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Original article

Effect of *Momordica charantia* L. on serum biochemical parameters in experimentally induced atypical acinar cell tumors in male wistar rats

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Abstract

The present investigation was carried out to study the effect of *Momordica charantia* L. (Bitter gourd) on serum biochemical parameters in male wistar rats induced with pancreatic atypical acinar cell tumor. Ninety six male wistar rats were randomized into four groups [control group, (i), azaserine group (ii), azaserine + paclitaxel (iii) and azaserine + *Momordica charantia* (MC) (iv) group] each comprising of 24 rats. Male wistar rats of group (ii, iii and iv) were administered with azaserine @ 30 mg per kg BW intraperitoneally (i.p.) on 21st day of age. Paclitaxel was administered to the azaserine + paclitaxel group (iii) @ 33 mg/kg BW intraperitoneally for 6 weeks after 8 weeks post initiation of tumor and aqueous extract of *Momordica charantia* @ 0.34 ml/rat was administered as oral gavage for 6 weeks after 8 weeks post initiation of tumor to azaserine + *Momordica charantia* group (iii). The blood was collected for estimation of serum biochemical parameters at the end of 24th week. Significant alterations in ALT, ALP, triglyceride, cholesterol, lipase and amylase levels were observed among the groups ii, iii and iv. The alterations were compared with the control and azaserine + paclitaxel group which revealed the high level of protective effect of aqueous extract of *Momordica charantia*, on the serum biochemical alterations.

Key words: *Momordica charantia* L., wistar rats, serum biochemical parameters, pancreatic atypical acinar cell tumor, paclitaxel

1. Introduction

Pancreatic cancer is an important public health problem. World-wide, carcinoma of the pancreas caused more than a quarter of a million deaths annually, being the 13th most common cancer and the seventh most frequent cause of death from cancer (Jimenez *et al.*, 2002; Parkin *et al.*, 2002). Given that the majority of cancers occurred in association with smoking, diabetes, pancreatitis, genetic factors, and others and with a growing population worldwide in mind, more cases would be expected in the near future giving further impetus to investigating prevention and treatment strategies to this international issue.

Azaserine (O-diazoacetyl-L-serine) ($C_5H_7N_3O_4$) is an antibiotic produced by *Streptomyces fragilis*. It is an analogue of glutamine. It is a strong mutagen in several *in vitro* and *in vivo* test system and has induced pancreatic atypical acinar cell nodules (AACNs), adenoma and carcinoma in rats. Paclitaxel (PTX) is a natural hydrophobic diterpenoid extract from the bark of the Pacific yew (*Taxus brevifolia)*. As mitotic inhibitor, paclitaxel could stabilize and protect microtubules from disassembly and interfere with the normal breakdown of microtubules during cell proliferation. As an effective cancer chemotherapy agent, it was widely used for the treatment of various tumours, including ovarian, breast, pancreatic, non-small cell lung, and prostate tumours (Kingston, 1991; Rowinsky *et al.*, 1992; Arbuck *et al.*, 1993).

Bitter gourd (*Momordica charantia* L.) is a common vegetable grown widely in Asia that is used as a traditional medicine. It is commonly known as bitter gourd and belongs to the family Cucurbitaceae. Two varieties of this plant are cultivated in India, *viz*., *M. charantia var. charantia* which were fusiform in shape and *M. charantia var. muricata* which are identified by small round fruit. The bitter flavour of both varieties is due to the alkaloid momordicine produced in fruits and leaves.

The pharmaceutical studies of unripened fruit extract of *M. charantia* (MC) had shown that the plant had antiallergic (Gupta *et al.*, 1993), anti-inflammatory, immunomodulatory (Manabe *et al.*, 2003) and anthelmintic (Grover and Yadav, 2004) properties

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and, hence, had been used in various Asian and African herbal medicine systems for a long time (Grover and Yadav, 2004; Beloin *et al.,* 2005).

The unripened fruits of vegetable MC had been used as folklore medicine for the management of ailments such as leprosy, eczema, piles, rheumatism, malaria, amenorrhoea, hypertensions, stomach pain, infections, cold, and cough and most efficiently for diabetes due to its antioxidant (Kubola and Siriamornpun, 2008), antimicrobial (Mwambete, 2009), hypoglycemic and hypolipidaemic action (El-Bakyn *et al*., 2009); anticancer activity, antiplasmodial, antileishmania (Gupta *et al.,* 2010) and antiulcer activity (Paul *et al.,* 2010).

Significant alterations in the ALT, AST and ALP levels were observed when male wistar rats were treated with azaserine (Sophia *et al*., 2014; Prajapati *et al.,* 2015, 2016). Mardani *et al.* (2014) reported no significant changes in the serum biochemical parameters upon administration of *M. charantia* fruit extracts along with the diet up to a level of 2 per cent of the diet.

Hence, the present study was undertaken to study the effects of *M. charantia* on serum biochemical parameters in experimentally induced pancreatic atypical acinar cell tumors in male wistar rats and its comparison with the standard drug paclitaxel.

2. Materials and Methods

The present work was carried out in the Department of Veterinary Pathology, Madras Veterinary College, Chennai with the approval of the Institutional Animal Ethical Committee, No.2345/18/DFBS/IAEC/2016. The experimental protocol met the national guidelines as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India.

2.1 Experimental animals

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, Bangalore-107. They were housed for a period of 24 weeks. Three rats each were housed in polycarbonate cages with corn cobb bedding and metal tops. Temperature was maintained between 18°C and 26°C and relative humidity ranging between 30 and 70 per cent was maintained. Light and dark cycles were controlled to give approximately a sequence of 12 h light and 12 h dark. Rats were acclimatized for five days prior to the treatment and randomly distributed to different groups based on their body weight.

2.2 Chemicals and drugs

Azaserine was obtained from M/s. Sigma Aldrich Inc., St. Louis, USA and stored at -20°C. The standard drug paclitaxel was obtained as *gratis* from Cipla Ltd. Mumbai - 83 and stored in dark at room temperature. Azaserine was dissolved in 0.9 per cent sodium chloride (NaCl) and paclitaxel was dissolved in 15 per cent dimethyl sulfoxide (DMSO) for administration.

2.3 *M. charantia* (MC) aqueous extract and its preparation

The unripened fruits of *M. charantia* (MC) were procured from the local market in the suburbs of chennai city and were identified by a Botanist (Ref: No.128DA/Dept. of AGR/Sample query2017/ dt.20.5.2017). The aqueous extract of MC was prepared from the locally purchased unripened fruits manually by extraction through blender and centrifugation. About 500 g of unripened fruits were slit horizontally and the pulp and seeds were removed. 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.

The collected extract was filled in centrifuge tubes and centrifuged at 3000 g for 30 min. at 4°C. The sediment at the bottom was discarded and the clear supernatant was collected in centrifuge tubes and stored at – 20°C until further use. A fraction of the collected aqueous extract was subjected for freeze drying at – 56°C and stored until further use. The freeze dried fraction was diluted to required concentration at the time of administration.

2.4 Experimental trial

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 were administered 33 mg/kg BW of paclitaxel intraperitoneally for 6 weeks after 8 weeks post initiation and azaserine + MC group rats were administered 0.34 ml of aqueous extract of MC as oral gavage for 6 weeks after 8 weeks post initiation. The dose rate of the aqueous extract was based on the reports by Kaur *et al.* (2013). Rats from each group were sacrificed on 24th week after the initiation of the experimental protocol.

2.5 Serum biochemical analysis

On the 24th week after CO_2 inhalation anaethesia, blood samples (about 2 ml) were collected by retro-orbital plexus method before every sacrifice. Plain serum collection tubes were used to collect the blood for serum biochemistry. All samples were analysed by using the readymade diagnostic reagent kits (M/s. Agappe Diagnostics Ltd., Kerala).

2.6 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

Serum biochemical values Mean ± SE of control, azaserine, azaserine + paclitaxel and azaserine + MC treated groups of male wistar rats are presented in Table 1 and Figures 1 and 2. A significant increase (p<0.05) was observed in the ALT values in the rats of azaserine, azaserine + paclitaxel groups when compared to control group. Whereas, a significant (p<0.05) decrease in ALT values was observed in rats of azaserine + MC group compared to the rats of azaserine, azaserine + paclitaxel groups.

The ALP values of rats in azaserine + paclitaxel group showed significant (p<0.05) increase when compared to control and azaserine

groups. However, a significant (p<0.05) decrease in the values of ALP was observed in the rats of azaserine + MC group compared to azaserine and azaserine + paclitaxel groups.

A significant (p<0.05) decrease in the triglyceride levels of the rats of azaserine + paclitaxel and azaserine + MC groups when compared to the rats of control and azaserine groups was observed.

Cholesterol was significantly (p<0.05) at low levels in the rats of different treatment groups when compared to the control group. There was no significant difference in the levels of blood urea nitrogen (BUN), creatinine, total protein, albumin, gamma glutamyltransferase (GGT), glucose, total bilirubin, direct bilirubin in the rats of azaserine, azaserine + paclitaxel and azaserine + MC groups when compared to the control group.

Table 1: Mean ± SE serum biochemical values of male wistar rats in the control, azaserine, azaserine + paclitaxel and azaserine + MC treated groups

Parameters	Control (I)	Azaserine (II)	Azaserine + Paclitaxel (III)	Azaserine + MC (IV)
BUN (mg/dl)	$28.28^{a} \pm 0.45$	$28.06^{a} \pm 0.99$	$29.15^{a} \pm 1.34$	$29.02^{a} \pm 0.74$
Creatinine (mg/dl)	$0.56^{a} \pm 0.01$	$0.54^{a} \pm 0.02$	$0.52^{a} \pm 0.02$	$0.51^{a} \pm 0.02$
Total protein (g/dl)	$6.59^{a} \pm 0.07$	$6.43^{a} \pm 0.09$	$6.58^{a} \pm 0.15$	$6.54^{a} \pm 0.14$
Albumin (g/dl)	$3.13^{a} \pm 0.03$	$3.13^{a} \pm 0.03$	$3.02^{a} \pm 0.07$	$3.19^{a} \pm 0.04$
ALT (U/l)	$64.42^{a} \pm 1.61$	$74.50^{b} \pm 1.85$	$71.89^{b} \pm 1.00$	$66.85^{a} \pm 1.54$
ALP (U/l)	$334.00^{a} \pm 9.13$	$427.85^{a} \pm 24.99$	$542.00^{c} \pm 12.35$	$403.90^{a} \pm 14.43$
GGT (U/l)	$15.46^{a} \pm 0.65$	$17.95^{a} \pm 1.06$	$16.06^{a} \pm 0.48$	$15.35^{a} \pm 0.65$
Glucose (mg/dl)	$109.92^{a} \pm 4.28$	$102.45^{a} \pm 5.81$	$101.39^{a} \pm 8.11$	$108.20^{a} \pm 4.02$
Total bilirubin (mg/dl)	$0.34^{a} \pm 0.02$	$0.39^{a} \pm 0.04$	$0.45^{a} \pm 0.08$	$0.37^{a} \pm 0.04$
Direct bilirubin (mg/dl)	$0.15^{a} \pm 0.03$	$0.13^{a} \pm 0.02$	$0.15^{a} \pm 0.03$	$0.14^{a} \pm 0.01$
Triglyceride (mg/dl)	$84.25^{b} \pm 1.86$	$84.25^{b} \pm 1.97$	$77.83^{a} \pm 1.73$	$74.55^{a} \pm 1.07$
Cholesterol (mg/dl)	$47.42^{b} \pm 1.19$	$38.75^{a} \pm 1.15$	$39.28^{a} \pm 1.32$	$38.55^{a} \pm 1.12$

Note: Means with same superscript within a row do not differ from each other (p<0.05)

a: Groups sharing common superscript "a" do not differ significantly at $p < 0.05$ (Duncan Multiple Range Test).

b,c: Groups with the superscripts "b" and "c", differ significantly at $p < 0.05$ (Duncan Multiple Range Test).

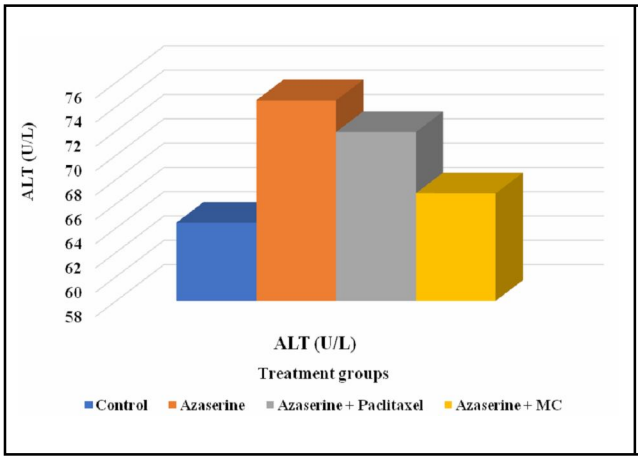

Figure 1: Comparative mean ALT (U/l) values of control and treated groups of male wistar rats.

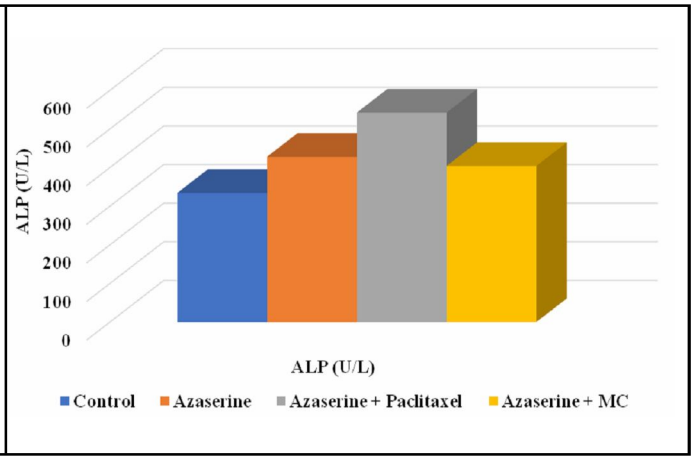

Figure 2: Comparative mean ALP (U/l) values of control and treated groups of male wistar rats.

3.1 Serum lipase and amylase

Mean ± SE serum lipase and amylase values of control, azaserine, azaserine + paclitaxel and azaserine + MC treated groups of male wistar rats are presented in Table 2 and Figures 3 and 4. There was a significant (p<0.05) increase in the lipase and amylase values in the rats of azaserine, azaserine + paclitaxel and azaserine + MC groups when compared to the control group. A significant (p<0.05) decrease was observed in the lipase and amylase values in the rats of azaserine + paclitaxel and azaserine + MC groups when compared to the azaserine group.

Table 2: Mean ± SE values of serum lipase and amylase of male wistar rats in the control, azaserine, azaserine + paclitaxel and azaserine + MC treated groups

Group	Lipase (U/l)	Amylase (U/l)
Control (i)	11.92^{a} ± 0.29	145.75^{a} ± 2.42
Azaserine (ii)	38.76^{d} ± 0.65	378.95^{d} ± 7.47
Azaserine + Paclitaxel (iii)	23.41^{c} ± 0.43	262.80^{c} ± 18.88
Azaserine + MC (iv)	16.35^{b} ± 0.29	221.00^{b} ± 59.92

Note: Means with same superscript within a column do not differ from each other (p<0.05)

a: Groups sharing common superscript "a" do not differ significantly at $p < 0.05$ (Duncan Multiple Range Test).

b,c: Groups with the superscripts "b" and "c", differ significantly at $p < 0.05$ (Duncan Multiple Range Test).

d: Values not sharing common superscript letters differ significantly at $p < 0.05$ (Duncan Multiple Range Test).

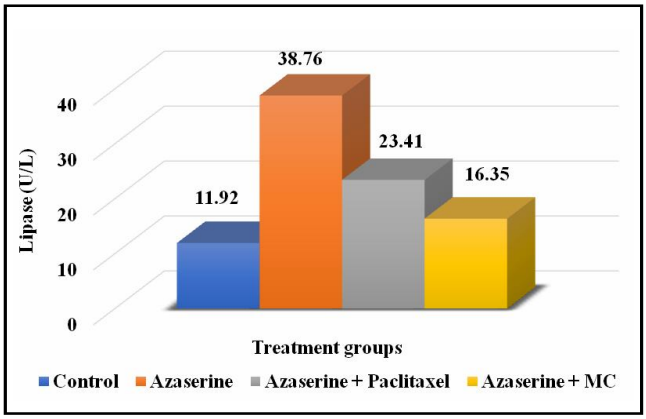

Figure 3: Comparative mean lipase (U/l) values of control and treated groups of male wistar rats.

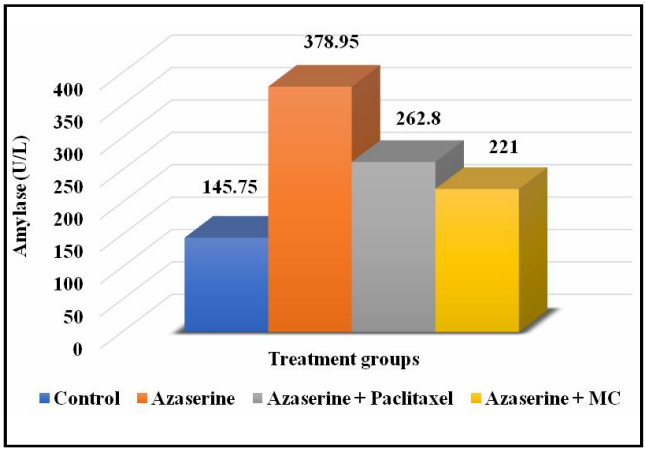

Figure 4: Comparative mean amylase (U/l) values of control and treated groups of male wistar rats.

4. Discussion

A significant increase (p<0.05) was observed in the ALT values in the rats of azaserine, azaserine + paclitaxel groups when compared to control group. The ALP values of rats in azaserine + paclitaxel group showed significant (p<0.05) increase when compared to control and azaserine groups. This was in conformation with the findings of Sophia *et al.* (2014) who reported that the elevation could potentially be attributed to the release of these enzymes from the cytoplasm into the blood circulation after rupture of the plasma membrane and cellular damage of the liver. Also,liver played an important role in the modulation of the process of carcinogenesis, as it was the primary site for the biotransformation of xenobiotics including carcinogens. Paclitaxel mediated a significant rise in the ALT and ALP levels which were reported by Itoh *et al.* (2004) and Holanda *et al.* (2008) in Sprague Dawley rats which were administered with paclitaxel. The injury that occurred during treatment could be attributed to a direct effect of paclitaxel in inhibiting microtubular function as it was largely metabolized by cytochrome P450 system (Scripture *et al.*, 2005).

A significant (p<0.05) decrease in the triglyceride levels of the rats of azaserine + paclitaxel and azaserine + MC groups when compared to the rats of control and azaserine groups was observed. Cholesterol was significantly (p<0.05) at low levels in the rats of different treatment groups when compared to the control group. The reduced levels of cholesterol was attributed to the active components present in bitter melon fruit (Senanayake *et al.* 2004) and also because of altered hepatic gene expression of cholesterol and bile acid regulating proteins (Matsui *et al.*, 2013). Moreover, there was no significant difference in the BUN, creatinine, total protein, albumin, GGT, glucose, total bilirubin, direct bilirubin levels which was in accordance with the findings of Mardani *et al.* (2014) who reported that no significant changes in the serum biochemical parameters were noticed after administration of MC fruit extracts along with the diet to wistar rats.

There was no significant difference in the levels of blood urea nitrogen (BUN), creatinine, total protein, albumin, gamma glutamyltransferase (GGT), glucose, total bilirubin, direct bilirubin in the rats of azaserine, azaserine + paclitaxel and azaserine + MC groups when compared to the control group. Hence, from the above findings, it might be evident that MC had lesser side effects and was comparatively more beneficial than paclitaxel therapy.

4.1 Serum lipase and amylase

There was a significant (p<0.05) increase in the lipase and amylase values in the rats of azaserine, azaserine + paclitaxel and azaserine + MC groups when compared to the control group. This was in accordance with the results recorded by Frulloni *et al.* (2005) and Revathi *et al.* (2012). The elevation of serum pancreatic lipase and amylase might be secondary to an increased release of enzymes due to neoplastic disease of the pancreas. The pathological mechanism was related to the disruption of pancreatic acini or an alteration of the normal exocytosis process with the secretion of the zymogen contents at the basolateral side of the acinar cells. The pancreatic enzymes were, therefore, released into the interstitial space and later reabsorbed directly or *via* the lymphatics into the bloodstream.

A significant (p<0.05) decrease was observed in the lipase and amylase values in the rats of azaserine + paclitaxel and azaserine + MC groups when compared to the azaserine group. Alam *et al.* (2015) reported the activity of *M. charantia* in inhibiting carbohydrate metabolizing enzymes like alpha-amylase, alpha-

glucosidase and pancreatic lipase in *in vitro* studies. Hence, from the above findings, MC has proven to be beneficial in lowering the levels of amylase and lipase better than paclitaxel.

5. Conclusion

Pancreatic cancer is one of the most lethal malignant neoplasms across the world and is one of the leading cause of cancer mortality in the recent years which is a life threatening entity by itself by becoming an enormous global health burden. The remote location of the organ, lack of specific diagnostic markers, difficulty in establishing a tissue diagnosis, and the aggressive nature of pancreatic adenocarcinomas, which respond poorly to chemotherapy contribute to the exceptional mortality rate in this type of tumor.

The side effects of current treatment options like radiotherapy and chemotherapeutic drugs add to the concern and have not been able to deliver extended survival periods. Added to this, the high level of inherent and acquired resistance to chemotherapy might be the underlying cause of poor prognosis of this diseaseHence, several other formulations part of complementary and alternative medicine are under trial for providing treatment regimens which could be used along with conventional medicine which might prolong the survival rate and enhance the curability.

Herbal drugs or extracts themselves hold back a combination of active components, wherein they interact within themselves and between other prescribed conventional medicines to either synergize or antagonize the therapeutic effect. The phytochemicalsmight increase the therapeutic effect by acting on signal transduction pathway or byincreasing the bioavailability or stabilizing the other drug in the system which can be made use of successfully in interfering the state of progression of the disease.

M. charantia is used extensively in folk medicine as a remedy for diabetes. It is traditionally used for its hypoglycemic effects and to regulate weight gain and lipid metabolism. In diabetic patients, it lowers blood sugar, delays complications such as nephropathy, neuropathy, gastroparesis, cataract and atherosclerosis. In recent years, there were also accumulating reports showing antimutagenic properties and apoptotic effects of *M. charantia*. Hence, it was chosen for the present study and might act as a better prospect against pancreatic cancer therapy.

The overall inference of the present study is that the aqueous extract of *M. charantia* has significantly indicated its ameliorative efficacy in lowering the damages caused by the carcinogen and surmounts the side effects better than conventional treatment options (paclitaxel) in the treatment of pancreatic atypical acinar cell tumors.

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Conflict of interest

We declare that we have no conflict of interest.

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