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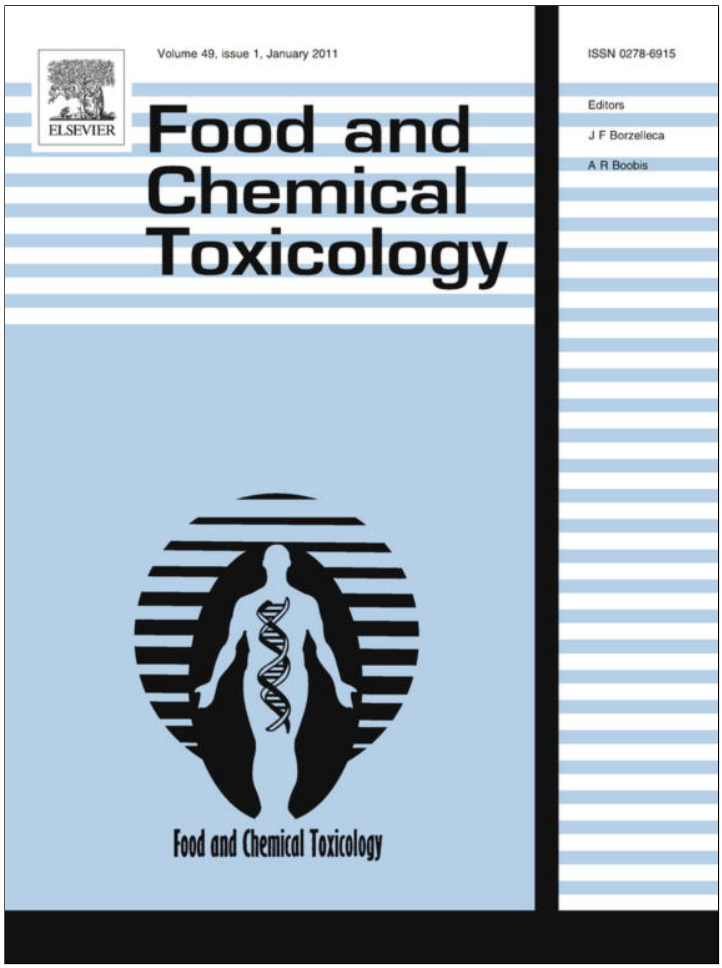

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Cisplatin induced toxicity in rat tissues: The protective effect of Lisosan G

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ABSTRACT

The protective effect of a powder of grain (Lisosan G) against cisplatin-induced toxicity in rats was studied. Male rats were fed with Lisosan G before injection of cisplatin and four days later they were killed and blood was collected along with hepatic, renal and testicular tissues. The results showed that cisplatin treatment increased plasma blood urea nitrogen, creatinine and hydrogen peroxide and decreased cytochrome P450 content in renal and hepatic tissues. It also reduced the plasmatic testosterone level and caused a depletion of testicular 17α-progesterone hydroxylase activity. In the group fed with Lisosan G and treated with cisplatin blood urea nitrogen and creatinine returned to the control level indicating a protective effect of Lisosan G. It was also observed that the ones fed with Lisosan G were able to attenuate the decrease in the P450-dependent activities and the activities of antioxidant enzymes as well. Lisosan G protected the testicular 17α-progesterone hydroxylase activity and increased the plasma testosterone level compared to animals treated only with cisplatin. Our results showed a protective effect of Lisosan G against the cisplatin induced toxicity. The protective effect of Lisosan G could be associated mainly with the attenuation of the oxidative stress and the preservation in antioxidant enzymes.

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1. Introduction

Cisplatin, cis-diaminedichloroplatinum (II), is one of the most frequently used anti-neoplastic agents for various types of tumors (Lebwohl and Canetta, 1998; Taguchi et al., 2005). It has a potent anti-tumor action against a wide range of malignancies and solid tumors. Despite its clinical usefulness, cisplatin treatment was associated with several toxic side effects including nephrotoxicity, neurotoxicity and ototoxicity (Ali and Al Moundhri, 2006; Chirino and Pedraza-Chaverri, 2009; Mollman et al., 1988). Although the mechanism of the side effects induced by cisplatin are not clearly understood, this drug, in addition to the formation of strong electrophilic intermediates that yield adducts with DNA via nucleophilic substitution reactions, causes many alterations of biochemical parameters in plasma, liver, kidney and testis (Badreldin et al., 2006). Besides, many reactive oxygen species are generated by cisplatin that could interfere with the antioxidant defense system and result in oxidative damage in the tissues (Badary et al., 2005).

Various studies from the last decade have shown that the administration of several antioxidant agents extracted from plants and dietary components may reduce some of the side effects of cisplatin without altering the effects of chemotherapy (Conklin, 2000; Pérez-Rojas et al., 2009; Sánchez-Pérez et al., 2010). Many examples have been reported in literature. The treatment with grape seed proanthocyanidin extract, a combination of biologically active bioflavonoids, prior and post the cisplatin administration protected against the toxicity induced by this chemotherapic (Saad et al., 2009; Yousef et al., 2009). An extract of curcuma comosa, through its antioxidant activity, revealed a protection against cisplatin-induced nephrotoxicity (Jariyawat et al., 2009). The caffeic acid phenethyl ester, a flavonoid present in honey, showed a partial protection on cisplatin-induced hepatotoxicity and the authors suggested that this effect could be due to a mechanism other than that relative to its antioxidant property (Iraz et al., 2006). Recently it was reported a protection of sulforaphane against cisplatin-induced nephrotoxicity and it was associated with the attenuation in oxidative/nitrosative stress and the preservation of antioxidant enzymes (Guerrero-Beltrán et al., 2010). Previously it was also reported that cereal grains may reduce the risk of coronary heart disease (Truswell, 2002).

When extracts of plant or natural chemical substances have to be used during drug-therapy, it is very important to verify that

Abbreviations: APD, aminopyrine-N-demethylase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CYP, cytochrome P450; ErD, Erythromycin-N-demethylase; EROD, Ethoxyresorufin-O-deethylase; ECOD, Ethoxycoumarin-O-deethylase; GSH, glutathione; GST, Glutathione-*S*-transferase; GSSG, Glutathione disulfide; H_2O_2, hydrogen peroxide; 7α, 6β, 16α, 2α, 2β and 17, the different position of hydroxylation of testosterone.

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they are not able to interact with the drug metabolizing system because this fact can alter the efficacy of drugs and/or produce adverse events (Ioannides, 1999; Zhou et al., 2004). We have found that the powder of grain of Triticum Sativum (Lisosan G), used as nutritional supplement, did not interfere with the phase 1 and 2 drug metabolizing enzymes (Nelson et al., 1996) but had hepatoprotective effects in rats intoxicated by carbon-tetrachloride. In addition, it has shown a good radical scavenger activity maybe due at the presence of antioxidant molecules occurring in this compound; in fact, in Lisosan G there is a good presence of vitamins, oligoelements, polyunsaturated fatty acids (Longo et al., 2007). On the basis of these results it was suggested that Lisosan G might be co-administrated during drug therapy.

To further support this suggestion, the present study was undertaken to evaluate whether the administration of Lisosan G in rats could have a protective effect against toxicity of cisplatin as measured in plasma, liver, kidney and testis by specific biochemical and enzymatic parameters.

2. Material and methods

2.1. Chemicals

Lisosan G is registered as nutritional supplement by the Italian Minister of Health and was supplied by Agrisan Company, Larciano (PT), Italy. All other chemicals and solvents were of standard brands available on the market.

2.2. Animals and experimental protocol

Sixteen male Wistar rats of 230–250 g were used and the experimental protocol was approved by the Ethic Committee for Animal care. Rats were divided in four groups. In the first group (Lis), the rats were fed by Lisosan G for fifteen days; the second group (Cis) received a single intraperitoneal dose of cisplatin (dissolved in corn oil) 10 mg/kg and was sacrificed after four days; the third group (Lis+Cis) was fed with Lisosan G and on the 11th day received a single intraperitoneal dose of cisplatin 10 mg/kg and sacrificed after four days; the fourth group of rats (control) was treated with corn oil only. The animals were killed and microsomal and 100,000*g* supernatant fractions were prepared from the liver, kidney and testis as previously described (Longo et al., 1991).

2.3. Enzymatic activities

Cytochrome P450 (CYP) content was measured by the method of Omura and Sato (1964). Aminopyrine-N-demethylase (APD) and Erythromycin-N-demethylase (ErD) activities were assayed by measuring the formation of formaldehyde (Tu and Yang, 1983). Ethoxyresorufin-O-deethylase (EROD) activity was determined by measuring the formation of resorufin spectrofluorimetrically (Lubet et al., 1985). Ethoxycoumarin-O-deethylase (ECOD) activity was assayed by the fluorimetric determination of 7-hydroxycoumarin (Aitio, 1978). NAD(P)H:quinone oxidoreductase (DT-diaphorase) activity was assayed by following the reduction of dichlorophenolindophenol at 600 nm and calculating the rate that could be inhibited by 1 μM dicoumarol (Wermuth et al., 1986). Glutathione-*S*-transferase (GST) activity was quantified as previously described (Habig et al., 1974) using as substrate 1-chloro-2,4-dinitrobenzene. The activities of GSSG reductase, and GSH peroxidase were measured monitoring the consumption of NADPH at 340 nm while the catalase activity was monitored following the H_2O_2 consumption at 240 nm, as described by Cao and Li (2002). Testosterone hydroxylase and progesterone hydroxylase activities were determined by separating the hydroxylated metabolites using a Waters 1525 high-performance liquid chromatography apparatus equipped with a Supelco LC-18 column (250 × 4.6 mm) as previously reported (Amato et al., 1996; Swinney et al., 1987). The hydroxylation rates of aniline to 4-aminophenol were determined using the method of Ko et al. (1987). Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) activities and testosterone, creatinine and BUN contents were measured in plasma according to the instructions of a commercial kits (Beckman Counter, USA). Hydrogen peroxides were measured in plasma according to the instructions of a commercial kits (Diacron, Italy).

2.4. Statistical analysis

Results are reported as means ± SD. Significant differences between means of various rat treatment groups were determined by analysis of variance (ANOVA) and means were compared using Dunnett's *t*-test. All the statistical analyses were carried out using Prism, GraphPad Software (San Diego, CA, USA).

3. Results

In Fig. 1 the rat plasma values of BUN, creatinine, hydrogen peroxide and testosterone have been reported. As expected, in rats treated with cisplatin, a significant increase of plasmatic BUN and creatinine, hydrogen peroxide, used as measure of oxidative stress, and a remarkable reduction of testosterone levels were observed. On the contrary, the administration of Lisosan G did not cause any significant effect on these parameters. The group of animals fed with Lisosan G and treated with cisplatin (Lis+cis) showed reduced levels of BUN, creatinine, and hydrogen peroxide if compared to those of Cis group, indicating that Lisosan G has a protection with respect to these data in the Cis group. A protective effect of Lisosan G was also seen in the testosterone level of the Lis+Cis group which was partially restored to control level.

In order to investigate the effect of cisplatin on drug metabolising system, we have measured the CYP content, and the activities of some CYP-dependent and detoxification enzymes in liver and kidney tissues.

The hepatic and renal CYP contents in the cisplatin group were significantly decreased if compared to those of control group, whereas the co-treatment of cisplatin with Lisosan G restored the CYP contents to their control values (Fig. 2).

The cisplatin treatment induced also a reduction of the ECOD, EROD, APD and ErD activities to 20–50% of the corresponding control values and some of which were totally (EROD) or partially (ECOD) restored by the co-administration of Lisosan G (Table 1). In addition, some antioxidant enzymes such as GSH peroxidase, GSH reductase and catalase, but not GST and DT-diaphorase, were depleted by cisplatin. The co-administration of Lisosan G restored the activity of GSH peroxidase and GSH reductase to the control values whereas the catalase activity not only recovered but rebound above the value of control group. It was also noted that the DT-diaphorase activity was not affected by cisplatin but it was found significantly increased in the Lis+Cis group. The treatment with Lisosan G only did not alter these activities, except catalase, that was significantly increased.

To further investigate the effect of the various treatments on the CYP activities, we also determined in liver microsomes the metabolism of testosterone (Fig. 3) an endogenous substrate selectively known to be oxidised by many CYPs (Longo et al., 1991). The testosterone hydroxylase activities in the positions 2α, 16α and 17, linked to CYP2C11 (Ryan and Levin, 1990) [the major CYP isoform constitutively present in male rats liver (Ohishi et al., 1994)], were decreased significantly by cisplatin treatment and partially recovered with Lisosan G. In addition, the 6β-testosterone hydroxylase, linked to CYP3A (Ohishi et al., 1994), following cisplatin treatment was reduced to 40% of the control value and recovered almost entirely in the Lis+Cis group.

In kidney, the treatment with cisplatin reduced significantly the activities of ECOD, EROD, GST, GSH reductase and catalase, but not the activity of GSH peroxidase and DT-diaphorase (Table 2). However, in the Lis+Cis group, the activities of ECOD, EROD and GST were restored at the control levels, whereas those of GSH reductase and catalase partially recovered with respect to their control values. By contrast, the GSH peroxidase activity was not reduced by cisplatin treatment but resulted to be induced in the rats fed with only Lisosan G. All the treatments used did not influence the DT-diaphorase activity in kidney. In Fig. 4 it was reported the 17β-progesterone hydroxylation activity performed in the testis microsomes. Cisplatin treatment reduced the activity to 20% of control group value whereas in the group Lis+Cis this activity partially recovered.

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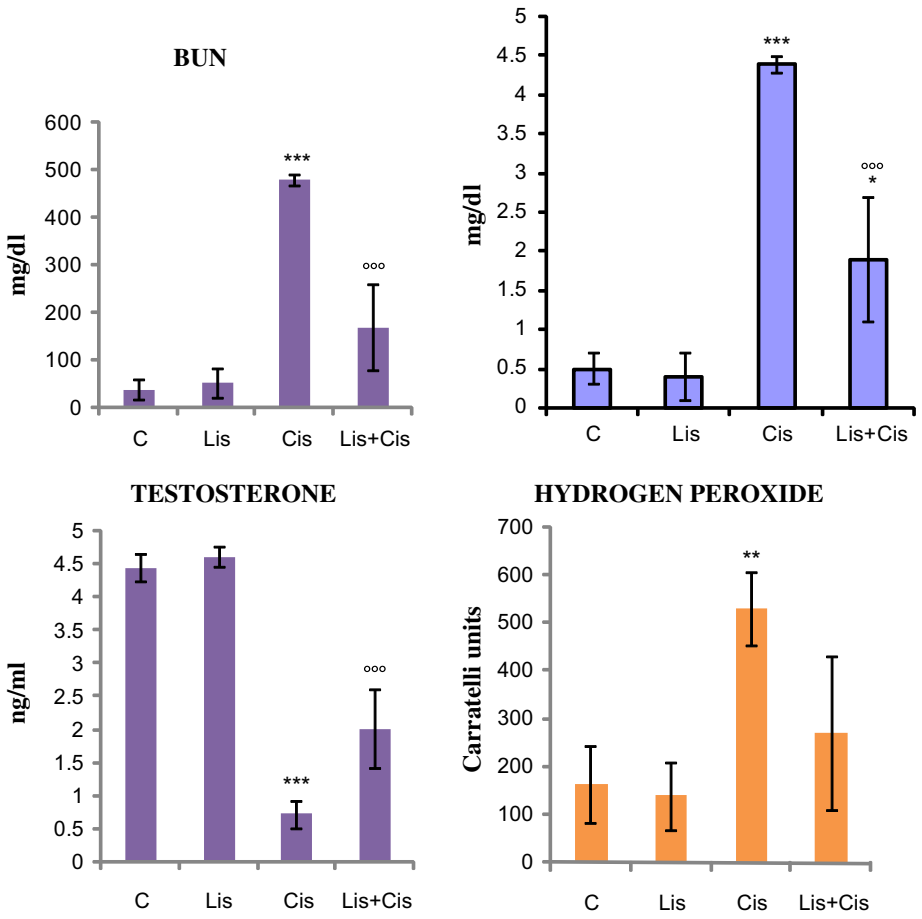

Fig. 1. BUN, Creatinine, Testosterone, Hydrogen peroxide levels in the plasma of rats. Values are means ± SD of four experiments performed with plasma of different animals. *($P < 0,05$) **($P < 0.01$) ***($P < 0.001$) Values differ significantly from the control; °°°($P < 0.001$) Values differ significantly from the cisplatin group (ANOVA). Carratelli units:1 CARR U corresponds to 0.8 mg/L hydrogen peroxide.

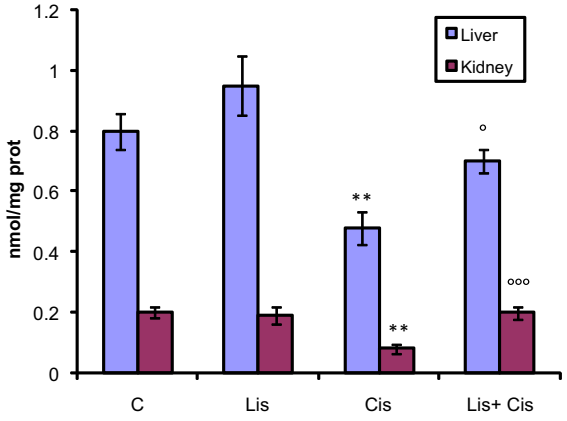

Fig. 2. Cytochrome P450 content in microsomes of liver and kidney. Values are means ± SD of four experiments performed with microsomes of different animals. **($P < 0.01$) Values differ significantly from the control; °($P < 0.05$) °°°($P < 0.001$) Values differ significantly from the cisplatin group(ANOVA).

Table 1
Cytochrome P450-dependent, phase 2 and antioxidant activities in microsome and citosol of liver.

	C	Lis	Cis	Cis+Lis
ECOD	0.55 ± 0.06	0.69 ± 0.04	0.13 ± 0.09***	0.3 ± 0.03**,°
EROD	0.13 ± 0.02	0.18 ± 0.03	0.07 ± 0.03***	0.12 ± 0.01°
APD	6.8 ± 0.5	7 ± 0.3	2.2 ± 0.3***	3 ± 0.2***
ErD	1.4 ± 0.3	1.5 ± 0.2	0.6 ± 0.2**	0.5 ± 0.1**
AnH	0.7 ± 0.2	0.8 ± 0.3	0.5 ± 0.2	0.6 ± 0.2
GST	586 ± 79	672 ± 29	499 ± 69	712 ± 50°°
GSH peroxidase	690 ± 47	745 ± 50	400 ± 20**	800 ± 108°°°
GSH reductase	161 ± 12	156 ± 5	113 ± 6***	158 ± 7°°°
Catalase^	475 ± 21	630 ± 20***	303 ± 28***	721 ± 20***,°°°
DT-diaphorase	51 ± 15	40 ± 12	71 ± 29	140 ± 47*

The activities are expressed as nmol/mg protein/min. Values are means ± SD of four experiments performed with microsomes or citosol of different animals.
^ As μmol/mg protein/min.
* ($P < 0.05$) Values differ significantly from the control.
** ($P < 0.01$) Values differ significantly from the control.
*** ($P < 0.001$) Values differ significantly from the control.
° ($P < 0.05$) Values differ significantly from the cisplatin group (ANOVA).
°° ($P < 0.01$) Values differ significantly from the cisplatin group (ANOVA).
°°° ($P < 0.001$) Values differ significantly from the cisplatin group (ANOVA).

4. Discussion

The present study evidenced that cisplatin treatment had a toxic effects on liver, kidney and testis of rats. The elevation of plasma hydrogen peroxide and hepatic and renal reduction of CYPs and antioxidant enzymes suggested that the oxidative stress due to free-radical damage is one of the possible mechanisms in the pathophysiology of cisplatin toxicity. In fact oxidative stress and involvement of oxidative reactive species in cisplatin toxicity have

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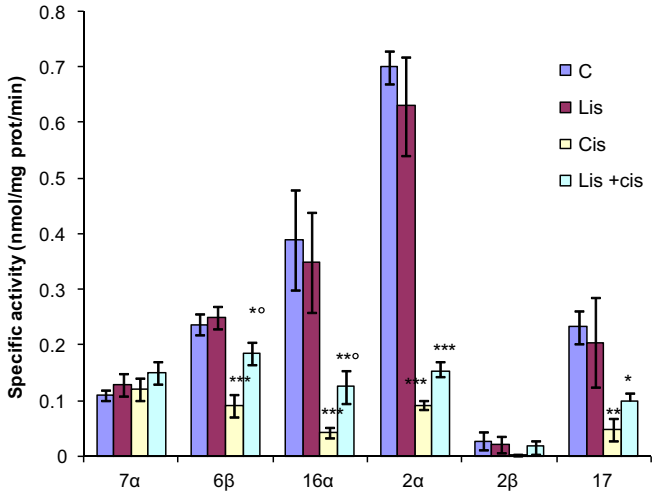

Fig. 3. Testosterone hydroxylase activities in hepatic microsomes. Values are means ± SD of four experiments performed with microsomes or citosol of different animals. *($P < 0.05$) **($P < 0.01$) ***($P < 0.001$) Values differ significantly from the control; °($P < 0.05$) Values differ significantly from the cisplatin group (ANOVA).

Table 2
Cytochrome P450-dependent, phase 2 and antioxidant activities in microsomes and citosol of kidney.

	C	Lis	Cis	Cis+Lis
ECOD^	5.7 ± 0.8	7 ± 1	1.7 ± 0.5*	8 ± 1.8°°°
EROD^	1.8 ± 0.6	2.8 ± 0.4	0.14 ± 0.09*	1.2 ± 0.3°°
GST	106 ± 6	84 ± 10	52 ± 6*	86 ± 10°°°
GSH reductase	217 ± 8	195 ± 6	116 ± 4*	171*,°°°
GSH peroxidase	193 ± 9	294 ± 5*	179 ± 18	295 ± 5*,°°°
Catalase#	140 ± 7	179 ± 21*	44 ± 6*	74 ± 7*,°°°
DT-diaphorase	25 ± 2	23 ± 4	21 ± 3	26 ± 2

The activities are expressed as nmol/mg protein/min. Values are means ± SD of four experiments performed with microsomes or citosol of different animals.
^ Expressed as pmol/mg protein/min.
# Expressed as μmol/mg protein/min.
* ($P < 0.001$) Values differ significantly from the control.
°° ($P < 0.01$) Values differ significantly from the cisplatin group (ANOVA).
°°° ($P < 0.001$) Values differ significantly from the cisplatin group (ANOVA).

been shown in many studies and were suggested to play an important role in the pathogenesis (Badary et al., 2005). In accordance with previous studies (Baliga et al., 1998; Chirino et al., 2008; Jariyawat et al., 2009) cisplatin treatment developed renal damage characterized by the increase in BUN and creatinine and a marked decrease of liver and renal CYP content and of various monooxygenase activities. Besides, it reduced the plasma testosterone level and caused a significant depletion of testicular 17β-progesterone hydroxylase activity required for androgen biosynthesis. This activity, catalysed by CYP17, is a key step in testicular steroidogenesis (Maines and Mayer, 1985). The effect on this enzymes was reported to be the biochemical basis for the testosterone reduction, and thought to contribute to infertility observed in patients receiving cisplatin (Maines and Mayer, 1985). Several free radical scavengers and antioxidants including vitamin C, vitamin E and flavonoids were reported to show some protective effects in cisplatin-induced toxicity (Badreldin and Al Moundhri, 2006). Lisosan G is a powder of grain with antioxidant properties due to the presence of tocopherols, vitamin B1, B2 and B6. The antioxidant activity of Lisosan G was previously evaluated by the *in vitro* and *in vivo* experiments (Longo et al., 2007). It is known that cisplatin is mainly nephrotoxic and in this paper the feed with Lisosan G in combination with cisplatin had an effect renoprotective. In fact in the animal group Lis+Cis the markers of renal damage such as BUN and creatinine returned to the control level indicating a protective effect of Lisosan G. It was observed that the feed with Lisosan G was able to attenuate the decrease in antioxidant enzymes provoked by cisplatin. The decrease in the activity of the antioxidant enzymes may be also involved in oxidative stress observed in cisplatin-treated rats (Koc et al., 2005; Ajith et al., 2007). Moreover our results show that feeding with only Lisosan G induced antioxidant enzymes such as catalase, gluthatione peroxidase. These data suggest that *in vivo* protective effect of Lisosan G was mediated, at least in part, by the induction and the preservation of the antioxidant system. In conclusion our results show protective effect of Lisosan G against the cisplatin induced toxicity. The underlying mechanisms of Lisosan G could be associated mainly with the attenuation of the oxidative stress and with the preservation in antioxidant enzymes. However, further investigation is necessary to demonstrate the exact mechanism of Lisosan G on cisplatin-induced toxicity.

Conflict of interest

The authors declare that there are no conflicts of interest.

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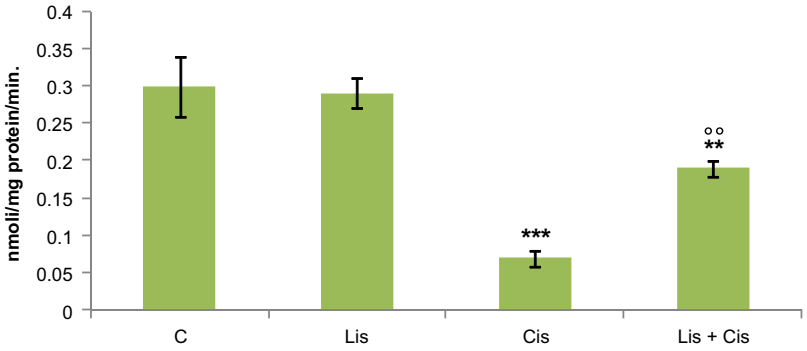

Fig. 4. 17 β-Progesterone hydroxylase activity in microsomes of testis. Values are means ± SD of four experiments performed with microsomes of different animals. **($P < 0.01$) ***($P < 0.001$) Values differ significantly from the control; °°($P < 0.01$) Values differ significantly from the cisplatin group (ANOVA).

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