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RESEARCH ARTICLE

A STUDY ON CISPLATIN-INDUCED TOXIC EFFECTS IN RATS WITH RESPECT TO HEMATOLOGY, PERFORMANCE, RELATIVE ORGAN WEIGHTS (%) AND GASTROINTESTINAL TOXICITY

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ABSTRACT

Cisplatin is one of the most remarkable successes in the war on cancer. The present study was aimed to evaluate the protective effect of turmeric in cisplatin induced toxicity in rats. A total of 48 rats which were divided into 4 groups and treated as follows: Group 1: sham control, 2: cisplatin control @ 2 mg/kg b.wt, 3: turmeric control @ 0.05 mg/kg b.wt and 4: cisplatin + turmeric each with the above mentioned doses. Body weights were recorded at weekly intervals and organ weights were recorded at the time of sacrifice on day 28. Whole blood was collected at fortnight intervals for estimation of hematological parameters like RBC, Hb, WBC and PCV. Stomach and intestines were collected for estimation of TBARS, GSH and protein carbonyls in tissue homogenates and for histopathology. Body weight gain, relative organ weight, RBC, WBC, Hb, PCV, were significantly ($P < 0.05$) decreased in cisplatin administered group. The ameliorative group 4 showed mild to moderate improvement in all parameters in comparison to group 2.Histopathological sections from group 2 stomach showed marked congestion and hemorrhages between the villi and at the base of villi. Intestine Sections from group 2 showed marked disruption of villi epithelium. Groups 1 and 3 did not reveal any lesions of pathological significance. From this study, it was concluded that the adverse effects of cisplatin can be reverted by administration of turmeric in a dose-dependent manner.

INTRODUCTION

Cisplatin is one of the most potent and widely used anti cancerous drugs today and most of the researchers use cisplatin as the gold standard against which new medicines are compared. It is a p latinum based chemotherapeutic drug used to treat various types o f cancers, including sarcomas, carcinomas(Stephen,2005).Thether apeuticeffects of cisplatin are significantly improved by dose escal ation. However, high dose therapy with cisplatin is limited by its dose-dependent cumulative nephrotoxicity, hepatotoxicity, ototoxi city (Naqsbandhi *et al.*, 2011), In view of the significance of adverse effects, the current research was planned to evaluate hematology, performance, relative organ weights (%) and gastrointestinal toxicity in cisplatin-treated rats.

MATERIALS AND METHODS

A total of 48 *Sprague dawley* female rats were randomly dividedinto4groupsconsisting of 12 in each group. Group 1 was m aintained as sham control, 2 was treated with cisplatin (@ 2 mg/k g b.wt, intraperitoneally on day 1, 7, 14 and 28), 3 was treated with turmeric (@ 0.05 mg/kg b.wt. p.o. once daily for 28 days) and 4 was treated with cisplatin + turmeric (as per above schedule). Body weights were recorded at weekly intervals. Blood was collected by retro orbital plexus at fortnight intervals. All the rats were euthanized on day 28 and stomach and intestines were collected and stored at -200 C, for oxidative stress analysis and they were fixed in formalin for histopathological studies. Experimental protocol was approved by Institutional Animal Ethics Committee. The organ weights were noted. Statistical analysis of experimental data was carried out with SPSS version 15.

RESULTS AND DISCUSSION

The mean TEC, Hb, TLC and PCV values of group 2 showed a significant reduction on day 14 and day 28 in comparison to other groups (Table 1). The reduction in these values might be due the affect of cisplatin on bone marrow. Nowis *et al.* (2007) also reported that cisplatin administration reduced erythropoietin, a haemopoietic growth factor, which further resulted in alteration of haematological parameters.

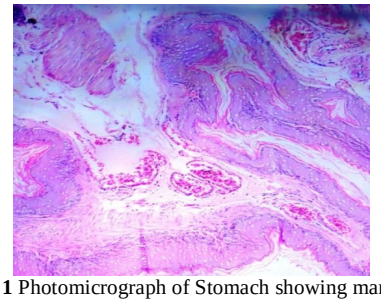

Fig. 1 Photomicrograph of Stomach showing marked Congestion and hemorrhages between the villus (Group 2, day 28). H&E X100

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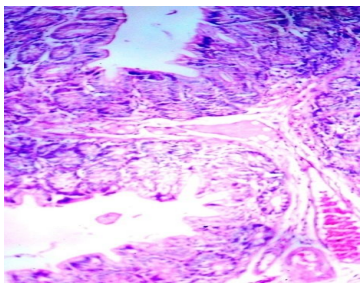

Fig. 2 Photomicrograph of stomach with few villi in showing loss of epithelium at tips, edematous fluid and congestion (Group 2, day 28). H&E X 100

In the present study, body weight gain of cisplatin-treated groups was significantly reduced, which may be due to decreased feed and water intake owing to hepatotoxicity due to cisplatin-induced oxidative stress (Table 2). This may be attributed due to reduction in feed intake, loss of skeletal muscles and adipose tissue. These results are in accordance with the studies of Vijayalakshmi *et al. (*2006) and Hassan *et al.* (2009).

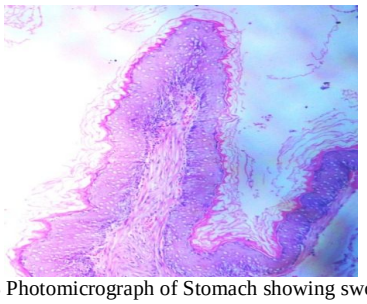

Fig. 3 Photomicrograph of Stomach showing swollen villus with mild edema (Group 2, day 14). H&E X 100

The body weight in group 4 was found to be increased as turmeric acted like appetizer and improved the feed intake in rats. These results are in accordance with Chattopadhyay *et al.* (2004) and Yousef *et al.* (2009).

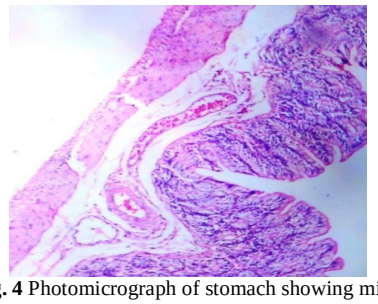

Fig. 4 Photomicrograph of stomach showing mild congestion (Group 4, day 14). H&E X 100

The relative weight (% of body weight) of kidney, liver, brain and heart on day 28 in group 2 was significantly ($P < 0.05$) reduced compared to groups 1 and 3. Values of groups 1 and 3 were comparable. The relative weights in group 4 were significantly ($P < 0.05$) increased when compared to group 2 (Table 3).

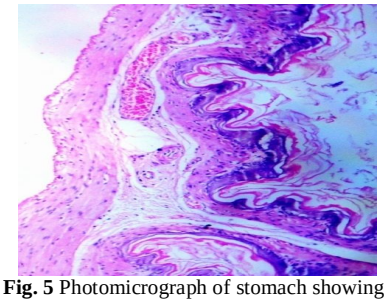

Fig. 5 Photomicrograph of stomach showing edema (Group 4, day 28). H&E X100

The decrease in relative (%) weights may be due to the action of free radicals on cell membrane leading to lipid peroxidation and protein denaturation. These findings are in accordance with Noori *et al.* (2010). An increased organ weight in groups 3 and 4 as compared to group 2 is attributed to free radical scavenging action of turmeric; thereby protecting cells from free radical damage.

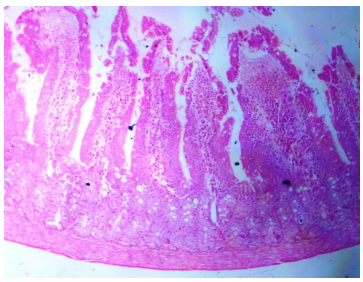

Fig. 6 Photomicrograph of intestine showing moderate disruption of villus epithelium (Group 2, day 14). H& E X100

Stomach

TBARS (6.73± 0.42) (table 4) level increased while GSH (32.51± 7.66) (table 5) level was decreased in rats of group 2, as compared to group 1and group 3.This might be due to cisplatin's ability to damage mitochondria which enhanced the ROS production and lead to oxidative stress or due to induction of apoptosis which was not ROS dependent. These findings were in accordance with Vijayalakshmi *et al.* (2006).There was improvement in group 4 compared to group 2.This was because turmeric had antioxidant property and combats ROS as was also observed by Chattopadhyay *et al.*(2004).

On histopathological observation of stomach sections, there was marked congestion and hemorrhages between the villus (Fig.1) and few villi showing loss of epithelium at tips, edematous fluid between villi along with congestion were observed from sections of group 2 on day 28 (Fig.2). Sections from group 2 on day 14 showed swollen villus with mild edema (Fig.3).Sections from group 4 on day 14 revealed mild congestion (Fig.4) and on day 28 edema was also seen (Fig.5).

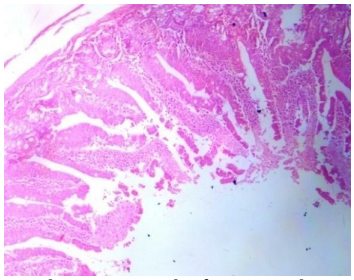

Fig. 7 Photomicrograph of intestine showing marked disruption of villus epithelium (Group 2, day 28). H&E X 100

Intestine

In rats of group 2, there was reduction in GSH (48.64 ±4.31) (table7) and increase in TBARS (12.54±0.76) (table 6) concentration. This was attributed to accumulation of cisplatin in mitochondria of enteroctyes which impair the intestinal permeability and reduce the ability to combat free oxygen radicals induced by cisplatin. These findings were in accordance with Jaime *et al.* (2003). Cisplatin initiated the release of serotonin through generation of free radicals and induced gastrointestinal toxicity.

Table 1 Haematological parameters in different groups of rats

Group	TEC (millions/cmm)		TLC (thousands/cmm)		Hb (g/dl)		PCV (%)	
	Day 14	Day 28	Day 14	Day 28	Day 14	Day 28	Day 14	Day 28
1.CONTROL	8.59±0.35^{a}	8.61±0.41^{a}	14.61±0.50^{a}	14.79±0.63^{a}	14.39±0.59^{a}	14.71±0.63^{a}	42.41±3.59^{a}	43.11±3.56^{a}
2. CISPLATIN	6.84±0.41^{b}	5.16±0.39^{b}	10.39±0.67^{b}	6.46±0.29^{b}	10.01±0.46^{b}	7.68±0.32^{b}	35.73±2.16^{b}	29.27±2.36^{b}
3.TURMERIC	8.97±0.46^{a}	9.37±0.46^{a}	14.66±0.72^{a}	15.07±0.69^{a}	14.66±0.68^{a}	15.11±0.72^{a}	43.17±3.36^{a}	45.08±3.62^{a}
4.CISPLATIN+ TURMERIC	7.01±0.38^{c}	6.94±0.46^{c}	12.37±0.48^{c}	9.14±0.41^{c}	12.16±0.52^{c}	11.91±0.56^{C}	38.27±2.22^{ab}	36.19±2.13^{c}

Values are Mean ± SE (n = 6); One way ANOVA (SPSS)
Means with different alphabets as superscripts differ significantly (P<0.05)

Table 2 Concentration of TBARS and GSH in stomach and intestine in different groups

Group	Stomach		Intestine	
	TBARS (nM of MDA/mg protein)	GSH(µM /mg protein)	TBARS (nM of MDA/mg protein)	GSH (µM /mg protein)
1. CONTROL	2.88 ±0.19^{a}	54.69± 6.31^{a}	5.67±0.32^{a}	84.43 ±5.27^{a}
2. CISPLATIN	6.73± 0.42^{b}	32.51± 7.66^{b}	12.54±0.76^{b}	48.64 ±4.31^{b}
3 .TURMERIC	2.87±0.26^{a}	59.11± 5.87^{a}	5.21±0.22^{a}	87.36 ±6.47^{a}
4.CISPLATIN+TURMERIC	4.46 ±0.61^{c}	49.47 ±7.06^{c}	7.26±0.55^{c}	76.47± 7.06^{a}

Values are Mean±SE (n=6); One way ANOVA (SPSS); Means with different alphabets as superscripts differ significantly (P<0.05)

Table 3 Relative organ weight (%) on day 28

Group	Kidney	Liver	Brain	Heart	Body weight gain (g)	
					Day 14	Day 28
1. CONTROL	0.80±0.017^{a}	4.39±0.051^{a}	0.91±0.028^{a}	0.56±0.007^{a}	24.80±1.83^{a}	18.80±1.50^{a}
2. CISPLATIN	0.56±0.011^{b}	3.83±0.037^{b}	0.82±0.014^{b}	0.48±0.004^{b}	15.77±1.51^{b}	7.66±1.32^{b}
3.TURMERIC	0.81±0.015^{a}	4.40±0.047^{a}	0.93±0.019^{a}	0.59±0.008^{a}	24.21±1.87^{a}	18.28±1.26^{a}
4.CISPLATIN+TURMERIC	0.71±0.012^{c}	4.00±0.041^{c}	0.88±0.022^{c}	0.51±0.004^{c}	17.70±1.73^{c}	12.45±1.04^{c}

Values are Mean ± SE (n = 6); One way ANOVA (SPSS)
Means with different alphabets as superscripts differ significantly (P<0.05).Small alphabets - Vertical Comparison between different groups

These findings were in accordance with Osama *et al*. (2006). There was reduction in toxicity in rats of group 4 due to antiemetic and antioxidant properties of turmeric which was attributable to its ability to react with free radicals generated by cisplatin. These findings were on par with Gupta *et al*. (1996). Histopathological sections from group 2 on day 14 revealed moderate disruption of villus epithelium (Fig.6) while sections on day 28 revealed marked disruption of villus epithelium (Fig. 7). Sections from group 4 on day 14 mild disruption of villus epithelium was noted (Fig.8). No lesions of pathological significance were observed in other groups.

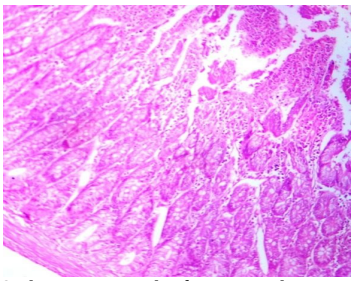

Fig. 8 Photomicrograph of intestine showing mild disruption of villus epithelium (Group 4, day 14). H&E X 200

Summary

Cisplatin-induced toxicity in rats was manifested by reduced weight gains and reduced relative organ weights, besides haematological alterations. Treatment with turmeric could counter the toxic effects of doxorubicin.

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