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RESEARCH ARTICLE
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ASSESSING THE PROTECTIVE EFFECT OF SYZYGIUM CUMINI ON VILDAGLIPTIN-INDUCED PANCREATIC TOXICITY: AN IN-VIVO STUDY

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ABSTRACT

Background: Many oral hypoglycemic drugs are available for the treatment of diabetes mellitus. Along with other hypoglycemics dipeptidylpeptidase-4 inhibitors i.e, vildagliptin is one of the new drug which are used for the treatment of diabetes. The DPP4 inhibitors are gliptins that are used orally. The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP) which inhibit glucagon release, which in turn increases insulin secretion.

Objectives: Vildagliptin may cause pancreatitis and infections so the combination of Vildagliptin and syzygium cumini can be helpful to reduce dose of Vildagliptin and can increase its safety and efficacy. Syzygium cumini belongs to family Myrtaceae. It is commonly known as Jambol fruit and locally as Jamun. The seeds of Jamun used as antidiabetic agent**.**

Methods: An in vivo study was conducted to evaluate the effects of vildagliptin on diabetes. Blood samples from normal and diabetic male rats were analyzed and compared to a control diabetic group.

Study Design: Experimental.

Place and Duration: Study was conducted at University of Karachi, from November 2023 to April 2024.

Results: The results showed that combination of vildagliptin and syzygium cumini showed its potential in managing diabetes and has synergistic hypoglycemic activity. Vildagliptin not only produced antidiabetic but it may produce severe pancreatitis and toxicity. Serum amylase and serum lipase level reduced with combination so it can increase protection against pancreatitis. **Conclusion**: The studied concluded that vildagliptin have marked good antidiabetic activity and combination of vildagliptin and syzygium cumini reduce the dose of vildagliptin which in turn its safety and efficacy and protecting the pancreas from damage and toxicity.

Keywords: DPP-4 inhibitors, vildagliptin, Syzygium cumini, antidiabetic, pancreatitis.

INTRODUCTION

The gliptins are DPP4 inhibitors that are administered orally in diabetic individuals. Gliptins are also available in combination with other hypoglycemic like metformin. They give its hypoglycemic activity by increasing levels of insulin. [1-3] The adverse effects of DPP4 inhibitors include headache, nausea, hypersensitivity skin reactions and pancreatitis. They inhibit inflammatory response of body by inhibiting chemokine CCL 11/eotaxin.

DPP4 inhibitors are new effective antidiabetic drugs. they have advantages over other antidiabetic agents, it has less chances of hypoglycemia and weight gain. But few adverse effects have reported i.e pancreatitis[4], pancreatic and thyroid cancer but still need to be investigated.Vildagliptin may cause Pancreatitis but it is controversial.[5-6] Patient treated with Vildagliptin have increase chance of upper respiratory tract infection[7] and it may cause cough, sore throat, and rhinorrhea.[8-9]

The U.S. Food and Drug Administration (FDA) warned about the cases of Pancreatitis as suggested by and it may cause cough, sore throat, and rhinorrhea. [8-9] Researchers find out that patient treated with Vildagliptin have increased chance of pancreatitis. A latest published study also found that Vildagliptin may double the chance of Acute Pancreatitis. FDA is investigating to found the safety of Vildagliptin.[10-11]

Syzygium cumini is widely found in Pakistan and India. Its fruits have hypoglycemic activity. Its seed powder and other aerial parts are also reported to have hypoglycemic activity. Its local urdu name is Jamun. Jamboline is glycoside that is widely found in Jamun. It also contains gallic and ellagic acids and tannins. [12, 13-20]

The oral hypoglycemic which are already available have major side effect reported as pancreatitis and increase risk of infection. Syzygium cumini have antimicrobial and improves lethal sepsis. [21-22]

The combination of S. cumini and vildagliptin was used to have more effective combination with less toxicity.

MATERIAL AND METHODS

Drugs: Vildagliptin, Syzygium cumini (purchased from local market), streptozotocin.

Extract Preparation: Air-dried seeds of S. cumini (2.0 kg) were ground and percolated in 80% ethanol at room temperature for 15 days. The percolate was filtered through whatman filter paper. The process was repeated for two times and the three residues obtained after filtration of the percolates were combined. Ethanol was evaporated under reduced pressure at 40ºC. The crude extract obtained was lyophilized and was kept for biological and pharmacological screening.

Animals

Antidiabetic activity: In this the study, male Wistar rats (200-250 g) were used, each group consist of 10 animals and total 4 groups used. Group 1: Non diabetic control group receiving normal saline. Group 1(b): Induction of diabetes with streptozotocin(55 mg/kg). Group 2(a): Non diabetic group receiving Vildagliptin (100mg/70kg). Group 2(b): Induction of diabetes with streptozotocin +Vildagliptin (100mg/70kg). Group 3(a): Non diabetic group receiving *Syzygium cumini* (200mg/kg). Group 3(b): Induction of diabetes with streptozotocin +*Syzygium cumini* (200mg/kg). Group 4(a): Non diabetic group receiving Vildagliptin (50mg/70 kg) +*Syzygium cumini* (100mg/kg). Group 4(b): Induction of diabetes with streptozotocin +Vildagliptin (50mg/70 kg) +*Syzygium cumini* (100mg/kg). Streptozotocin should be given to non-fasted animals, food and water was given immediately to animals after recovery from anesthesia to prevent mortalities during hypoglycemic phase. After giving streptozotocin injection, at 4, 8, and 12 hours 10ml of 5% glucose solution was given by subcutaneous route and 20% glucose solution for 2 days to prevent hypoglycemic shock.The DPP4 inhibitor i.e vildagliptin and *S. cumini* was administer orally in the morning for three months. For biochemical analysis, blood samples were taken at the end of experiment. [23-24]

Biochemistry Analysis: Plasma was taken for analysis by centrifugation of blood samples at 2500g for 20min. centrifugation was done at 4°C, and stored at−20°C. HbA1C, serum amylase, serum lipase level, and c- reactive protein were analysed.

Preparation of Tissue Sample: At the end of 3 months, organs were isolated and preserved in

formalin for histopathology. For histological studies, tissue samples were prepared from the pancreas.

RESULT

The random blood glucose and HbA1c of control non- diabetic rat was observed as 112 ± 3.47; 3.9± 0.12, which when vildagliptin was given become 121± 4.13; 5 ±0.69. Random sugar and HbA1c of control diabetic animal was 160 ± 2.96; 7.7 ± 0.26, and after vildagliptin administration it became 107± 302; 4.3± 0.5 (Table 1). The blood glucose and HbA1c of control non-diabetic rat was 112±3.47; 3.9± 0.12 which after syzygium cumini administration became 97± 0.80; 3.7 ± 0.19. The glucose level and HbA1c of control diabetic rat was 160± 2.96;7.7 ± 0.26 which after syzygium administration reduced to 100± 1.21; 4.1±0.43 (Table 2). The blood glucose and HbA1c of control non-diabetic rat pre and post administration of combination i.e. Vildagliptin and Syzygium was observed as 112 ± 3.47; 3.9± 0.12 and 105± 3.17; 4.6 ± 0.19 respectively. The blood glucose and HbA1c of control diabetic animal was 181± 2.96; 7.7± 0.26 which after combination administration was reduced to 121± 3.09; 6.3 ±0.43 (Table 3).

The c reactive protein of control non-diabetic was 12 ± 1.08, which when vildagliptin was given to this group, become 21± 0.73. The c reactive protein of control diabetic animal was 74 ± 1.11, after vildagliptin it increased to 125± 1.66 (Table 1). The c reactive protein of control non-diabetic rat was 12 ± 1.08, which when syzygium was given became 28± 1.08. The c reactive protein of control diabetic rat was 74 ± 1.11 and after syzygium administration it became 77± 1.16 (Table 2). The c reactive protein of control non-diabetic rat was 12 ± 1.08, which when combination of vildagliptin and syzygium was given, became 25± 1.11. c-reactive protein value of control diabetic rat was 74 ± 1.11, and after administration of combination it became 156± 1.10 (Table3).

Serum lipase and Serum amylase level of control non- diabetic rat was observed as 109 ± 1.00; 53 ± 1.58, which after vildagliptin, become 185± 1.82; 90± 1.84. Serum lipase and amylase level of control diabetic rat was 178 ± 1.14 and 160 ± 2.63, while after vildagliptin administration it became 204± 1.34; 211± 1.30 (Table 1).

Serum lipase and amylase level of control non-diabetic rat was 109 ± 1.00 and 53 ± 1.58, which after Syzygium administration, become 118± 1.38 and 79± 1.14. Serum lipase and amylase level of control diabetic rat was 178 ± 1.14 and 160 ± 2.63, while after Syzygium administration it became 130± 1.05 and 140± 1.52 (Table 2). Serum lipase and amylase level of control non-diabetic animal was 109 ± 1.00 and 53 ± 1.58, which when combination of vildagliptin and Syzygium was given, become 101± 1.36 and 55± 1.41. Serum lipase and amylase level of control diabetic animal after combination was observed 133 ± 1.14 and 125 ± 2.63. (Table 3).

Table. 1: Effect of Vildagliptin on Diabetic and Non Diabetic Rat.

	Control (Non-diabetic)	Control (Diabetic)	Treated with Vildagliptin (Non- diabetic)	Treated with Vildagliptin (Diabetic)
Blood Glucose Random	112 ± 3.47	181 ± 2.96	121 ± 4.13*	128 ± 3.02*
HbA1C	3.9 ± 0.12	7.7 ± 0.26	5 ± 0.09	4.3 ± 0.50*
C-reactive protein	12 ± 1.08	74 ± 1.11	21 ± 0.73*	125 ± 1.66*
Serum lipase	109 ± 1.00	178 ± 1.14	185 ± 1.82*	204± 1.34*
Serum amylase	53 ± 1.58	160 ± 2.63	90 ± 1.84*	211 ± 1.30*

Values are expressed in Mean ± SEM, n=10, $p<0.05$ is significant and is denoted by *. Control and treated Non- diabetic groups are compared; Control and treated Diabetic groups are compared.

Table. 2: Effect of Syzygium on Diabetic and Non Diabetic Rat.

	Control (Non-diabetic)	Control (Diabetic)	Treated with Syzygium (Non- diabetic)	Treated with Syzygium (Diabetic)
Blood Glucose Random	112 ± 3.47	181 ± 2.96	97 ± 0.86*	121 ± 1.21*
HbA1C	3.9 ± 0.12	7.7 ±0.26	3.7 ± 0.19	4.1 ± 0.43*
C-reactive protein	12 ± 1.08	74 ± 1.11	28 ± 1.08*	77 ± 1.16*
Serum lipase	109 ± 1.00	178 ± 1.14	118± 1.38*	130 ± 1.05*
Serum amylase	83 ± 1.58	160 ± 2.63	79 ± 1.14*	140± 1.52*

Values are expressed in Mean ± SEM, n=10, p<0.05 is significant and is denoted by *. Control and treated Non- diabetic groups are compared; Control and treated Diabetic groups are compared.

Table. 3: Effect of Combination (Vildagliptin + Syzygium) on Non Diabetic and Diabetic Rat

	Control (Non Diabetic)	Control (Diabetic)	Treated with Combinati-on (Non- Diabetic)	Treated with Combinati- on (Diabetic)
Blood Glucose Random	112 ± 3.47	181 ± 2.96	105 ± 3.17	121 ± 3.09*
HbA1C	3.9 ± 0.12	7.7 ± 0.26	4.6 ± 0.16*	6.3 ± 0.26*
C-reactive protein	12 ± 1.08	74 ± 1.11	25 ± 1.11*	156 ± 1.10*
Serum lipase	109 ± 1.00	178 ± 1.14	101 ± 1.36*	133 ± 2.42*
Serum amylase	53 ± 1.58	160 ± 2.63	55 ± 1.41*	125± 1.14*

Values are expressed in Mean ± SEM, n=10, p<0.05 is significant and is denoted by *. Control and treated Non- diabetic groups are compared; Control and treated Diabetic groups are compared.

HISTOPATHOLOGICAL OBSERVATIONS

Control Non diabetic Group

Microscopic studies showed that the Islets cells secretions and exocrine cell of pancreas were regular as showed in fig 1.

Control diabetic Group Microscopic studies showed that the decrease in the size of pancreatic islet cells was observed, whereas the size reduction was consistently observed with moderate vacuolization of islets of Langerhans across different microscopic fields as shown in Figure 2

Diabetic treated Group (Vildagliptin) The pancreatic section of the diabetic treated Group with vildagliptin exhibited a slight decrease in the number and size of pancreatic islet cells was observed with mild to moderate vacuolization of islets of Langerhans as shown in Figure 3.

Diabetic treated Group (Vildagliptin & Syzygium cumini) The pancreatic section of the diabetic treated Group with vildagliptin and syzygium cumini exhibited a normal pancreatic architecture with mild vacuolization of islets of Langerhans as showed in fig 4.

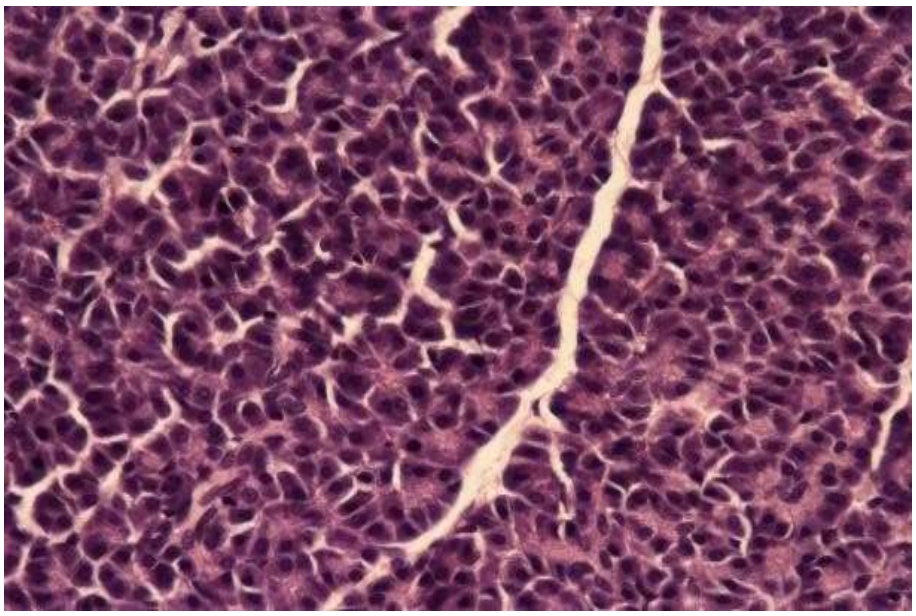

Fig. 1: 40X Photomicrograph of pancreas looks normal. No significant change in control non-diabetic rat).

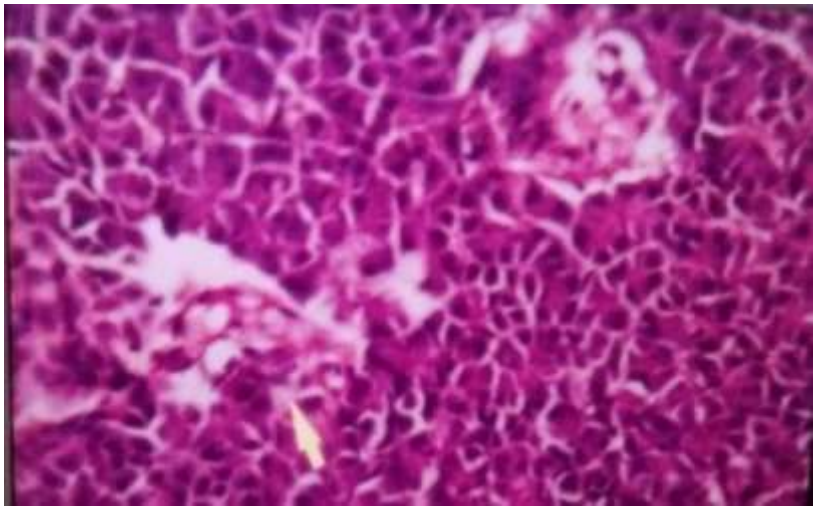

Fig. 2: 40X Photomicrograph of parenchyma of pancreas with moderate vacuolization of islets of Langerhans in control diabetic rat.

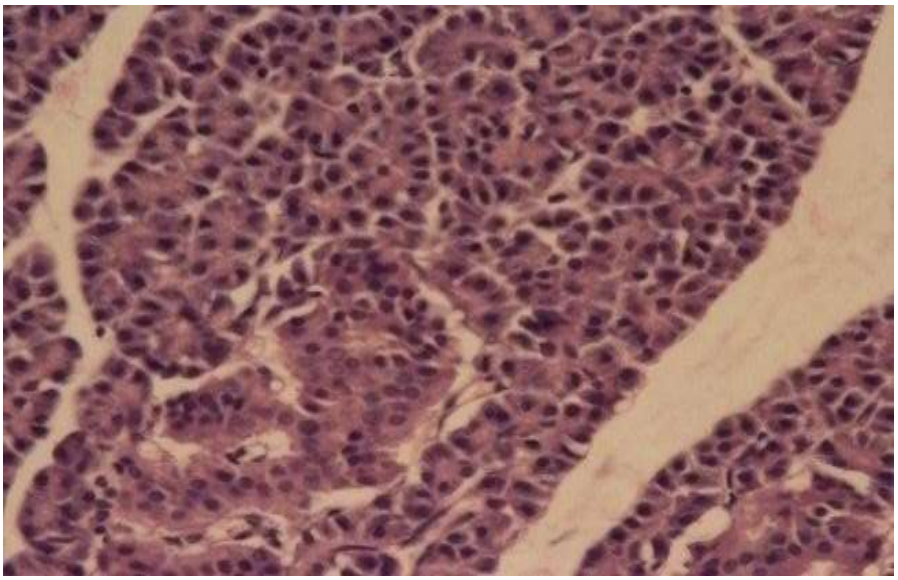

Figure. 3: 40X Photomicrograph of parenchyma of pancreas with mild to moderate vacuolization of islets of Langerhans of diabetic rat treated with vildagliptin.

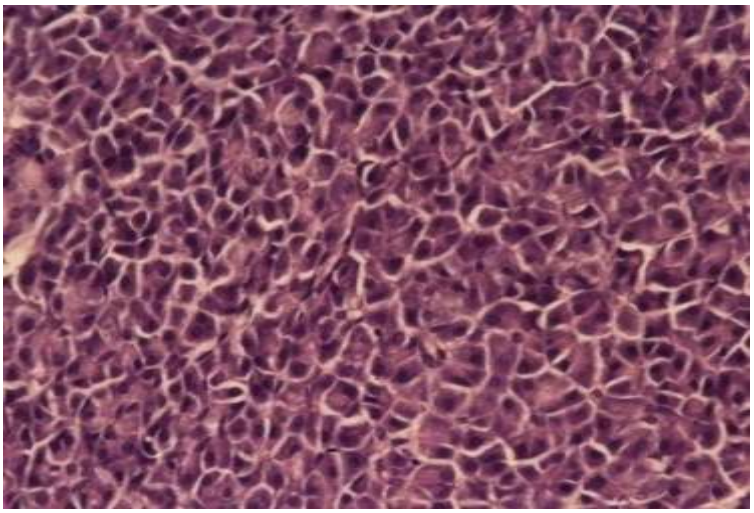

Figure. 4: 40X Photomicrograph of parenchyma of pancreas with mild vacuolization of islets of Langerhans of diabetic rat treated with combination of vildagliptin and syzygium cumini

DISCUSSION

Diabetes is one of the most common disorders throughout the world. Many antidiabetics drugs are available for the management of diabetes. One of them is DPP4 inhibitors. The U.S. Food and Drug Administration (FDA) warned about the cases of Pancreatitis as suggested by researchers that patients treated with Vildagliptin have increased chance of pancreatitis. Elashoff and Dore worked on Vildagliptin and analysed that it may cause pancreatitis but it is controversial. [5-6]

Present study is conducted to evaluate the toxicity of vildagliptin and its possible side effects on pancreas. Patient treated with drug Vildagliptin have high chance of upper respiratory tract infection [7] and may cause cough, sore throat, and rhinorrhea.[8-9] The study was conducted on diabetic as well as on non diabetic rats. When vildagliptin alone was given to non diabetic group their blood sugar raised slightly. In diabetic group blood sugar reduced too much. There was significant difference in both, control non diabetic and diabetic group with the group taking vildagliptin (0.0022 and 0.0001). When syzygium alone was given to diabetic and non diabetic animals, blood sugar reduced in both, significant reduction seen in diabetic group and p-value gives significant difference in both groups. When combination of vildagliptin and syzygium was given, blood sugar reduced in both groups of rats, significant reduction seen in diabetic group. p value gives significant difference in diabetic group i.e control with vildagliptin treated group (0.0001). In combination blood sugar reduced in both diabetic and non diabetic groups as compared to vildagliptin alone in which blood sugar reduced only in diabetic group but effect seems to be good in combination as vildagliptin dose is reduced to half in combination but reduction of blood sugar is more than vildagliptin alone and chances of toxicity of vildagliptin seems to be reduced.

HbA1C studies also conducted on rats. When vildagliptin alone was given to non diabetic group, HbA1C level raised slightly in non diabetic group. In diabetic group, HbA1C reduced too much. p-value gives significant difference in diabetic group i.e control and vildagliptin treated diabetic group (0.0001). When syzygium alone was given to diabetic and non diabetic, HbA1C reduced in both groups, significant reduction seen in diabetic group. p-value gives significant difference in diabetic group i.e control and group treated with syzygium (0.0001). When combination of vildagliptin and syzygium was given, HbA1C level reduced in both, significant reduction seen in diabetic group. p-value gives significant difference in both groups i.e. non diabetic control and treated group with combination (0.0058). Similarly, results are significant in diabetic group i.e. control and treated with combination 0.0001). In combination HbA1C level reduced in both diabetic and non diabetic groups as compared to vildagliptin alone in which HbA1C reduced only in diabetic group. But effect seems to be good in combination as vildagliptin.

Olansky worked on vildagliptin and analysed that when peoples are treated with vildagliptin, there are several cases of pancreatitis [4] and the U.S. package insert carries a warning to this, although the relation between vildagliptin and pancreatitis has not yet been fully substantiated. One study on rats published in 2009 established that risks of pancreatitis, or pancreatic cancer from drug vildagliptin may be reduced when it is used with other drugs like metformin or any other combinations. DDP-4 inhibitors showed an increase in such risk factors, as according to that study. In the present study C-reactive protein, serum amylase and serum lipase levels were measured to find possible chances of infection and pancreatitis.

When vildagliptin alone was given to diabetic and non diabetic group, in both groups c-reactive protein increased. p-value (0.0001) gives significant difference in diabetic and non diabetic groups. When syzygium alone was given, in both groups c-reactive protein increased. p- value (0.0001) gives significant difference in diabetic and non diabetic groups. When combination of vildagliptin and syzygium was given, in both groups c- reactive protein increased. p- value (0.0001) gives significant difference in diabetic and non diabetic groups. So there is no difference between vildagliptin alone and in combination with *S. cumini*. Hence combination has no role in preventing infection.

A 2014 meta-analysis found no evidence for increased pancreatic cancer risk in individuals treated with DPP IV inhibitors, but owing to the modest amount of data available, was not able to completely exclude possible risk.[25] They may cause severe joint pain.[26] Serum lipase levels were also determined on animals.

When vildagliptin alone was given to diabetic and non diabetic groups, in both groups serum and amylase level increased. When syzygium alone was given, in both groups serum lipase and amylase level reduced slightly ,p-value (0.0001) gives significant results. When combination of vildagliptin and syzygium was given in both groups serum lipase and amylase reduced significantly in diabetic group and p-value (0.0001) gives significant difference in diabetic and non diabetic animals.

In the present study the histopathological slides showed that animals treated with vildagliptin have moderate inflammation and vacuolization in pancreas. The animals treated with the combination of vildagliptin and *S. cumini* treated animals have mild inflammation and exhibited a normal pancreatic architecture in pancreas.

CONCLUSION

Vildagliptin has different effects on various functions of body in diabetic animals. Effects are good in combination of vildagliptin with syzygium, as vildagliptin dose is reduced half in combination but reductioin of blood sugar is more than vildagliptin alone and chances of toxicity of vildagliptin seems to be reduced. Combination has no effect to reduce chances of infection and no positive effect seen on c-reactive protein by combination. Chances of mild pancreatitis seen by vildagliptin as amylase and lipase levels increased. Combination protects too much elevation in amylase and lipase level. But no significant protection against toxicity is observed.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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