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Anti hyperglycemic and antihyperlipidemic activity of aerial parts of *Aerva lanata* Linn Juss in streptozotocin induced diabetic rats

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ABSTRACT

Objective: To evaluate the effect of methanol extract (MEAL) and aqueous extract (AEAL) of the aerial parts of *Aerva lanata* Linn Juss (*A. lanata*) in streptozotocin induced diabetic rat. **Methods:** The streptozotocin induced diabetic rats were orally treated with vehicle (Normal saline), glibenclamide (0.5 mg/kg), MEAL (200 and 400 mg/kg) and AEAL (200 and 400 mg/ kg) to the respective treatment groups. The blood glucose level, lipid profile, body weight on 0 day, 1 week and 2 week and biochemical parameters on 2 week of treatment were measured and are compared to the diabetic control rats. **Results:** MEAL, AEAL and glibenclamide were found to significantly ($P<0.01$ and $P<0.05$) reduce the blood glucose level, lipid profile, increase body weight and reduce serum glutamate- oxaloacetate transaminase (SGOT), serum glutamate- pyruvate transaminase (SGPT), creatinine, alkaline phosphatase (ALP), blood urea nitrogen (BUN) and total bilirubin to significant level. The antidiabetic effect was sustained from 1 week onwards till the end of the study. **Conclusions:** It has been concluded that MEAL and AEAL in addition to the antidiabetic activity, also possess antihyperlipidemic and the normal value of the hepatic biochemical parameters reveals the safety profile of the extract on liver function in the streptozotocin induced diabetic model.

1. Introduction

India is a rich source of medicinal plants and a number of plant extracts have been used in various systems of medicines such as Ayurveda, Siddha and Unani etc to cure various diseases. Only a few of them have been scientifically explored. Plant derived natural products such as flavanoids, terpenoids, alkaloids etc have received considerable attention in recent years due to their diverse pharmacological properties including cytotoxic and cancer chemo preventive effects [1]. Herbal medicine is based on the premise that plants contain natural substances that can promote health and alleviate illness. In recent times, focus on plant research has increased throughout the world and the immense potential of medicinal plants used in various traditional systems has been established scientifically. Screening plants with such ethno medical uses is believed to increase the odds in discovering new medicines. Diabetes mellitus is a metabolic disorder characterized by disturbances in carbohydrate, protein and lipid metabolism and by complications like micro vascular (retinopathy, neuropathy and nephropathy) and macro vascular (heart attack, stroke and peripheral vascular disease) complications [2]. A world wide survey has reported that diabetes mellitus affects nearly 10% of the population. It has been predicted that the prevalence of diabetes in adults will increase from 135 million in 1995 to 350 million in 2030 as given by International Diabetes Federation [3]. Currently available synthetic antidiabetic agents produce serious side effects like hypoglycemic coma and hepatorenal disturbances [4, 5]. Patients are therefore using herbal medicines which have fewer side effects and have the potential to impart therapeutic effect in complicated disorders like diabetes and its complication [6]. Following the WHO's recommendation for research on the beneficial uses of medicinal plants in the treatment of diabetes mellitus, investigations on hypoglycemic agents derived from medicinal plants have also gained momentum. Antidiabetic agents from medicinal plants could serve as a good source for drug design and much attention has been fixed on formulation of herbal medicine [7]. *Aerva lanata* Linn Juss (Family: Amaranthaceae) (*A. lanata*) is an important source of chemicals of immense medicinal and pharmaceutical importance. The plant is distributed throughout Tropical India as a common weed in fields

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and wasteland and is also found to be grown in Arabia, Tropical Africa, Sri Lanka, Philippines and Java [8]. The *A. lanata* Linn Juss is useful for curing anthelmintic [9] and urolithiasis[10]. The *A. lanata* has been reported to possess anti-inflammatory [11], diuretic [12] and nephroprotective actions in rats [13]. The whole plant of *A. lanata* showed significant antimicrobial activities [14]. Alcoholic extracts of *A. lanata* has shown significant antidiabetic activity in rats[15]. The partially TLC purified fraction of petroleum ether extract was proved to be cytotoxic [16]. Hepatoprotective activity was studied on the aqueous alcoholic extracts of leaf and root [17]. Anticancer activity of aerial parts of *A. lanata* Linn Juss ex Schult against Dalton's ascitic Lymphoma was studied [18]. *A. lanata* Linn are reported to be used in diabetes in folklore and traditional medicine [19] and based on the above perspective, an effort was made to ascertain the possible role of MEAL and AEAL in Streptozotocin-induced diabetes mellitus in vivo.

2. Materials and methods

2.1. Collection and authentication of plant

Fresh aerial parts of the plant *A. lanata* Linn Juss were collected from Tirunelveli district in Tamil Nadu, India during the month of November and it is identified and authenticated by Dr. Shiddamallayya N, Asst. Director in charge from Regional Research Institute (AY.), Bangalore and Voucher specimens (RRCBI- 5588) was deposited in the Institute for future reference. The aerial parts of *A. lanata* Linn Juss were dried in the shade and it is milled into coarse powder by a mechanical grinder and it is stored in closed vessel for further use.

2.2. Plant crude extracts

The air dried coarse powder of the aerial parts of *A. lanata* was extracted successively with organic solvents of increasing polarity like petroleum ether, chloroform, acetone, methanol using soxhlet's apparatus and water by maceration for 7 days. Each time before extracting with next solvent, the marc was dried in the air and it is then repacked in the apparatus. After each extraction was completed, the extracts were cooled at room temperature, filtered and concentrated under reduced pressure in the rotator evaporator; it is then dried and kept in the desiccators. The extracts of aerial parts of *A. lanata* were subjected to qualitative test for the identification of various active constituents.

2.3. Chemicals and reagents

Streptozotocin (Sigma chemical co., U.S.A), glibenclamide (micro labs, India), glucose, triglyceride and total cholesterol estimation kit (Accurex Biomedical pvt Ltd, India). Other chemicals and reagents used for the study were of analytical grade and procured from approved organizations.

2.4. Preliminary phytochemical screening

MEAL and AEAL was screened for the presence of various phytoconstituents [20, 21].

2.5. Experimental animals

Male Sprague Dawley (150-180 g) rats were used for the present study. The animals were maintained under standard environmental conditions and were fed with standard pellet diet and water *ad libitum*. The experimental protocol was approved by the Institutional animal ethics committee, Approval no IAEC- XII/ SRU/80/ 2008. CPCSEA guidelines were adhered during the maintenance and experiment.

2.6. Acute toxicity studies

Acute oral toxicity study of MEAL and AEAL was studied in healthy rats (n=3) according to the guidelines set by Organisation for Economic Cooperation and development (OECD) guidelines [22]. Starting dose was selected to be 2 000 mg/kg b.w. and finally a dose of 4 000 mg/kg b.w. was evaluated for toxicity. The animals were observed continuously for 24 h for mortality.

2.7. Evaluation of anti diabetic activity

2.7.1. Treatment protocol

The animals were divided into seven groups of six animals each as follows:

Group I- Vehicle control, Normal saline (0.9% w/v NaCl); Group II- Diabetic control; Group III- Diabetic standard treated, 0.5 mg/kg of glibenclamide, *p.o.* (micro labs); Group IV- Diabetes MEAL 200 mg/ kg, *p.o.*; Group V- Diabetes MEAL 400 mg/ kg, *p.o.*; Group VI- Diabetes AEAL 200 mg/ kg, p.o.; Group VII- Diabetes AEAL 400 mg/ kg, *p.o.*.

Diabetes was induced in all groups except normal control by a single intraperitoneal injection of 60 mg/ kg of Streptozotocin (STZ) dissolved in a freshly prepared 0.1 M citrate buffer (pH 4.5). The animals in the vehicle control (Group I) received normal saline orally (0.9% w/v NaCl). The rats with blood glucose levels above 250 mg/dL were considered as diabetic and used in this study [23]. After 72 h, the blood was withdrawn by retro orbital puncture under light ether anaesthesia and the blood glucose level was estimated. Serum was separated by centrifugation at 3 000 rpm for about 5 minutes. The clear straw coloured serum was collected and stored at 4 ^{0}C for the measurement of marker enzymes level to assess the liver functions. Blood glucose levels and body weight were measured on day 0, 7 and 14 of the study. Finally on day 14, blood was collected to perform various biochemical parameters [24].

2.7.2. Estimation of plasma glucose and lipid profile

Every week, following overnight fasting (16 h fasting with free access to water), the blood samples were withdrawn from the animals by retro orbital puncture under light ether anaesthesia. The plasma glucose estimation was done based on enzymatic method using glucose oxidase/ peroxidase (GOD/POD) method using a standard kit obtained from Accurex Biomedical pvt Ltd, India. Serum glucose levels are expressed in mg/ dL. The serum triglycerides (TG), total cholesterol (TC) levels and various biochemical parameters were also estimated.

2.7.3. Effect on body weight

During the study period of 21 days the mice were weighed daily and the body weight of all experimental animals was recorded using a digital weighing scale and SEM were calculated and tabulated[25].

2.7.4. Biochemical estimation

The effect of MEAL and AEAL treatment on the biochemical parameters of the experimental rats were evaluated by the estimation of serum biochemical enzymes such as, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP) , Creatinine , Blood Urea Nitrogen (Bun) and total bilirubin was analysed in the serum of normal control, diabetic control, standard, MEAL and AEAL treated rats to assess the protective activities of *A. lanata* by standard enzymatic methods using standard kits obtained from Accurex Biomedical pvt Ltd, India.

2.8. Statistical analysis

The results are expressed as mean±S.E.M. Statistical difference was tested by using one-way analysis of variance (ANOVA) followed by Dunnet's test. Values are expressed as mean ± SEM (n=6) in each group.

3. Results

3.1. Acute toxicity study

The various observations showed the normal behaviour of the treated rats. No toxic effects were observed at a higher dose of 4 g/kg body weight. Hence, there were no lethal effects in any of the groups.

3.2. Preliminary phytochemical screening

Preliminary phytochemical screening revealed the presence of alkaloids, tannin like phenolic compounds, saponins, flavanoids and steroids.

3.3. Effect of AEAL and MEAL on fasting blood glucose

Treatment with methanol and aqueous extracts of aerial parts of *A. lanata* Linn Juss at the dose of 200 and 400 mg/kg body weight for 1 week exhibited a significant (P<0.01) decrease in the fasting blood glucose in streptozotocin induced diabetic animals as compared to diabetic control (Table 1). Blood glucose level of diabetic animals started decreasing from the first week of drug treatment that was continued to maintain till 2nd week, which was comparable to glibenclamide 0.5 mg/ kg (Table 1).

3.4. Effect of AEAL and MEAL on lipid profile

The level of serum total cholesterol was increased in all the diabetic groups on 0 day. Treatment with MEAL, AEAL and glibenclamide significantly (P<0.01) decreased the elevated total cholesterol level from the first week of treatment onwards and this effect was observed throughout till the end of the study (Table 2). Similarly there was also a rise in the level of serum triglycerides with diabetic animals. MEAL and AEAL significantly (P<0.01) decreased the elevated serum triglycerides after 1 week of initiation of treatment and it was observed throughout the study (Table 3).

3.5. Effect of AEAL and MEAL on Body weight

Table 1
Effect of MEAL and AEAL on blood glucose.

Treatment	Blood glucose (mg/ dL)		
	0 day	1 week	2 week
Normal control	90.08 ± 3.21	94.52 ± 3.42	85.11 ± 4.14
Diabetic control	287.20 ± 6.46	265.96 ± 4.95	258.23 ± 8.68
Standard 0.5 mg/ kg	267.78 ± 8.74	224.78 ± 4.89**	203.50 ± 3.44**
MEAL 200 mg/kg	273.21 ± 13.13	227.20 ± 9.91**	185.30 ± 6.48**
MEAL 400 mg/kg	276.86 ± 3.07	228.15 ± 9.56**	176.60 ± 4.34**
AEAL 200 mg/kg	294.33 ± 7.42	229.40 ± 5.79**	198.30 ± 5.27**
AEAL 400 mg/kg	290.71 ± 5.0	230.83 ± 6.18**	188.9 ± 6.59**

Values are expressed as mean ± SEM (n=6) in each group. Values were found out by using one way anova followed by Dunnet's test. **Values were significantly different from hyperglycemic control at P< 0.01. '0 day' indicates the initial day in which the treatment commenced.

Table 2
Effect of MEAL and AEAL on cholesterol.

Treatment	Cholesterol(mg/ dL)		
	0 day	1 week	2 week
Normal control	56.25 ± 2.45	52.16 ± 3.45	37.67 ± 4.05
Diabetic control	57.07 ± 3.32	68.37 ± 2.81	60.46 ± 3.14
Standard 0.5mg/ kg	43.30 ± 3.11	48.63 ± 1.83**	38.28 ± 1.56**
MEAL 200mg/kg	45.61 ± 1.17	49.82 ± 2.27**	39.51 ± 2.34**
MEAL 400mg/kg	47.01 ± 2.73	48.82 ± 1.40**	40.47 ± 1.89**
AEAL 200mg/kg	53.68 ± 6.00	51.57 ± 2.93**	41.52 ± 1.49**
AEAL 400mg/kg	51.92 ± 6.90	52.62 ± 4.47**	41.15 ± 1.38**

Values are expressed as mean ± SEM (n=6) in each group. Values were found out by using one way anova followed by Dunnet's test. **Values were significantly different from hyperglycemic control at P< 0.01. '0 day' indicates the initial day in which the treatment commenced.

Table 3
Effect of MEAL and AEAL on triglycerides.

Treatment	Triglycerides (mg/ dL)		
	0 day	1 week	2 week
Normal control	87.11 ± 2.11	84.22 ± 3.51	63.72 ± 3.36
Diabetic control	261.31 ± 7.61	167.90 ± 7.58	93.26 ± 1.3
Standard 0.5 mg/ kg	254.01 ± 6.69	70.98 ± 8.34**	65.91 ± 1.41**
MEAL 200 mg/kg	257.35 ± 4.01	77.40 ± 9.54**	68.70 ± 2.24**
MEAL 400 mg/kg	256.21 ± 3.6	86.31 ± 7.73**	66.48 ± 0.82**
AEAL 200 mg/kg	258.83 ± 2.96	95.58 ± 9.98**	74.36 ± 2.59**
AEAL 400 mg/kg	260.50 ± 4.8	98.58 ± 8.32**	71.02 ± 2.36**

Values are expressed as mean ± SEM (n=6) in each group. Values were found out by using one way anova followed by Dunnet's test. **Values were significantly different from hyperglycemic control at $P< 0.01$. '0 day' indicates the initial day in which the treatment commenced.

Table 4.
Effect of MEAL and AEAL on Body weight

Treatment	Body weight(g)		
	0 day	1 week	2 week
Normal control	159.16 ± 6.77	162.66 ± 0.88	161.83 ± 9.58
Diabetic control	152.60 ± 2.49	133.66 ± 1.30	122.80 ± 2.22
Standard 0.5 mg/ kg	160.00 ± 6.47	161.66 ± 4.9**	151.10 ± 1.81**
MEAL 200 mg/kg	166.66 ± 8.11	158.00 ± 2.72**	148.50 ± 1.47**
MEAL 400 mg/kg	161.83 ± 8.39	157.10 ± 4.86**	146.00 ± 1.18**
AEAL 200 mg/kg	157.83 ± 8.34	155.10 ± 0.44**	145.20 ± 1.2**
AEAL 400 mg/kg	161.33 ± 6.25	156.50 ± 1.31**	137.60 ± 1.24**

Values are expressed as mean ± SEM (n=6) in each group. Values were found out by using one way anova followed by Dunnet's test. **Values were significantly different from hyperglycemic control at $P< 0.01$. '0 day' indicates the initial day in which the treatment commenced.

Table 5.
Effect of MEAL and AEAL on Biochemical parameters

Treatment	SGOT (IU/ dl)	SGPT(IU/ dl)	Creatinine(mg/ dl)	ALP(IU/ dl)	BUN(mg/ dl)	T.Bilirubin(mg/ dl)
Normal control	169.66 ± 17.14	123.17 ±1.91	1.64 ± 0.04	256.08 ±17.53	20.63 ± 1.13	0.63 ± 0.03
Diabetic control	297.46 ± 62.17	208.3 ±37.83	1.85 ± 0.01	1614.8 ±114.21	38.87 ±0.67	0.4 ± 0.04
Standard	180.33 ±12.21**	121.43 ±9.59**	1.69 ±0.009**	901.18 ±9.06**	21.91 ±1.81**	0.61 ± 0.03**
MEAL(200 zg/ kg)	189.60 ± 12.01*	122.58 ± 6.41**	1.71 ± 0.02**	954.5 ± 11.66**	28.2 ± 1.26**	0.60 ± 0.02**
MEAL(400 mg/ kg)	183.93 ± 14.03*	111.4 ± 5.98**	1.72 ± 0.01**	933.2 ± 14.43**	22.39 ± 2.52**	0.60 ± 0.03**
AEAL(200 mg/ kg)	204.00 ± 12.1*	128.54 ± 10.33*	1.7 ± 0.02**	859.2 ± 58.13**	30.02 ± 0.52**	0.56 ± 0.02**
AEAL(400 mg/ kg)	196.91 ± 7.89*	135.29 ± 9.65*	1.69 ± 0.01**	955.1 ± 15.06**	28.82 ± 2.22**	0.58 ± 0.03**

Values are expressed as mean ± SEM (n=6) in each group. Values were found out by using one way anova followed by Dunnet's test. **Values were significantly different from hyperglycemic control at $P< 0.01$. * Values were significantly different from hyperglycaemic control at $P< 0.05$. '0 day' indicates the initial day in which the treatment commenced.

Body weight of streptozotocin induced diabetic rats was found to be significantly ($P<0.01$) less compared to normal rats (Table 4). After 1 week of treatment with MEAL and AEAL, the body weight had significantly ($P<0.01$) increased compared to diabetic control. Progress in weight gain of animals in drug treated group was continued to be observed till the end of the study (Table 4).

3.6. Effect of AEAL and MEAL on Biochemical parameters

The efficacy of MEAL and AEAL at the dose of 200 mg/kg and 400 mg/ kg on serum SGOT, SGPT, ALP, BUN and total bilirubin in diabetic rats. The above biochemical parameters were significantly ($P<0.01$) altered in STZ induced diabetic rats compared to normal control rats. In diabetic rats, administration of both doses of MEAL and AEAL and glibenclamide significantly ($P<0.05$, $P< 0.01$) reduced SGOT, SGPT, ALP, BUN and total bilirubin level compared to diabetic control rats (Table 5).

4. Discussion

In light of the results, our study indicates that aerial parts of *A. lanata* Linn Juss have significant antihyperglycemic activities in Streptozotocin [2- deoxy -2- (3-methyl -3-nitrosoureido)- D- gluco pyranose] induced hyperglycaemic rats. They can also improve the condition of diabetes as indicated by parameters like lipid and biochemical parameters. Streptozotocin was known to destroy the β-cells of the pancreas, which causes selective pancreatic islet β-cell cytotoxicity mediated through the release of nitric oxide (NO), methyl cations, methyl radicals, reactive oxygen species (ROS). This results in rapid reduction in pancreatic islet pyridine nucleotide concentration and subsequent β-cell necrosis. The action of STZ on mitochondria generates SOD anions, which leads to diabetic complications [26]. Based on the above perspectives, in the present study, the oxidative stress has

been assessed in rats made diabetic by STZ[27]. Sulfonylureas such as glibenclamide are often used as a standard antidiabetic drug in STZ-induced diabetes to compare the efficacy of variety of antihyperglycemic compounds. In our study, there was a significant elevation in blood glucose level in diabetic control group as compared with normal animals. Over production of glucose by means of excessive hepatic glycogenolysis and gluconeogenesis and decreased utilization of glucose by the tissues is one of the fundamental basis of hyperglycemia in diabetes mellitus[28]. The MEAL and AEAL treated group exhibited significant reduction of fasting plasma glucose levels as compared to the diabetic control group. Hence, the hypoglycemic activity of MEAL and AEAL may be due to its protective action against STZ- mediated damage to the pancreatic beta cells and also possibly because of regeneration of damaged beta cells or increased insulin secretion[29] . The most commonly observed lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia [30]. This might have occurred in the diabetic rats as a result of lack of insulin which activates the lipase enzymes, hydrolyzing the stored TG and releasing large amounts of fatty acids and glycerol in the circulating blood [31]. Consequently, the excess of fatty acids in the plasma may promote the hepatic conversion of fatty acids into phospholipids and cholesterol, the main product of lipid metabolism. The increase level of TG and cholesterol in the blood of diabetic rats may lead to cardiovascular disease. The accelerated coronary heart disease has emerged as a leading cause of morbidity and mortality in diabetic patients in the world wide [32]. In the present study, administration of STZ showed alteration of normal lipid profiles such as increased total cholesterol and triglycerides level compared to normal control rats. These altered lipid profile were reversed to near normal level after the treatment of both doses of MEAL, AEAL in STZ induced diabetic rats. The improvements in the lipid profile in diabetic animals after treatment with MEAL and AEAL could be beneficial in preventing diabetic complications as well as improving lipid metabolism [33]. Diabetes mellitus has been attributed to the gluconeogenesis i.e., catabolism of proteins and fats, which is associated with the characteristic loss of body weight due to increased muscle wasting and loss of tissue proteins [34]. In the present study, diabetic rats treated with MEAL and AEAL showed an increase in body weight as compared to the diabetic control, which may be due to its protective effect in controlling muscle wasting i.e., reversal of gluconeogenesis. The ability of aerial parts of *A. lanata* Linn Juss in effectively increasing the body weight may be attributed to its anti hyperglycemic activity. Elevation of serum biomarker enzymes such as SGOT, SGPT and SALP were observed in diabetic rats indicating impaired liver function, which is obviously due to hepatocellular necrosis. In STZ induced diabetic rats, elevated level of SGOT and SGPT were observed and it may be due to STZ mediated liver damages which may cause leakage of above enzymes into the blood [35]. Restoration of these biomarker enzymes towards normal level indicates decreased diabetic complications in MEAL and AEAL treated groups. Elevated levels of urea are observed during increased protein breakdown [36]. This elevation in serum urea was controlled significantly on treatment with MEAL and AEAL. The decrease in lipids and urea levels on treatment with MEAL and AEAL suggests that the gluconeogenesis is in control and substantiates that the mechanism of antidiabetic activity may be due to improvisation of glucose utilization, thereby decreasing gluconeogenesis. The mechanism of action of α-glucosidase inhibitors is the inhibition of glucose absorption and hence, does not contribute for decrease in the gluconeogenesis. However, the present study shows increase in the glucose metabolism and decrease in the gluconeogenesis as evidenced by increase in liver and serum lipids and urea levels. This substantiates that other active ingredient(s) may contribute for the in vivo antihyperglycemic effect and the decrease in blood glucose may be attributed to the stimulation of glucose uptake by peripheral tissues and decrease in the gluconeogenesis. Hence, the antihyperglycemic effect may be probably brought about by an extra pancreatic mechanism. Traditional medicinal plants with various active principles and properties have been used from ancient times by physicians and laymen to treat a great variety of human diseases such as diabetes, coronary heart disease and cancer. Beneficial multiple activities like manipulating carbohydrate metabolism by various mechanisms, preventing and restoring the integrity and function of β-cells, releasing insulin activity, improving glucose uptake and utilization, and the antioxidant properties present in medicinal plants, offer an exciting opportunity to develop them into novel therapeutics. Hence further phytopharmacological studies on the basis of its ethno botanical use can help to explore and establish the bioactive constituents which can be used safely for the treatment of various diseases and disorders in future. The antihyperglycemic, antihyperlipidemic effects and biochemical parameters of aerial parts of *A. lanata* Linn. Juss mediated through the peripheral mechanisms and the effects may be attributed to the components such as flavonoids, triterpenoids and antioxidant principles present in the MEAL and AEAL. Flavanoids are known to have bioactive antidiabetic principles [37]. The present findings may pave the way for the bioactivity guided fractionation and the isolation of novel lead compounds in *A. lanata* for the antidiabetic activity which will be useful for the design and synthesis of potent antidiabetic and antihyperlipidemic components hence beneficial for the patients. However, further studies are underway to isolate the lead molecule(s) responsible for the activity and also to pinpoint on the mechanism of action of the same.

Conflict of interest

We declare that we have no conflict of interest.

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