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Haematological changes in experimentally induced pancreatic atypical acinar cell tumor in male wistar rats and its alleviation by *Momordica charantia*

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Abstract
The aim of the study was to investigate the hematological changes in Wistar rats induced with pancreatic atypical acinar cell tumor and its alleviation by *Momordica charantia* (MC). Rats were administered with a single dose of azaserine at the rate of 30 mg/kg BW intraperitoneally (i.p.) on 21st day of age. Paclitaxel was administered to the azaserine + paclitaxel group (33mg/kg BW i.p.) for 6 weeks after 8 weeks post initiation and aqueous extract of MC (0.34mL/rat) was administered as oral gavage for 6 weeks after 8 weeks post initiation.
Blood samples were collected at the end of the experiment and processed for hematological studies. There was significant reduction in the level of haemoglobin, packed cell volume, erythrocyte count and neutrophils in the azaserine and azaserine + paclitaxel group. Azaserine + MC did not reveal any significant difference compared to the control group.

Keywords: *Momordica charantia*, haematological changes, pancreatic atypical acinar cell tumor, male wistar rats, paclitaxel, azaserine

1. Introduction
Cancer has a major impact on society across the world. Based on the GLOBOCAN 2012 estimate, pancreatic cancer causes more than 3, 31, 000 deaths per year, ranking as the seventh leading cause of cancer death in both sexes together. It has a negligible survival rate of 5 per cent and has seen a rise in India, in the recent years. The frequency of pancreatic tumors in dogs relates to 0.5 to 1.88 per cent of all tumors (Priester, 1974) [11].
Azaserine has been established as a carcinogen for inducing pancreatic tumor in rats. Paclitaxel has been widely used for the treatment of pancreatic cancer, however, the side effects of paclitaxel therapy has always been a great concern (Ma and Hidalgo, 2013) [7]. *Momordica charantia* (MC) (Bitter melon or Bitter gourd) of the family Cucurbitaceae is a common food ingredient in Indian cuisine and is used extensively in alternative medicine. In recent years, there were also accumulating reports showing anticancer efficacy and antimutagenic properties of the bitter melon (Meera and Nagarjuna, 2009) [8]. Therefore, a study was undertaken to assess the beneficial effects of bitter gourd on the haematological changes in experimentally induced pancreatic atypical acinar cell tumor in rats.

2. Materials and Methods
The study was conducted with the approval of the Institutional Animal Ethical Committee (Lr. No. 2345/18/DFBS/IAEC/2016).
Ninety six numbers of less than 3 weeks old male albino rats of Wistar strain were obtained from Laboratory Animal Unit, Madhavaram, Chennai-51. The standard commercial pellet laboratory animal diet was procured from M/s. Biogen Laboratory Animal Facility, Bengaluru-562 107.
Azaserine was obtained from M/s. Sigma Aldrich Inc., St. Louis, USA and stored at -20 ºC. The standard drug Paclitaxel was obtained as *gratis* from Cipla Ltd. Mumbai-83 and stored in dark at room temperature.
The aqueous extract of MC was prepared from the locally purchased unripened fruits. About 500g of unripened fruits were slit horizontally to remove pulp and seeds and the remaining portions of the fruits were chopped and thoroughly grounded with addition of clean water (approx. 100 mL) using a blender. It was allowed to strain through a muslin cloth into a beaker and the collected extract was filled in centrifuge tubes and centrifuged at 3000g for 30

minutes at 4 ºC. The sediment at the bottom was discarded and the clear supernatant was collected in centrifuge tubes and stored at -20 ºC until further use.

Pancreatic atypical acinar cell tumors were experimentally induced with azaserine in 2-3 week old male Wistar rats. Ninety six male Wistar rats were randomized into four groups each of 24 numbers *viz.* control (group I), azaserine (group II), azaserine + paclitaxel (group III) and azaserine + MC (group IV). Azaserine (0.9 per cent sodium chloride as vehicle) was administered as single intraperitoneal (i.p.) dose of 30 mg/kg BW/rat on the 21st day of age to rats of group II, III and IV. Azaserine + paclitaxel group rats was administered 33 mg/kg BW of paclitaxel (in 15 per cent dimethyl sulfoxide) i.p. for 6 weeks after 8 weeks post initiation and azaserine + MC group rats were administered 0.34 mL (Kaur *et al.* 2013) [5] of aqueous extract of MC as oral gavage for 6 weeks after 8 weeks post initiation. Rats from each group were sacrificed on the 16th and 24th week after the initiation of the experimental protocol.

2.1 Haematological analysis

On the 24th week after CO_2 inhalation anaethesia, blood samples were collected by retroorbital plexus method before every sacrifice. The EDTA vacutainers were used to collect the blood for haematology. All haematological samples were analysed by BC-2800 Vet by using the readymade diagnostic reagent kits (M/s. Agappe Diagnostics Ltd. Kerala).

2.2 Statistical analysis

The data generated from different parameters of the experimental study were subjected to one- way analysis of variance (ANOVA) test using statistical package for the social sciences (SPSS) software version 20 for Windows.

3. Results and Discussion

The haematological values Mean (±SE) of the control, azaserine, azaserine + paclitaxel and azaserine + MC treated groups of the male Wistar rats are presented in Table 1.

A significant (P<0.05) decrease was observed in the value of haemoglobin (Hb), packed cell volume (PCV), red blood cell count (RBC) and neutrophil count between the rats of the control and the different treatment groups.

The difference in the values of platelets, white blood cell count and lymphocytes were not significant among the different treatment groups.

The values of Hb, PCV, RBC and neutrophil count of rats treated with azaserine + paclitaxel group was significantly (P<0.05) decreased when compared to the azaserine and azaserine + MC groups. Significant decrease in the haematocrit levels in the azaserine group agreed with that of Prajapati *et al.* (2014) who reported that the reduced levels were due to defective haematopoiesis.

Significant reduced levels of Hb, RBC and PCV in azaserine + paclitaxel group when compared to the control group agreed with the findings of Panis *et al.* (2011) [9] and Utreja *et al.* (2012) [12] and Harisa (2015) [3] who opined that the changes in the haematocrit levels were mainly due to the oxidative stress induced by paclitaxel on the endothelial cells and erythrocyte membrane leading to anemia.

Neutropenia in the azaserine + paclitaxel group was in agreement with the results observed by Hajek *et al.* (1996) [2] who reported that neutropenia was encountered in human clinical trials as dose limiting adverse effects of paclitaxel. This might be due to myelosuppression effects of paclitaxel which was reported by Kumar *et al.* (2010) [6] in their human clinical trials.

There was no significant difference in the haematological parameters of azaserine + MC group which was in accordance with Husna *et al.* (2013) [4] who reported that oral administration of MC at a dose rate of 300 mg/kg BW to Sprague Dawley rats daily for 14 days did not reveal significant alterations in the haematological parameters in acute oral toxicity studies.

This implied that the MC treatment can significantly alleviate the adverse effects of chemotherapeutic regimens and overcome the side effects better than paclitaxel in the treatment of pancreatic tumors.

4. Conclusions

The study revealed that the *Momordica charantia* treatment can significantly alleviate the effects of chemotherapeutic regimens and overcome the side effects better than paclitaxel in the treatment of pancreatic atypical acinar cell tumors.

5. Acknowledgments

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Table 1: Haematological values Mean (±SE) of the male Wistar rats in the control, azaserine, azaserine + paclitaxel and azaserine + MC groups

Parameters	Control	Azaserine	Azaserine + Paclitaxel	Azaserine + MC
Hb (g/dL)	$16.39^{d} \pm 0.13$	$13.54^{b} \pm 0.62$	$11.45^{a} \pm 0.25$	$14.71^{c} \pm 0.16$
PCV (%)	$38.88^{c} \pm 0.35$	$35.28^{ab} \pm 1.53$	$32.78^{a} \pm 1.33$	$37.46^{bc} \pm 0.89$
RBC ($\times 10^6$/cmm)	$8.51^{c} \pm 0.75$	$7.41^{b} \pm 0.32$	$6.77^{a} \pm 0.20$	$7.57^{b} \pm 0.14$
WBC (cells/cmm)	$13261.67^{a} \pm 3322.89$	$8630.00^{a} \pm 593.48$	$7838.89^{a} \pm 696.78$	$8430.00^{a} \pm 789.54$
Platelets ($\times 10^3$/cmm)	$885750.00^{a} \pm 37770.25$	$770699.90^{a} \pm 75935.35$	$855277.78^{a} \pm 55725.51$	$862550.00^{a} \pm 71517.41$
Neutrophils (%)	$36.12^{b} \pm 0.89$	$32.80^{ab} \pm 1.65$	$31.47^{a} \pm 1.75$	$34.99^{ab} \pm 0.41$
Lymphocytes (%)	$58.68^{a} \pm 0.81$	$59.10^{a} \pm 3.16$	$63.59^{a} \pm 2.04$	$59.60^{a} \pm 0.49$

Means with same superscript within a row do not differ from each other (P>0.05)

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