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Effect of fractionated pectin powder capped zinc oxide nanoparticle in hematological and biochemical parameters of 5-fluorouracil induced toxicity in male rats

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Abstract
5-Fluorouracil (5-FU) is an anticancer drug widely used for the treatment of cancers especially colorectal cancer. In spite of treating cancer, it also causes toxicity to other rapidly dividing cells. The present study was carried out to evaluate the effect of the Fractionated Pectin Powder (FPP) capped nano Zinc oxide (nZnO) in 5-Fluorouracil induced toxicity in haematological of male rats. Experimental rats were divided into four groups (n = 10) which received normal saline (Group I), 5-FU @20gm/kg b.wt (Group II), FPP capped nZnO @ 40mg/kg b.wt (Group III), 5-FU @20gm/kg b.wt and FPP capped nZnO @ 40mg/kg b.wt (Group IV). All treatments were given orally upto14 days. On 15th day of sacrifice blood samples was collected after serum separation used for respective analysis. Treatment with FPP capped nZnO significantly. This study highlights the protective role of FPP capped nZnO against 5-FU induced oxidative stress to the testicular and epididymal cells.

Keywords: 5-Fluorouracil, FPP capped nZnO, Serum

Introduction
Cancer chemotherapy involves the use of drugs that destroy the rapidly growing cells, a characteristic of the cancer cells, leading to toxicities of all systems including haemopoietic, gastrointestinal, skin and hair follicles, the nervous system, hepatic, urinary, cardio-pulmonary and reproductive [1-2].

The anticancer drug 5-FU is an antimetabolite approved by the FDA for the treatment of colorectal cancer and various gastrointestinal tumours [3]. 5-FU, an analogue of uracil with a fluorine atom at the C-5 position rapidly enters the cell and gets converted intracellular to several active metabolites. 5-FU and its metabolites get incorporated into DNA or RNA by inhibiting the enzyme thymidylate synthase [4]. In one pathway, 5-FU gets converted into 5-FdUMP which binds to thymidylate synthase and inhibits DNA synthesis, while in the other it is converted into 5-FUTP and inhibits RNA synthesis by blocking the incorporation of uracil and orotic acid [5].

Several authors have documented the cardio, hepato and CNS toxicities of this compound including the appearance of micronuclei and chromosomal aberration [6-8]. Kadagi *et al.* [9] reported that degenerative changes are noticed in several vital organs with LD_{50} cut off values ranging between 200 and 300 mg/kg in an acute oral toxicity study in rats.

Pectin is a complex mixture of polysaccharides present in the cell wall of higher plants which consists of D-Galacturonic acid joined in chains by α- (1-4) glycosidic linkage [10]. Pectins exert a variety of pharmacological activities such as cholesterol reducing property, adsorbent in poisoning conditions, antibacterial [11] and antitumour activity *in vivo* and *in vitro* in various types of cancers including colon, breast, melanoma and multiple myeloma [12-14]. Pectin was able to afford protection against lead acetate [15] and cadmium [16] induced testicular oxidative stress and sperm abnormalities.

Zinc is also a well-known antioxidant factor since it is a core constituent of free radical scavenging enzymes such as SOD and a recognized protector of sulfhydryl groups. Nanotechnology has paved the way for the engineering of organized materials capable of improved performances in cancer therapy [17]. The advantages of using nanoparticles include: (1) carrying the concentrated drug to its destination to maximize the drug effect after endocytosis (2) preventing degradation of the drug by body fluids and increasing its retention time in the body (3) by virtue of its large surface area, carrying more drug molecules and increasing the solubility of some hydrophobic drugs (4) by surface modification, loading

another targeting molecules to achieve specific delivery [18]. Hence, the present study was designed to explore the role of FPP capped nZnO against 5-FU induced toxicity in haematological and serum parameters.

Materials and Methods

a) Experimental protocol: Male Wistar rats (90-100 days old), were maintained under standard laboratory conditions with with *an ad libitum* supply of feed and purified water during the study period. Rats were acclimatized for one week and then randomized based on the body weight and distributed to different groups such that the mean body weight variation does not exceed 20%. All treatments were given orally up to 14 days.

Groups	Treatments	No. of Rats
I	Control	10
II	5-Fluorouracil (5-FU) contro l@ 20mg/kg B.wt (p.o for 14 days)	10
III	Modified Pectin (FPP capped nZnO) control @ 40mg/kg b.wt (p.o for 14 days)	10
IV	5-FU @ 20mg/kg b.wt (p.o for 14 days) + FPP capped nZnO@ 40mg/kg b.wt (p.o for 14 days)	10

b) Haematological parameters

At the end of experiment, all the animals were sacrificed and blood was collected. RBC, WBC counts, PCV, hemoglobin and platelets counts were determined by routine clinical laboratory techniques.

c) Serum Biochemistry- Enzymic indices of cellular integrity

Serum was separated by centrifuging the blood at 7000 rpm for 12 min. The markers for cellular integrity Alanine amino transferase [ALT], Aspartate amino transferase [AST], Alkaline phosphatase [ALP], Blood urea nitrogen [BUN] and creatinine were estimated in the serum by using standard kits (Agappe Diagnostics® India) as per the manufactures protocol.

Results

Hematological parameters of the experimental animals were represented in Table-1. A sharp reduction in the WBC and Hb were noticed in the 5- FU group as compared to the control and no significant differences were observed in the RBC, PCV and PLT values among the groups. On treatment with FPP capped nZnO, marked increase in WBC ($P< 0.01$) and Hb ($P< 0.05$) were noticed in the 5-FU group.

Table 1: Effect of FPP capped nZnO on haematological parameters

Groups	Hb* (g/dl)	RBC (x10^6/µl)	PCV (%)	WBC** (x10^6/ µl)	PLT (10^3/cmm)
Control	11.33^{ab}±0.78	7.75± 0.55	38.20±6.83	10916^b±19.74	313000^a± 6.72
5-FU control	11.15^a± 0.30	7.69± 0.21	36.70 ± 2.62	4683^a± 8.40	396833^a±6.42
FPP capped nZnO control	12.53^{ab}±0.27	8.46± 0.17	40.11± 2.48	8400^b ± 4.09	374500^a ±3.82
5-FU + FPP capped nZnO	12.73^b± 0.18	8.52± 0.12	41.50±2.25	8866± 6.61	379000^a ±7.20

Biochemical parameters of the experimental animals were represented in Table-2. A sharp increase in the serum BUN, ALT, AST and ALP values were noticed in the 5- FU group as compared to the control. Significant restoration in the activities of BUN ($P< 0.005$), ALT, AST and ALP ($P< 0.01$) were observed on treatment with FPP capped nZnO in the 5-FU group. No appreciable differences in the creatinine levels were noticed among the groups.

Table 2: Effect of FPP capped nZnO on serum biochemical parameters

Groups	BUN* (m g/dl)	Creatinine (mg/dl)	ALT** (IU/L)	AST** (IU/L)	ALP** (IU/L)
Control	14.08^a±0.91	0.45^a±0.00	69.20^a±1.48	192.50^b±2.32	335.60^a±15.08
5-FU control	18.79^b±1.67	0.40^a±0.01	98.60^b±3.07	226.70^c±4.71	394.70^b±18.41
FPP capped nZnO control	15.59^a±0.88	0.45^a±0.02	60.60^a±2.99	173.30^a±7.13	336.80^a±45.06
5-FU + FPP capped nZnO	15.10^a±0.80	0.45^a±0.02	75.50^a±3.15	186.40^{ab}±3.2	330.50^a±6.95

Discussion

5-FU administration caused a pronounced decline in the haematological parameters. This can be attributed to the side effects associated with 5-FU administration which is in accordance with the findings of Kadoyama *et al.* [19]. The decrease in haematological parameters might be in response to the oxidative stress-induced myelosuppression due to 5-FU administration as reported Numazawa *et al.* [20].

Similarly, 5-FU administration strikingly increased the cytosolic enzymes associated with hepatic and renal injury, which is in agreement with the findings of Bano *et al.* [21]. The hepatic and renal injury due to 5-FU chemotherapy might have resulted in the leakage of the cytosolic enzymes, contributing to the increased levels of enzymes. FPP capped nZnO treatment conspicuously decreased the cytosolic levels of the enzymes associated with hepatic and renal injury, which might be due to the hepato- and nephroprotective properties of FPP. The results agree with the findings of Baisakhi *et al.* [22].

Conclusion

The present study concluded that treatment with FPP capped nZnO significantly restored the levels of altered haematological and biochemical parameters. It is obvious that FPP capped nZnO could be used as combination therapy with anticancer drugs to reduce the possible side effects. Further rigorous studies are needed to explore mechanisms.

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