآونه الأخيرة ازداد الإهتمام بالطب البديل و دور الأعشاب في الوقاية و العلاج من الأمراض المختلفة. لذا تم اختبار دور الشاى الأخضر الوقائي في هذه الدراسة ضد التسمم الكبدي الحاد المستحدث في فئران التجارب. واثبتت نتائج البحث فاعلية الشاي الأخضر للوقاية من التسمم الكبدي حيث ارتفعت نسب المركبات المضادة للأكسدة وتبعها انخفاض الدلالات الحيوية المميزة لوظائف الكبد مقارنة بمجموعة الفئران المسممة برباعي كلوريد الكربون. ومن ناحية اخري فقد ارتفعت الإستجابة المناعية في الفئران بعد استخدام الشاي الأخضر. كذلك أوضحت هذه الدراسة قدرة الشاي الأخضر علي اصلاح التلف الحادث في الحامض النووي الديوكسي ريبوزي مقارنة بمجموعة الفئران المسممة برباعي كلوريد الكربون. لذا نستنتج من هذه النتائج أهمية الدور الوقائي للشاي الأخضر ضد التسمم الحاد المستحدث بواسطة رباعي كلوريد الكربون في الفئران.