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Study of the Physiological Alterations Induced by Cisplatin in Miceandthe Possible Protective Role of Green Tea

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Abstract

Cisplatin (CDDP) isan anti-cancerDNA alkylating chemotherapeutic agent act against a variety of tumors.The present study aimed to evaluate the possible protective effects of green tea on the physiological parameters in mice chronically treated with CDDP. Four groups of mice were examined: a control mice saline PBS solution (group I), mice treated with CDDP (group II), mice treated with CDDP and green tea (group III), and normal mice treated with green tea (group IV). All animals were treated for successively five days and killed one week after the last treatment. The results recorded that CDDP treatment significantly decreasedthe levels of white blood cells (WBCs), red blood cell distribution width (RDW) and lymphocytes count. Also, CDDP increased the hepatocytes oxidative stress which characterized by increasing prooxidants xanthine oxidase (XO), thiobarbituric acid-reactive substances (TBARS), and decreasing of antioxidants glutathione peroxidase (GPx). As a result, hepatocytes injury took place that characterized with serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) andalkaline phosphatase (ALP) activities. The treatment of mice with green tea to CDDP group (group III) or mice treated with green tea alone group (group IV) successfully normalized the physiological parameters in form returning WBCs, RDW and lymphocytes counts to normal levels, and decreased the hepatocytes oxidative stress which characterized by decreasing Prooxidants (OX, TBARS) and increasing of antioxidants GPx reflected by significant decrease in the serum activities of AST, ALTand(ALP) activities.

Keywords: Cisplatin, green tea, oxidative stress, chemotherapy, antioxidant, blood count, mice.

Introduction

CDDP is one of the most potent antitumor agents. Its activity has been demonstrated against a variety of tumors, notably in head and neck, testicular, ovarian, bladder and small-cell lung cancers [1]. The clinical success of CDDP for the treatment of cancer is clear however it causes severe side effects (nephrotoxic and hepatotoxic) while intrinsic or acquired resistance limits its application in high doses [2]. The therapeutic effects of CDDP are based on the interaction with DNA in the cell which prevents proliferation [3] as well as on induction of apoptosis in tumor cells.On the other hand,CDDP is highly mutagenic,inducing chromosome aberrations in peripheral blood lymphocytes in patients and in rats[4].CDDP causes oxidative stress in human lymphocytes, which might reflect on their life expectancyand induction of apoptosis by ultimately reduce the number of these cells in the blood.

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On the other hand, the decrease in the leukocyte number could be the consequence of infection and inflammation during CDDP treatment and metabolism. CDDP is a very effective chemotherapeutic agent, used in the treatment of a wide range of malignant diseases. However, it exhibits certain toxic effects on the kidneys, blood and liver which interfere with its therapeutic efficiency [**5**].

Herbal medicines derived from plant extracts are being increasingly utilized to treat a wide variety of clinical disease[6]. Because of the concerns about the side effects of conventional medicine, the use of natural products as an alternative or supportive for conventional treatment in healing and treatment of various diseases has been on the rise in the last few decades[7].A larger number of these plants and theirisolated constituents have shown beneficial therapeutic effects, including anti-oxidant, anti-inflammatory, anti-cancer and anti-microbialeffects[8].Green tea polyphenolsare

the secondary metabolites in tea plants and accounts for 30% to 36%weight of the water extractable materials in tea leaves. The main polyphenolic components in green tea are epigallocatechingallate (EGCG),epicatechin(EC),epigallocatechin(EGC), epicatechingallate (ECG) and gallic acid[9].EGCG, the majorand most active component of green tea catechins, acts as an antioxidant in the biological system [10] and is rapidly absorbed and distributed mainly into the membranes of the liver; more interestingly, it can cross the blood brain barrier [11].Moreover, Green tea also contains carotenoids, tocopherols, ascorbic acid (vitamin C), minerals such as Cr, Mn, Se or Zn, and certain phytochemical compounds.The polyphenols in green tea can neutralize free radicals and may reduce or even help to prevent some of the damage caused by reactive oxygen species (ROS) [12]. Long-term intake of green tea catechins may be important because cells are constantly exposed to oxidative stress. It has been reported that, in addition to directly quenching reactive oxygen species, tea polyphenolshave the ability to participate in vitamin E recycling[13].Green tea is also associated with many therapeutic effects, including anti-blood coagulation, the reduction of hypertension, oxidative damage repair, and cancer prevention and treatment[14].The major hypothesisof the beneficial health effects of green tea is associated with its antioxidant properties[15&16]. However it was determined that theaflavins in black tea and catechins in green tea are equally effective as antioxidant**[**17**]**.The present study aimed to investigate the evaluate oxidative stress effects of chronically applied CDDPand the possible preventive action of green tea.

Material and Methods

Experimental Animals:Adult female Swiss albino mice weighting 23±2 g were used in this study. Animals were housed (5animals per cage) at the animal house at Zoology Department, Faculty of Science (Omar AL-Mukhtar University, Albida) in clean and dry plastic cages, in 12h/12h dark/lightcycle under laboratory condition of temperature and humidity. Mice were divided into four groups, a control mice with saline PBS solution (group I), mice injected with a single dose of CDDPat a dose 200 mg/Kg "4mg/mouse" (group II), mice treated with CDDP at a dose 200 mg/Kg and administered with green tea at a dose of green tea "200µg/mouse orally" (group III), and normal mice administeredwith asingle dose of green tea alone "200µg/mouse orally" (group IV).

Evaluation of Hematological Parameters:

Blood samples with anti-coagulant EDTA were analyzed for hematological parameters of red blood cells distribution width (RDW) counts, White Blood Cell (WBC) counts and total number of lymphocytes according to Feldman [18] .

Serum Biochemical Analysis:

Serum total proteinand activities of aspartate aminotransferase (AST),alanine aminotransferase (ALT) andalkaline phosphatase (ALP) were determined colorimetrically using kits obtained from Diamond Diagnostic, Egypt according to the methods of Burits and Ashwood [19] or Kind and King [20], respectively.The level of thiobarbituric acid reactive substances (TBARS) and xanthine oxidase (XO) as prooxidants indicator weremeasured according to Tappeland Zalkin [21] and Litwack et al. [22], respectively.The level of liver TBARS was calculated with the following equation (nmol/ml)= (*At*/0.156) × 10, where *At* is the absorbance of the test sample and ε = 0.156 is the extinction coefficient. The liver XO activity (nmol/min/ml) was estimated as follows: (C) ×10/ (0.284 × xanthine M. Wt), where 0.284 is a constant and C is the concentration in the test sample. The activity of the antioxidant enzyme glutathione peroxidase (GPx) was measured according toPaglia and Valentine[23]. The enzyme activity was calculated by using the following equation; GPx activity (nmol/min/ml) = (*At*× 6.2 × 10 × 10)/ (13.1 × 0.05 × 10), where ε1 = 6.2 and ε2 = 13.1 are extinction coefficients for H_2O_2 and DTNB (5, 5′-dithiobis-(2-nitrobenzoic acid).

Statistical analysis

Data was statistically analyzed by ANOVA with post-hock Dunnett's multiple comparisons testusing statistical software program (GraphPad Prism version 7.30). Differences were considered significant at $p<0.05$.

Results and Discussion

Table 1showed that CDDP treatment significantly decrease the total numbers of white blood cells coincided with decrease in the number of lymphocytes when compared to normal group($p<0.001$). The co-treatment of CDDP with green tea returned the WBC to its normal coinciding with recovery of the relative number of lymphocytes and RDW as compared to control values (PBS group) ($p<0.01$).The treatment of mice with green tea only increased the number of WBC as compared to PBS.The treatment with combination of green tea significantly increased the numbers of RDW($p<0.01$)

and WBC as compared to CDDP with green tea group which was higher to PBS group counts.

Table 1:Effect of different treatments on blood cell counts.

Groups	WBCs($\times10^3$)	RDW($\times10^4$)	Lymphocytes/ cmm
PBS	5. 4±0.13	0.5±4.82	606±39.9
CDDP	1.71±0.1***	19.1±5.14^{ns}	952.3±16.9***
CDDP + green tea	5.60±0.1^{ns}	55.67±5.8**	2282±38.2^{ns}
Green tea	6.35±0.2^{ns}	61.48±1.2**	2385±38.4^{ns}

CDDP, Cisplatin; PBS, Phosphate buffer saline; WBCs, White blood cells; RDW, Red blood cell distribution width; ns, non-significant; **, ***significant difference compared to PBS group at P≤ 0.01and 0.001respectively.

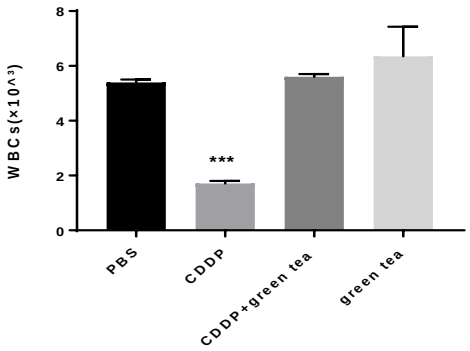

Figure 1:Effect of different treatments on WBCcounts.***p< 0.001 CDDP treated group compared to PBSgroup.

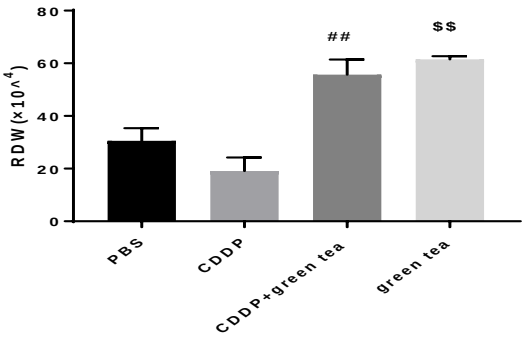

Figure 2:Effect of different treatments on RDWcounts.$^{##}$p< 0.01 CDDP+green tea treatedgroup compared to PBS group, $^{\$\$}$p< 0.01, green tea treated group compared to PBS group.

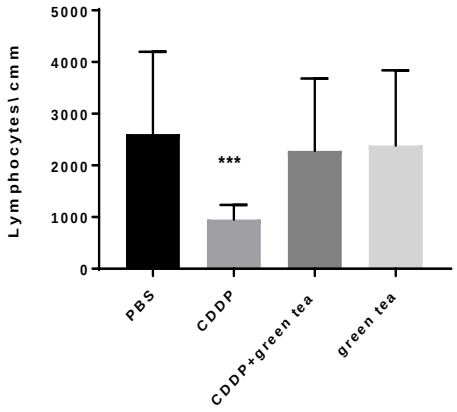

Figure 3:Effect of different treatments on Lymphocytes counts. ***p< 0.001,CDDP treated group compared to PBS group.

Table 2showed that CDDP increases the level of TBARS and XO activity($p<0.05$) with a decrease in GPx activity comparing to control. Co-administration of CDDP with green tea decreased the XO and TBARS activities, respectively with the increase ofthe GPx level as compared to CDDP group. However, treatment with green tea to CDDP group decreasedthe pro-oxidants parameters (TBARS and XO) and increasedthe anti-oxidants ones to their normal level.

Table 2:Effect of different treatments on hepatic pro-oxidant/anti-oxidant status.

Groups	GPx(nmol/min/ml)	XO(nmol/min/ml)	TBARS(nmol/ml)
PBS	1.64±0.30	4.69±0.58	1.36±0.44
CDDP	1.28±0. 72^{ns}	6.80±0.92*	3.72±0.31*
CDDP + green tea	2.52±0.80^{ns}	3.78±0.64^{ns}	2.23±1.31^{ns}
Green tea	3.68±1.73*	4.33±0.38^{ns}	1.47±0.14^{ns}

CDDP, Cisplatin; PBS, Phosphate buffer saline;GPx,Glutathione Peroxidase;XO,xanthine oxidase;TBARS, Thiobarbituric acid-reactive substances; ns, non-significant; * significant difference compared to PBS group at P≤ 0.05.respectively.

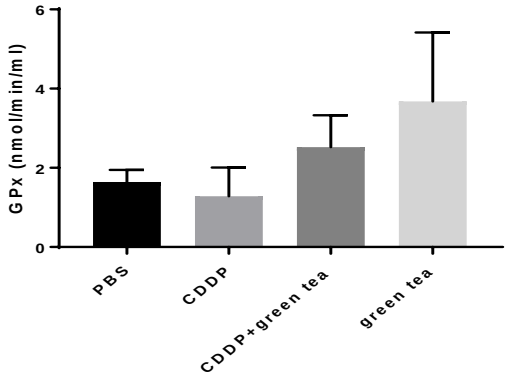

Figure 4: Changes in liver GPx activity after different treatment. $p≤ 0.01, green tea treated group compared to PBS group.

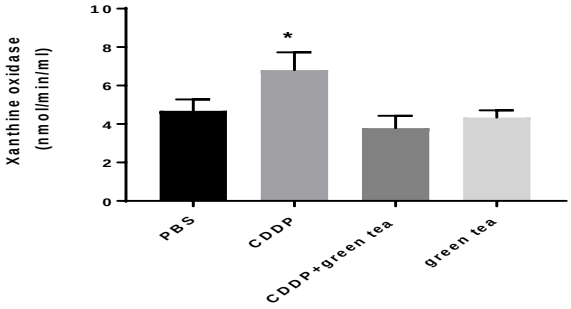

Figure 5: Changes in liver xanthine oxidase activity of different groups. *p≤ 0.05 CDDP treated group compared to PBS group.

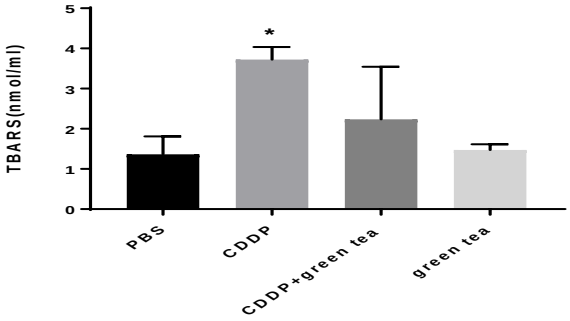

Figure 6: Changes in serum liver TBARs level of different groups. *p≤ 0.05,CDDPtreated group compared to PBS group.

Table 3 recorded changes in the concentrations of ALT, AST and ALP during the treatment of mice with CDDP alone. The results showed that ALT, AST and ALP concentration significantly increased in serum activities of mice treated of CDDP ($p \leq 0.001$) in comparison to control. The treatment with CDDP with green tea was very effective in the prevention of oxidative damage induced by green tea, which resulted in significantly lower ALT, ATS and ALP concentration. While green tea alone treatment reversed this change to control values.

Table 3: Effect of different treatments on serum liver function parameters.

Groups	ALT(U/L)	AST(U/L)	ALP(U/L)
PBS	39.23±0.4	72.07±0.5	40.7±1.2
CDDP	51.94±2.9***	81.5±6.9ns	68.8±1.0***
CDDP + green tea	37.1±0.6ns	71.9±8.6ns	36.93±1.2**
Green tea	35.0±2.5*	70.7±0.5ns	31.8±0.9***

CDDP, Cisplatin; PBS, Phosphate buffer saline; ALT, Alanine amino transferase; AST, Aspartate amino transferase and alkaline phosphataseALP; ns, non-significant; *,**,*** significant difference compared to PBS group at P≤0.05,0.01 and 0.001, respectively.

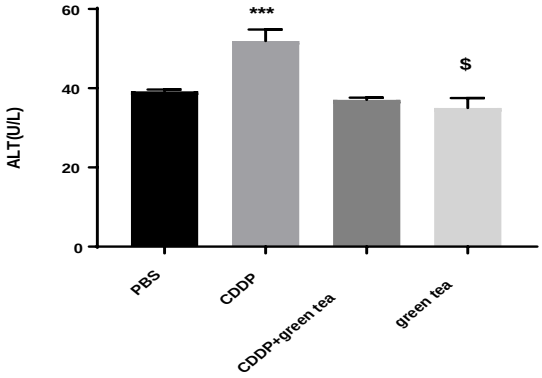

Figure7:Changes in liver ALT activity after different treatment. *** p≤ 0.001CDDP treated group compared to PBS group, $p≤ 0.01, green tea treated group compared to PBS group.

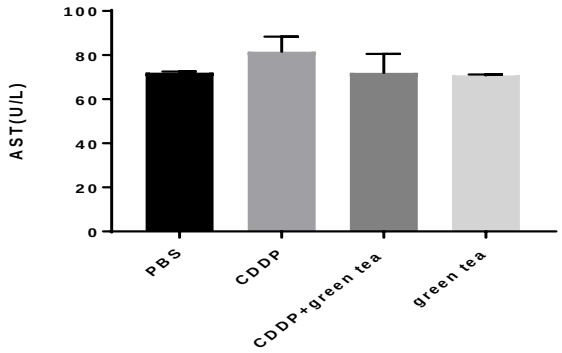

Figure 8:Changes in liver AST activity after different treatment.

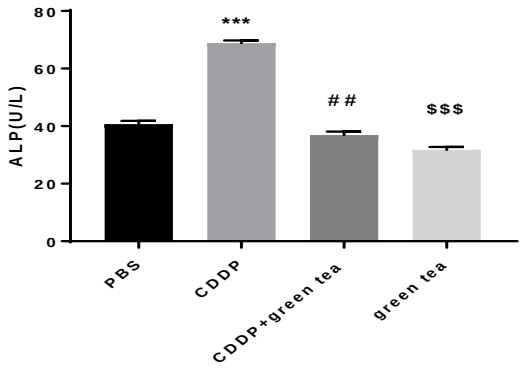

Figure 9:Changes in liver ALP activity after different treatment.* p≤0.001,CDDP treated group compared to PBS group,## p≤0.01CDDP+green tea treated group compared to PBS group, $$$ p≤0.001, green tea treated group compared to PBS group.**

The previous results showed that high doses of CDDP were affecting the RDW maturation in rats [24]. The present results are in accordance with literature data, and showed that chronic application of CDDP induced depletion in RDW number and maturation. In accordance[25]. showed that CDDP caused oxidative stress in human lymphocytes, which might reflect on their life expectancy, the induction of apoptosis, and thereby ultimately reduce the number of these cells in the blood.In the present study green tea extract administration to CDDP group caused a significant ($p<0.05$) increase in RDW, WBCs and lymphocytes count, values showed statistical different from controlgroup, The administrated of mice withgreen tea to CDDP inthe prerent work can prevent the toxic effects of CDDP on the reduction of RDW number. The green tea caused a significant increase in RDW and WBCs values compared control group, The improvement in blood parameters after green tea intake might be related to the strong antioxidant effect of green tea extract catechins on hematopoietic cells. Hematopoietic cells appear to be particularly vulnerable in the presence of unchecked accumulation of ROS, because deficiencies in several ROS scavengers result in either anemia that is severe or even lethal in some cases and/or malignancies ofhematopoietic tissues [26&27].

In the mice given CDDPin the present work, GPx levels were decreased in comparison with the PBS group. GPx is an enzymatic endogenous antioxidant. Under physiological conditions, the oxidant/antioxidant balance is maintained with predominance of antioxidants. The disruption of this equilibrium causes tissue damage named oxidative stress. Therefore, oxidant/antioxidant balance is used to assess if tissue damage emerges [28]. GPx reduces oxidized glutathione (GSSG) by transferring one electron from NADPH to the disulfide bonds of GSSG [29].CDDPatin also induces the production of reactive oxygen species (ROS) in hepatocytes mainly by decreasing the activity of antioxidant enzymes and by depleting intercellular concentrations of reduced glutathione Peroxidase (GPx)[30].

Results of the current study revealed that green tea extract reversed the elevation of lipid peroxidation. Hence, it is possible that the mechanism of green tea extract may be attributed to epicatechins (antioxidant present in green tea) that scavenge a wide range of free radicals including the most active hydroxyl radical, which may initiate lipid peroxidation. Therefore, it may decrease the concentration of lipid free radicals[31].Moreover, it was reported previously that it chelated metal ions, especially iron and copper, which, in turn inhibit generation of hydroxyl radicals and degradation of lipid hydroperoxides[32].Nephrotoxicity could also be explained by the impaired antioxidant enzyme activities in the liver of the rats. Indeed, the antioxidant enzymes GPx limit the effects of oxidant molecules in tissues and act in the defense against oxidative cells injury by means of their being free radical scavengers.These enzymes work together to eliminate active oxygen species[33].

Enhanced levels of TBARS and XO in liver of CDDP treated mice inthe present study indicated the increased levels of peroxidation. Reports have shown that CDDP promotes the formation of ROS by fenton transition equation, such as hydrogen peroxides

production of peroxidations and the highly reactive hydroxyl radical [34&35]. Simultaneously, administration of green tea extract decreased the formation of peroxidation products, and it possesses antioxidant activity [36]. Thus, this agent might provide more medical benefit because the use of this agent could simultaneously alleviate oxidative damage [37]. The ability of green tea, consumed within a balanced controlled diet, to improve overall the antioxidants status and to protect against oxidative damage in humans [38].

Increase in serum levels of AST in the present study showed hepatic injuries similar to viral hepatitis, infarction ALT, which mediates conversion of alanine to pyruvate and glutamate, is specific for liver and is a suitable indicator of hepatic injuries[39]. Increased levels of these enzymes are an indicator of cellular infiltration and functional disturbance of liver cell membranes in addition, ALP is membrane bound and its alteration is likely to affect the membrane permeability and produce derangement in the transport of metabolites [40].Treatment of green tea extract markedly improved biochemical status of rats with CDDPand return of the above enzymes to normal serum values following green tea extract treatment. It may be due to prevention of intracellular enzyme leakage resulting from cell membrane stability or cellular regeneration [41].

Conclusion

green tea has best antioxidant effect, that demonstrated in the return of the number of white blood cells,red blood cells and lymphocytes count of CDDP group to the normal range in comparable to control PBS group, and also it returned the changes in liver enzymes to normal level.Therefore, the present study recommends to use the green tea as a natural product such for patients put on CDDP therapy to reduce its toxicity.

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