



COMPARATIVE EFFECT OF ANTIDIABETIC DRUG SITAGLIPTIN WITH SZYGIUM CUMINI ON PANCREATIC ACTIVITY

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ABSTRACT

Many oral hypoglycemic drugs are available for the treatment of diabetes mellitus. Along with other hypoglycemics dipeptidylpeptidase-4 inhibitors that is Sitagliptins are one of the new drugs 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. Sitagliptin may cause pancreatitis and infections so the combination of Sitagliptin and *S. cumini* can be helpful to reduce dose of Sitagliptin and can increase safety and efficacy of Sitagliptin. The seeds of Jamun used as antidiabetic agent. *Szygium cumini* belongs to family Myrtaceae. It is commonly known as Jambol fruit and locally as Jamun. Results showed that combination has synergistic hypoglycemic activity. Sitagliptin not produced severe pancreatitis and with the combination it gives more improved activity. C-reactive protein and serum lipase levels not altered significantly. Serum amylase level reduced with combination so it can increase protection against pancreatitis.

KEYWORDS: DPP-4 inhibitors, sitagliptin, *Szygium cumini*, antidiabetic, pancreatitis.

INTRODUCTION

The gliptins are DPP4 inhibitors that are administered orally to 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.

Sitagliptin may cause Pancreatitis but it is controversial.^[5-6] Patient treated with Sitagliptin 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

researchers that patient treated with Sitagliptin have increased chance of pancreatitis. A latest published study also found that Sitagliptin may double the chance of Acute Pancreatitis. FDA is investigating to found the safety of Sitagliptin.^[10-11]

Szygium 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. *S. cumini* have antimicrobial and improves lethal sepsis.^[21-22] The combination of *S. cumini* and sitagliptin was used to have more effective combination with less toxicity.

MATERIAL AND METHODS

Drugs: Sitagliptin, *Szygium cumini* (purchased from local market), Alloxan.

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 40°C. The crude extract obtained was lyophilized and was kept for biological and pharmacological screening.

Animals: Albino rabbits of same sex and weight of 1 kg were used. Ethical committee approval number is IRB-507/DUHS/-14.

Antidiabetic activity: Each group was of 05 animals and total 4 groups used. Group 1(a): Non diabetic control group receiving normal saline. Group 1(b): Induction of diabetes with Alloxan. Group 2(a): Non diabetic group receiving Sitagliptin (100mg/70kg). Group 2(b): Induction of diabetes with Alloxan+Sitagliptin (100mg/70kg). Group 3(a): Non diabetic group receiving *Szygium cumini* (200mg/kg). Group 3(b): Induction of diabetes with Alloxan+*Szygium cumini* (200mg/kg). Group 4(a): Non diabetic group receiving Sitagliptin (50mg/70kg)+*Szygium cumini* (100mg/kg). Group 4(b): Induction of diabetes with Alloxan+Sitagliptin (50mg/70kg)+*Szygium cumini* (100mg/kg).

Animals were housed singly with different floors (40 × 60 × 80cm) on a 12:12 hour light dark cycle in temperature (16–22°C) and humidity (30–70%). Cage racks were cleaned once per week and cage pans were cleaned thrice weekly. In the whole study, laboratory Rabbit diet and filtered tap water has been given. Fresh vegetables were provided once per week. Animals have intake oral glucose solution and no other water supply has been provided to them.

For the alloxan injection, rabbit's weights were recorded. Ketamine hydrochloride 30mg/kg and xylazine 3mg/kg was given to the rabbits to be lightly anesthetized. Normal sterile saline containing alloxan monohydrate(100mg/kg) dissolved as 5% (W/V) was administer intravenously with 25 guage butterfly catheter for 2 minutes. Alloxan 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 alloxan injection, at 4, 8, and 12 hours 10ml of 5% glucose solution was given by subcutaneous route and 20% glucose solution with help of water bottle for 2 days to prevent hypoglycemic shock when hypoglycemia confirmed (less than 70mg/dl). Automated watering system restricted during this period, to encourage intake of oral glucose solution.

Following initial alloxan injection, those rabbit whose blood glucose level <180mg/dl for more than one week was given second dose of alloxan (100mg/kg IV). During study, their blood glucose was maintain >180mg/dl. In

the first 4 weeks, blood glucose was measured using blood glucose strips once a day than once weekly thereafter in morning. When fasting blood glucose level (BGL) remained higher than 180mg/dl, than DPP4 inhibitor 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: Rabbits were anesthetized with 100mg/kg pentobarbital (IV) 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 rabbit was observed as 112 ± 3.47; 3.9 ± 0.12, which when sitagliptin 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 sitagliptin administration it became 107 ± 3.02; 4.3 ± 0.5 (Table 1). The blood glucose and HbA1c of control non-diabetic rabbit was 112 ± 3.47; 3.9 ± 0.12 which after szygium administration became 97 ± 0.80; 3.7 ± 0.19. The glucose level and HbA1c of control diabetic rabbit was 160 ± 2.96; 7.7 ± 0.26 which after szygium administration reduced to 100 ± 1.21; 4.1 ± 0.43 (Table 2). The blood glucose and HbA1c of control non-diabetic rabbit pre and post administration of combination i.e. Sitagliptin and Szygium 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 sitagliptin was given to this group, become 21 ± 0.73. The c reactive protein of control diabetic animal was 74 ± 1.11, after sitagliptin it increased to 125 ± 1.66 (Table 1). The c reactive protein of control non-diabetic rabbit was 12 ± 1.08, which when szygium was given became 28 ± 1.08. The c reactive protein of control diabetic rabbit was 74 ± 1.11 and after szygium administration it became 177 ± 1.16 (Table 2). The c reactive protein of control non-diabetic rabbit was 12 ± 1.08, which when combination of sitagliptin and szygium was given, became 25 ± 1.11. c-reactive protein value of control diabetic rabbit was 74 ± 1.11, and after administration of combination it became 156 ± 1.10 (Table 3).

Serum lipase and Serum amylase level of control non-diabetic rabbit was observed as 109 ± 1.00; 53 ± 1.58, which after sitagliptin, become 185 ± 1.82; 90 ± 1.84.

Serum lipase and amylase level of control diabetic rabbit was 178 ± 1.14 and 160 ± 2.63 , while after sitagliptin administration it became 204 ± 1.34 ; 211 ± 1.30 (Table 1). Serum lipase and amylase level of control non-diabetic rabbit was 109 ± 1.00 and 53 ± 1.58 , which after Szygium administration, become 250 ± 1.38 and 121 ± 1.14 . Serum lipase and amylase level of control diabetic rabbit was 178 ± 1.14 and 160 ± 2.63 , while after Szygium administration it became 280 ± 1.05 and

200 ± 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 sitagliptin and Szygium was given, become 220 ± 1.36 and 102 ± 1.41 . Serum lipase and amylase level of control diabetic animal was observed as 178 ± 1.14 and 160 ± 2.63 , after combination it became 266 ± 2.42 and 180 ± 1.14 (Table 3).

Table 1: Effect of Sitagliptin on Diabetic and Non Diabetic Rabbit.

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

Values are expressed in Mean \pm 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 Szygium on Diabetic and Non Diabetic Rabbit.

	Control (Non- diabetic)	Control (Diabetic)	Treated with Szygium (Non- diabetic)	Treated with Szygium (Diabetic)
Blood Glucose Random	112 ± 3.47	181 ± 2.96	$97 \pm 0.86^*$	$121 \pm 1.21^*$
HbA1C	3.9 ± 0.12	7.7 ± 0.26	3.7 ± 0.19	$4.1 \pm 0.43^*$
C-reactive protein	12 ± 1.08	74 ± 1.11	$28 \pm 1.08^*$	$177 \pm 1.16^*$
Serum lipase	109 ± 1.00	178 ± 1.14	$250 \pm 1.38^*$	$280 \pm 1.05^*$
Serum amylase	53 ± 1.58	160 ± 2.63	$121 \pm 1.14^*$	$200 \pm 1.52^*$

Values are expressed in Mean \pm 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 (Sitagliptin + Szygium) on Non Diabetic and Diabetic Rabbit

	Control (Non Diabetic)	Control (Diabetic)	Treated with Combination (Non- Diabetic)	Treated with Combination (Diabetic)
Blood Glucose Random	112 ± 3.47	181 ± 2.96	105 ± 3.17	$121 \pm 3.09^*$
HbA1C	3.9 ± 0.12	7.7 ± 0.26	$4.6 \pm 0.16^*$	$6.3 \pm 0.26^*$
C-reactive protein	12 ± 1.08	74 ± 1.11	$25 \pm 1.11^*$	$156 \pm 1.10^*$
Serum lipase	109 ± 1.00	178 ± 1.14	$220 \pm 1.36^*$	$266 \pm 2.42^*$
Serum amylase	53 ± 1.58	160 ± 2.63	$102 \pm 1.41^*$	$180 \pm 1.14^*$

Values are expressed in Mean \pm 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 4: Effect of Sitagliptin, Szygium and Combination on Diabetic Rabbit.

	Combination (Diabetic)	Sitagliptin (Diabetic)	Szygium (Diabetic)
Blood glucose random	121 ± 3.09	$128 \pm 3.02^*$	121 ± 1.21
HbA1C	6.3 ± 0.26	$4.3 \pm 0.50^*$	$4.1 \pm 0.43^*$
C-reactive protein	156 ± 1.10	$125 \pm 1.66^*$	$177 \pm 1.16^*$
Serum lipase	266 ± 1.92	$204 \pm 2.33^*$	280 ± 1.58
Serum amylase	180 ± 1.14	$211 \pm 1.30^*$	$200 \pm 1.52^*$

Values are expressed in Mean \pm SEM, n=10, p<0.05 is significant and is denoted by *. Sitagliptin and combination receiving groups are compared; Szygium and combination receiving groups are compared.

Table. 5: Effect of Sitagliptin, Szygium and Combination on Non Diabetic Rabbit.

	Combinati-on (Non diabetic)	Sitagliptin (Non diabetic)	Szygium (Non diabetic)
Blood glucose random	105 ± 3.17	121 ± 4.13*	97 ± 3.17*
HbA1C	4.6 ± 0.16	5 ± 0.09	3.7 ± 0.16*
C-reactive protein	25 ± 1.11	21 ± 0.73*	28 ± 1.08
Serum lipase	220 ± 1.36	185 ± 1.82*	250± 1.38*
Serum amylase	102 ± 1.41	90 ± 1.84*	121 ± 1.14*

Values are expressed in Mean ± SEM, n=10, p<0.05 is significant and is denoted by *. Sitagliptin and combination receiving groups are compared; Szygium and combination receiving groups are compared.

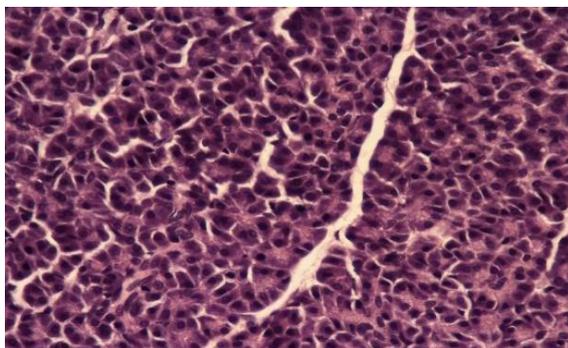


Fig. 1: 40X Photomicrograph of pancreas looks normal. No significant change in control non-diabetic rabbit).

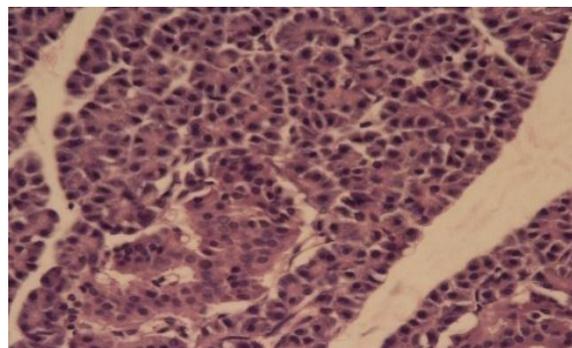


Figure. 4: 40X Photomicrograph of parenchyma of pancreas with mild vacuolization of islets of Langerhans of diabetic rabbit treated with S. cumini.

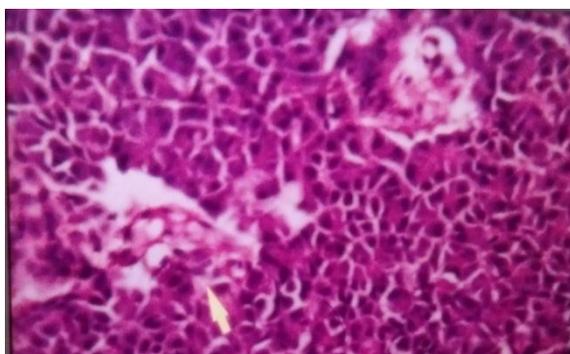


Fig. 2: 40X Photomicrograph of parenchyma of pancreas with mild vacuolization of islets of Langerhans in control diabetic rabbit.

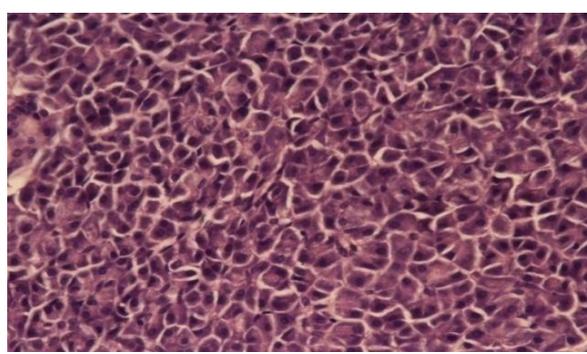


Figure. 5: 40X Photomicrograph of parenchyma of pancreas with mild vacuolization of islets of Langerhans of diabetic rabbit treated with combination.

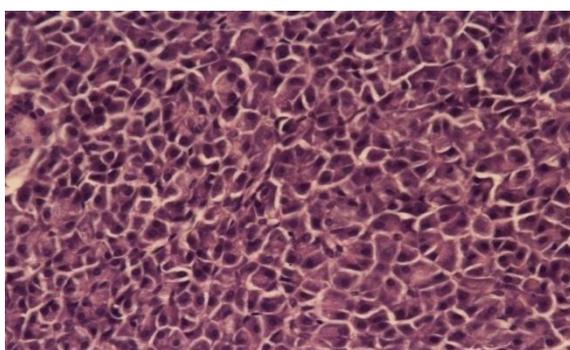


Figure. 3: 40X Photomicrograph of parenchyma of pancreas with moderate vacuolization of islets of Langerhans, of diabetic rabbit treated with sitagliptin.

DISCUSSION

Diabetes is one of the most common disorders throughout the world. Many antidiabetic 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 Sitagliptin have increased chance of pancreatitis. Elashoff and Dore worked on Sitagliptin and analysed that it may cause pancreatitis but it is controversial.^[5-6]

Present study is conducted to evaluate the toxicity of sitagliptin and its possible side effects on pancreas. Patient treated with drug Sitagliptin have high chance of upper respiratory tract infection^[7] and may cause cough, sore throat, and rhinorrhea.^[8-9] The study is conducted on

diabetic as well as on non diabetic rabbits. When sitagliptin 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 sitagliptin (0.0022 and 0.0001). When szygium 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 sitagliptin and szygium was given, blood sugar reduced in both groups of rabbits, significant reduction seen in diabetic group. p value gives significant difference in diabetic group i.e control with sitagliptin treated group (0.0001). In combination blood sugar reduced in both diabetic and non diabetic groups as compared to sitagliptin alone in which blood sugar reduced only in diabetic group but effect seems to be good in combination as sitagliptin dose is reduced to half in combination but reduction of blood sugar is more than sitagliptin alone and chances of toxicity of sitagliptin seems to be reduced.

HbA1C studies also conducted on rabbits. When sitagliptin 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 sitagliptin treated diabetic group (0.0001). When szygium 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 szygium (0.0001). When combination of sitagliptin and szygium 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 sitagliptin alone in which HbA1C reduced only in diabetic group. But effect seems to be good in combination as sitagliptin.

Olansky worked on sitagliptin and analysed that when peoples are treated with sitagliptin, there are several cases of pancreatitis^[4] and the U.S. package insert carries a warning to this, although the relation between sitagliptin 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 sitagliptin may be reduced when it is used with other drugs like metformin or any other combinations. DPP-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 sitagliptin 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 szygium 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 sitagliptin and szygium 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 sitagliptin 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 sitagliptin alone was given to diabetic and non diabetic groups, in both groups serum lipase level increased. p-value (0.0001) gives significant difference in both diabetic and non diabetic groups. When szygium alone was given, in both groups serum lipase level increased. p-value (0.0001) gives significant difference in diabetic and non diabetic animals. When combination of sitagliptin and szygium was given in both groups serum lipase level increased. p-value (0.0001) gives significant difference in diabetic and non diabetic animals. So there is no difference between sitagliptin alone and in combination with *Szygium cumini*.

In serum amylase level no significant change was observed. When sitagliptin alone was given to diabetic and non diabetic group, in both groups serum amylase level increased. p-value (0.0001) gives significant difference in both diabetic and non diabetic animals. When szygium alone was given, in both groups serum amylase level increased. p-value (0.0001) gives significant difference in diabetic and non diabetic groups. When combination of sitagliptin and szygium was given in diabetic group serum amylase level was not much altered (0.0134). So it is analysed that in diabetic animals combination elevation in amylase level.

In the present study the histopathological slides showed that animals treated with sitagliptin have moderate inflammation in pancreas and liver. The animals treated with *S. cumini* showed mild inflammation and the combination of sitagliptin and *S. cumini* treated animals have mild inflammation in pancreas.

CONCLUSION

Sitagliptin has different effects on various functions of body in diabetic animals. Effects are good in combination of sitagliptin with szygium, as sitagliptin dose is reduced half in combination but reduction of blood sugar is more than sitagliptin alone and chances of toxicity of sitagliptin 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 sitagliptin as amylase and lipase levels increased. Combination protects too much elevation in amylase level. But no significant protection against toxicity is observed.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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