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Additive Effect of Aloe vera and Fenugreek Extracts on Alloxan-Induced Diabetes in Wistar Rats

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ABSTRACT

The present study was carried out to evaluate the synergistic effects of Aloe vera and fenugreek extracts on alloxan-induced diabetic rats. Diabetes is induced by treating male Wistar rats with alloxan at a dose of 100 mg/kg, i.p.; after 72 hrs of induction of diabetes, the fasting blood glucose (FBG) levels were checked by Accu check glucometer. Those animals with FBG higher than 200 mg/dL, were separated and grouped for further study. Upon treatment with oral Aloe vera (300 mg/kg,p.o) and Fenugreek (800 mg/kg, p.o) extracts alone and combinations (150 mg of aloe vera + 400 mg of fenugreek) for 14 days, there was a significant decrease in the blood glucose level while the levels of plasma insulin increased. The extracts also significantly decreased the total cholesterol, LDL, and triglycerides levels while increasing the levels of HDL. In extract-treated groups, urinary pH and urinary output were restored to normal and creatinine levels were regulated. Histopathology of the pancreas revealed that aloe vera and fenugreek alone and in combination have shown significantly good results in restoring the pancreas damage and function. The combined formulation showed better efficacy than individual extracts. Kidney histopathology revealed that a damaged kidney was seen in the diabetic group, but the treatment with Aloe vera and Fenugreek extracts alone and combinations for 14 days rendered the damaged kidney areas normal, compared to the standard group. With our study, it was concluded that diabetes can be well-managed with aloe vera and fenugreek alone and in combination.

Keywords: Aloe vera, Fenugreek, Additive effects, Anti-diabetic activity, Combined formulation, Alloxan.

1. INTRODUCTION

Diabetes is a global health problem due to its serious complications. It is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Hyperglycaemia is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body systems, especially the nerves and blood vessels.

The use of chemical agents to produce diabetes permits a detailed study of the biochemical, hormonal, and morphologic events that occur during and after the induction of a diabetic state. Alloxan (2,4,5,6-tetraoxypyrimidine; 5,6-dioxyuracil) was first described by Brugnatelli in 1818. Wohler and Liebig used the name "alloxan" and described its synthesis by uric acid oxidation.[1] The diabetogenic properties of this drug were reported many years later, the effect of its administration in rabbits was studied and specific necrosis of pancreatic islets was reported.[2]

Aloe vera is well known for its marvelous medicinal properties. The leaves of Aloe vera exhibit many pharmacological properties including laxative, immune modulator, antibacterial, antifungal, antiviral, antineoplastic, anti-inflammatory, and antiulcer activity.[3] Preparations made from fenugreek seeds have been studied for effects in improving blood glucose control in people with diabetes and in preventing progression from prediabetes to type 2 diabetes.[4] Thus, the present study aims to know the additive effect of aloe vera and fenugreek extracts on alloxan-induced diabetes in Wistar rats.

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2. MATERIALS AND METHODS

2.1. Preparation of Plant Extracts

The A. vera extract was prepared by boiling 50 gms of the plant with l00ml dist. Water for 10 min. After cooling to room temperature, the extract was filtered and stored in the refrigerator.

The fenugreek extract was prepared by washing the plant with refined water, sun-drying for 72 h, and processing in a blender. 500 g of the powder was soaked in 5-liter refined water for 72 h under constant shaking with intervals of 30 min. The blend was filtered using 250 mm filter paper, and afterward, the filtrate was freeze-dried at -52°C.

2.2. Experimental Animals

3 months old male Wistar albino rats weighing 180 ± 20 gm were obtained from the National Institution of Nutrition (NIN). Animal care and husbandry were maintained according to Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. They were housed in four per each polycarbonate cages under standard laboratory conditions at a room temperature of 24 ± 2°C, and humidity of 45-64% with a 12 h light/dark cycle. The animals were maintained on standard rat feed supplied through plastic bottles provided with nipples. This project was approved by IAEC with protocol number (I/IAEC/AGI/002/2021 WR ◎)

2.3. Induction of Diabetes

Alloxan is used to induce insulin-dependent diabetes mellitus (IDDM) (type-1). A single injection of alloxan at a dosage concentration of 100 mg/kg body weight was usually enough for induction. so, after fasting for 72 hours, rats were injected intraperitoneally with a single dose of 100 mg/kg body weight, alloxan freshly dissolved in saline.[5]

2.4. Grouping of Animals

Group 1 : Normal control: Normal saline (0.9%, w/v, 1 mL/kg, p.o)

Group 2 : Diabetic control - Alloxan monohydrate (100 mg/kg, i.p)

Group 3 : Standard- Glibenclamide (10 mg/kg, p.o)

Group 4 : Aloe vera extract (300 mg/kg. p.o)

Group 5 : Fenugreek (800 mg/kg, p.o)

Group 6 : Aloe vera + Fenugreek (150 + 400 mg/kg, p.o)

2.5. Estimation of FBG Levels

Treatment of hyperglycemia was carried out after 3rd day of alloxan administration. All groups except groups I and II received the standard drug and different extracts for 15 days and blood glucose level was analyzed at 1 hour after 1st day of treatment, and then on the 7th and 14th day of treatment by the GOD-POD method.[3]

2.6. Estimation of Body Weight

Body weights of diabetic and normal rats were recorded before alloxan administration and on the 7th and 14th day of treatment with the extract. The weights of the corresponding control group of rats were simultaneously recorded.

2.7. Estimation of Urine Volume and Creatinine

At the end of the 8th week, rats were kept individually in metabolic cages for 24 hours to collect urine for the measurement of urine output and pH. Urine pH was measured using litmus paper. Urine creatinine was analyzed by the modified Jaffe method using a commercially available assay kit.[6]

2.8. Estimation of Serum Insulin and HbA1C

Twenty-eight days after diabetes confirmation, animals were anesthetized deeply by chloroform vapor and blood was taken from their heart. They were subsequently euthanized under chloroform vapor. Pancreases were fixed in 10% formalin. Blood samples were transferred to EDTA containing tube, 500 µL was used for the measurement of glycosylated hemoglobin (HbA1c) and the remainder was centrifuged at 3000 rpm for 15 min to separate plasma for insulin measurement.[7]

2.9. Estimation of Total cholesterol, Triglycerides, LDL, and HDL

Blood glucose concentration was monitored by the glucose oxidase method using an Accu-check glucometer. One animal was randomly selected per group, each time, for the assay. Animals were sacrificed last day of the experiment. Blood samples were collected in plain bottles and organs (namely pancreas and kidneys) were excised; preserved in 10% formalin. Biochemical assays for total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol, and triglyceride (TG) levels were estimated in plasma.[8]

2.10. Histopathological Examination

Observation of pancreas histology was conducted at the end of the experimental period. A sample of the pancreas was isolated, fixed with 10% formalin, and stained with Hematoxylin-eosin (HE) for observation of islet Langerhans morphology.[9]

The excised kidneys were cut into about 2 mm thick transverse slices and fixed in 10% formalin. After being embedded in paraffin, several transverse sections were

obtained from the kidney and stained with Periodic acid-Schiff (PAS) for histological examination.[10]

2.11. Statistical Analysis

All data are presented as Mean ± S.E.M. The significance of difference among the groups was assessed using a one-way analysis of variance (ANOVA) followed by Tukey's test using GraphPad Prism 5 software and $P < 0.05$ was considered significant.

3. RESULTS

3.1. Effect of Aloe Vera and Fenugreek Extracts on FBG

Both the extracts and their combined preparation showed a significant ($P < 0.001$) reduction in FBG levels in a dose-dependent manner. Administration of A. vera + Fenugreek was found to show optimum activity; on the 14th day, FBG levels were restored to normal in the A. vera + Fenugreek-treated group, compared to the glibenclamide-treated group (Table 1).

3.2. Effect of Plant Extract Treatment on Body Weight

Before the induction of diabetes, there were no significant changes in the body weights of all six groups. On the 7th and 14th day, body weight was decreased in the diabetic control group when compared to the control group, whereas it was increased in A. vera, fenugreek, A. vera + fenugreek, and glibenclamide group ($P < 0.001$, $P < 0.01$, $P < 0.001$, $P < 0.001$) (Table 2).

Table 1. Effect of aloe vera and fenugreek extracts on FBG

Groups	*1 hour after 1st day of treatment (mg/dL)*	*7th day (mg/dL)*	*14th day (mg/dL)*
Control	88.03 ± 3.1	87.75 ± 4.9	89.51 ± 2.8
Diabetic control Alloxan (100 mg/kg, i.p)	254.6 ± 18.5$^{###}$	268.7 ± 16.0$^{###}$	263.3 ± 18.7$^{###}$
Glibenclamide (10 mg/kg, p.o)	236 ± 5.0***	146.25 ± 4.0***	86.75 ± 3.1***
Aloe vera (300 mg/kg, p.o)	218.8 ± 7.9***	128.8 ± 5.7***	91.7 ± 6.2***
Fenugreek (800mg/kg, p.o)	215.8 ± 6.2***	139 ± 4.3***	105.5 ± 3.9***
Aloe vera + Fenugreek (150 + 400 mg/kg, p.o)	224.3 ± 8.5***	105.2 ± 6.3***	87.05 ± 4.1***

Data are expressed as mean ± SD (n=6) and analyzed by one-way ANOVA followed by Tukey's multiple comparison test. $^{###}P < 0.001$ as compared to control group, $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ as compared to the diabetic control group.

3.3. Effect of Plant Extracts on Urine Volume and Creatinine

Urine pH was decreased in the diabetic control group when compared to the control group ($P < 0.001$), whereas the pH was increased in A. vera, fenugreek, A. vera + fenugreek, and glibenclamide group ($P < 0.001$, $P < 0.01$, $P < 0.001$, $P < 0.001$) when compared to the diabetic control group. Urine volume was increased in the diabetic control group when compared to the control group ($P < 0.001$), whereas the levels were decreased in A. vera, fenugreek, A. vera + fenugreek, and glibenclamide group ($P < 0.001$, $P < 0.01$, $P < 0.001$, $P < 0.001$) when compared to the diabetic control group. Creatinine levels were increased in the diabetic control group when compared to the control group ($P < 0.001$), whereas the levels were decreased in A. vera, fenugreek, A. vera + fenugreek, and glibenclamide group ($P < 0.001$, $P < 0.01$, $P < 0.001$, $P < 0.001$) when compared to the diabetic control group (Table 3).

3.4. Effect of Plant Extracts on Serum Insulin and HbA1C

Insulin levels were decreased in the diabetic group ($P < 0.001$), when compared to the control group, these levels were increased in all treatment groups ($P < 0.001$). HbA1C levels were increased in diabetic control ($P < 0.001$), when compared to the control group, the levels were decreased in all treatment groups ($P < 0.001$) (Table 4).

Table 2. Effect of plant extract treatment on body weight

Groups	*Before inducing diabetes (g)*	*7th day (g)*	*14th day (g)*
Control	213.0 ± 5.2	236.25 ± 7.47	258.14 ± 8.31
Diabetic control Alloxan (100 mg/kg, i.p)	212.35 ± 3.3$^{9###}$	186.25 ± 3.47$^{###}$	157.22 ± 3.73$^{###}$
Glibenclamide (10 mg/kg, p.o)	226.0 ± 3.48***	231.08 ± 8.87***	245.28 ± 5.65***
Aloe vera (300mg/kg, p.o)	223.3 ± 4.39	244.68 ± 6.54**	256.24 ± 7.74***
Fenugreek (800mg/kg, p.o)	214.3 ± 4.77	226.34 ± 3.95***	232.04 ± 3.98***
Aloe vera + Fenugreek (150 + 400 mg/kg, p.o)	216.2 ± 6.62***	236.26 ± 4.72***	247.25 ± 5.21***

Data are expressed as mean ± SD (n=6) and analyzed by one-way ANOVA followed by Tukey's multiple comparison test. $^{###}P < 0.001$ as compared to control group, $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ as compared to the diabetic control group.

Table 3: Effect of plant extracts on urine volume and creatinine

Groups	Urine pH	Urine volume	Creatinine
Control	6.22 ± 0.27	8.22 ± 3.36	0.73 ± 1.43
Diabetic control Alloxan (100 mg/kg, i.p)	3.64 ± 0.62###	23.14 ± 5.69###	2.53 ± 0.61###
Glibenclamide (10 mg/kg, p.o)	5.89 ± 0.77***	12.37 ± 3.68***	0.89 ± 0.17***
Aloe vera (300 mg/kg, p.o)	5.50 ± 0.29***	13.42 ± 4.80***	0.90 ± 0.13***
Fenugreek (800 mg/kg, p.o)	5.75 ± 0.87***	15.66 ± 2.62***	0.96 ± 0.14***
Aloe vera + Fenugreek (150 + 400 mg/kg, p.o)	6.02 ± 0.33***	11.01 ± 3.23***	0.81 ± 0.17***

Data are expressed as mean ± SD (n=4) and analyzed by one-way ANOVA followed by Tukey's multiple comparison test. ###P < 0.001 as compared to control group, ***P < 0.001 as compared to the diabetic control group.

3.5. Effect of Plant Extracts on Total cholesterol, Triglycerides, LDL, and HDL

Total cholesterol levels were increased in the diabetic group ($P < 0.001$), when compared to the control group, and these levels were decreased in treatment groups ($P < 0.001$) when compared to the diabetic group. Triglyceride levels were increased in the diabetic group ($P < 0.001$), when compared to the control group, the levels were decreased in treatment groups ($P < 0.001$). LDL levels were increased in the diabetic group ($P < 0.001$), when compared to the control group, the levels were significantly decreased in all treatment groups ($P < 0.001$). HDL levels were decreased in the diabetic group ($P < 0.001$), when compared with the control group, these levels were increased in treatment groups ($P < 0.001$) (Table 5).

3.6. Histopathology

Treatment with alloxan caused degeneration of β cells along with atrophy of pancreatic cells in the diabetic group (Figure 1). However, A. vera, fenugreek, A. vera + fenugreek, and glibenclamide-treated groups exhibited noticeable improvement of the cellular injury, as apparent by the partial restoration of islet cells, hyperplasia, and hypertrophy of β-cells and growth in the number of islet cells.

A microscopic study of the kidney showed dilation and degeneration of tubules in the negative control group (Figure 1). Following treatment with A. vera and fenugreek extracts, there was the regeneration of tubules. The

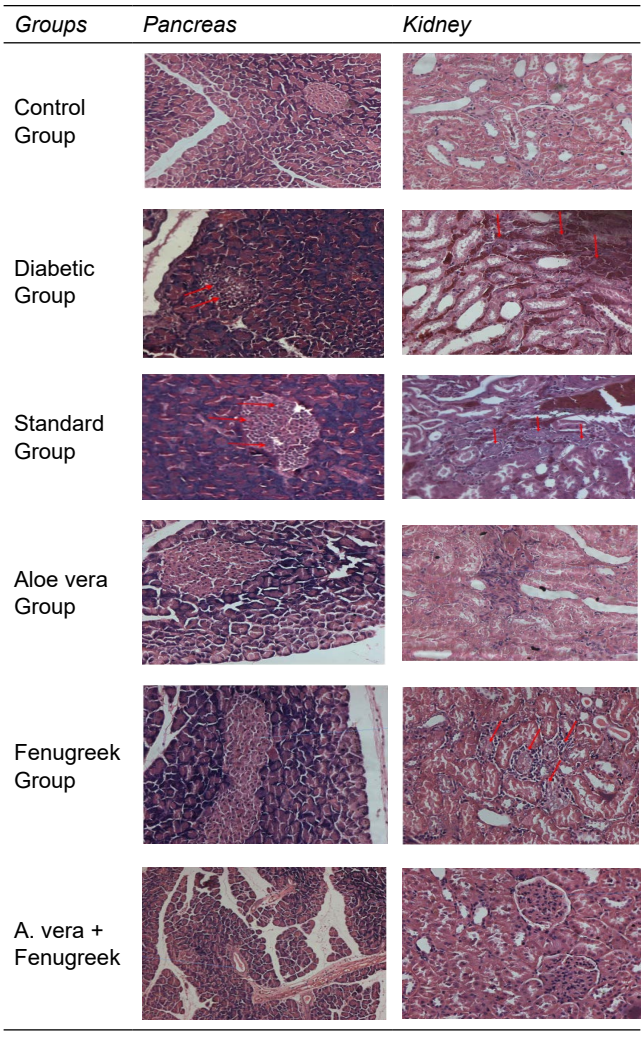

Figure 1: Histopathological examination of pancreatic and kidney tissues.

combined preparation of two extracts showed significant activity, similar to the standard glibenclamide.

Control group: Normal morphology of pancreas, Normal morphology of glomerulus and tubules. Diabetic group: Degeneration of beta cells with atrophy of islets of the pancreas, Multifocal tubular/interstitial hemorrhages in collecting tubules. Standard group: Hyperplasia of beta cells along with hypertrophy of islets of Langerhans, Multifocal tubular regeneration. A. Vera group: Mild hypertrophy of islets of the pancreas- normal morphology of acinar cells, Mild tubular/interstitial inflammation. Fenugreek group: Moderate hypertrophy of islets of the pancreas with moderate hyperplasia of beta cells, Foci of regenerated tubules along with infiltration of inflammatory cells in interstitial region. A. vera + Fenugreek: Normal morphology of ductular pancreas- normal acinar cells, Normal morphology of tubules.

4. DISCUSSION

The fundamental mechanism underlying hyperglycemia involves over-production (excessive hepatic glycogen-

Table 4. Effect of plant extracts on serum insulin and HbA1C

Groups	*Serum Insulin*	*HbA1C*
Control	1.92 ± 0.10	5.05 ± 0.50
Diabetic control Alloxan (100 mg/kg, i.p)	0.38 ± 0.31$^{###}$	8.66 ± 0.63$^{###}$
Glibenclamide (10 mg/kg, p.o)	1.79 ± 0.03***	5.23 ± 0.33***
Aloe vera (300 mg/kg, p.o)	1.53 ± 0.27***	5.34 ± 0.80***
Fenugreek (800 mg/kg, p.o)	1.46 ± 0.19***	5.66 ± 0.85***
Aloe vera + Fenugreek (150 + 400 mg/kg, p.o)	1.74 ± 0.24***	5.16 ± 0.55***

Data are expressed as mean ± SD (n=4) and analyzed by one way ANOVA followed by Tukey's multiple comparison test. $^{###}P <$ 0.001 as compared to control group,$^{***}P <$0.001 as compared to the diabetic control group.

olysis and gluconeogenesis) and decreased utilization of glucose by the tissues. The results of the present study indicate that oral administration of Aloe vera and Fenugreek extracts alone and in combinations for 14 days caused a significant decrease in the blood glucose level while increasing the level of plasma insulin. Previous studies have also established the blood glucose-lowering effects of fenugreek and A. vera.[11,12] The possible mechanism of action in Aloe vera and Fenugreek extracts treated groups could be potentiating the pancreatic secretion of insulin from β-cells of islets, as was evident by significantly elevating the level of insulin.

Body weight is determined by energy intake on one hand and expenditure on the other. The imbalance between energy intake and expenditure results in a change in body weight. Alloxan-induced diabetic rats show decreased levels of body weight, which was restored after administration of plant extracts. The decrease in body weight in diabetic rats clearly shows a loss (or) degradation of structural proteins. Weight loss which is one of the clinical features of diabetes mellitus may be due to the degeneration of the energy lost from the body due to frequent urination and the conversion of glycogen to glucose. This shows that the plant extracts limit the degeneration of the adipose and muscle tissues which occurs during diabetic stress. Similar findings were observed when A. vera and fenugreek were studied individually in previous studies.[13,14]

While the diabetic group had significantly higher amounts of creatinine in the serum, the A. vera, fenugreek, and A. vera + fenugreek extracts administered to diabetic rats exhibited significantly lower creatinine levels. Similar findings were observed in previous studies.[15,16] This reduction could be a result of improved renal function due to a reduced blood glucose concentration and subsequent glycosylation of renal basement membranes.

In diabetic rats, alloxan enhanced the level of glycated hemoglobin (A1c) due to the excessive production of glucose in the blood which further react with blood hemoglobin and prepared the glycated hemoglobin. Oral administration of A. Vera and Fenugreek extract alone and in combinations for 14 days caused significantly lower blood glucose, which lead to decreasing the level of glycated hemoglobin. The possible mechanism of action decreasing the blood glucose which is directly propositional to reducing the glycated hemoglobin.

Alloxan lowers insulin-mediated glucose disposal and promotes the conversion of excess fatty acids into phospholipids and cholesterol in the liver. These two substances along with excess triglycerides formed at the same time in the liver may be discharged into the blood in the form of lipoprotein.[17] Both increased hepatic production of triglycerides and decreased peripheral removal have been demonstrated. Hypercholesteremia and hypertriglyceridemia have been reported to occur in diabetic rats. Oral administration of A. Vera and Fenugreek extract alone and in combinations for 14 days caused a significant decrease in the total cholesterol, LDL, and triglycerides

Table 5. Effect of plant extracts on total cholesterol, triglycerides, LDL, and HDL

Groups	*Total cholesterol (mg/dL)*	*Triglycerides (mg/dL)*	*LDL (mg/dL)*	*HDL(mg/dL)*
Control	120.2 ± 5.7	93.4 ± 4.6	95.6 ± 2.4	58.3 ± 3.8
Diabetic control Alloxan (100 mg/kg, i.p)	229.4 ± 12.2$^{###}$	223.7 ± 24.5$^{###}$	174.0 ± 3.5$^{###}$	21.5 ± 3.8$^{###}$
Glibenclamide (10 mg/kg, p.o)	156.5 ± 6.6***	145.4 ± 8.7***	126.3 ± 4.5***	49.4 ± 5.3***
Aloe vera (300mg/kg, p.o)	137.7 ± 8.6***	117.8 ± 12.5***	123.1 ± 8.4***	59.6 ± 5.4**
Fenugreek (800mg/kg, p.o)	149.4 ± 7.3***	123.3 ± 6.1***	115.3 ± 8.25***	56.3 ± 5.7***
Aloe vera + Fenugreek (150 + 400 mg/kg, p.o)	126.2 ± 4.8***	104.4 ± 7.0***	97.6 ± 6.3***	63.4 ± 7.3***

Data are expressed as mean ± SD (n=4) and analyzed by one-way ANOVA followed by Tukey's multiple comparison test. $^{###}P <$ 0.001 as compared to control group, ***P<0.001 as compared to the diabetic control group.

levels while increasing the levels of HDL. The findings were in agreement with previous studies on fenugreek and A. vera extracts.[18,19]

Alloxan has been shown to induce free radical production and cause tissue injury. The pancreas is especially susceptible to the action of alloxan-induced free-radical damage. According to our findings, A. vera and fenugreek extract has a protective impact on the structure and activity of Langerhans cells and enhances the histological structure of the islet cells. The enhancement in the activity of the pancreas' enzymatic antioxidants, which are crucial to the defense system against free radical damage to the pancreas, may be the reason for the beneficial effect of the extracts.[20]

The kidney is a major organ involved in diabetic complications. As known, the function and structure of the kidney may be affected by changes in the levels of insulin. Diabetic kidney exhibits characteristic changes leading to renal insufficiency or complete kidney failure. Histological studies indicate the characteristic changes in the kidney. The findings have shown that plant extracts reverse the damage in the kidneys of diabetic animals. In the present study, histological findings in the extract-treated group were in agreement with the results of other studies.[21,22]

5. CONCLUSION

With our study, it is concluded that diabetes can be well-managed with A. vera and fenugreek alone and in combination. The results of the additive effect of the combination group were more significant than the individual. A significant improvement was observed in the combination group than individual groups in blood glucose, body weight, cholesterols, creatinine, HbA1c, urine output, and pancreas and kidney histopathology. Present findings provide a scientific rationale for the use of A. vera gel and fenugreek combined formulation. Moreover, it seems that further research into the combined effects of the two extracts in the other animal models of diabetes and the conduction of clinical trials on the anti-hyperglycemic effect of their combined formulation in diabetic patients is warranted

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