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Antidiabetic, Analgesic and Anti-Inflammatory activity of Aqueous extracts of Stem and Leaves of *Alangium salvifolium* and *Pavonia zeylanica*

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Abstract

The present study is aimed to investigate the antidiabetic, analgesic and anti-inflammatory effect of aqueous extracts of stem and leaves of *Alangium Salvifolium* (AEAS) and *Pavonia Zeylanica* (AEPZ). The antidiabetic activity was evaluated by measuring blood glucose level in normal and streptozotocin (STZ) induced diabetic rats, the acetic acid induced writhing and hot plate methods in mice were used to assess analgesic activity and Carrageenan induced paw edema in rats, which is an acute model used to assess anti-inflammatory activity. The results support the traditional usage of the plants of *Alangium Salvifolium* and *Pavonia zeylanica* by ayurvedic physicians for the control of diabetes, pain and inflammation.

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INTRODUCTION

Diabetes mellitus is a syndrome of impaired carbohydrate, fat and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin. There are two general types of diabetes mellitus: Type I diabetes,

also called insulin dependent diabetes mellitus (IDDM), and is caused by lack of insulin secretion. Type II diabetes, also called non-insulin dependent diabetes mellitus (NIDDM), and is caused by decreased sensitivity of target tissues to the metabolic effect of insulin. This reduced sensitivity to insulin is often referred to as insulin resistance. In both types of diabetes mellitus, metabolism of all the main foodstuffs is altered. The basic effect of insulin lack or insulin resistance on glucose metabolism is to prevent the efficient uptake and utilization of glucose by most cells of the body, except those of the brain. As a result, blood glucose concentration increases, cell utilization of glucose falls increasingly lower, and utilization of fats and protein increases [1].

Pain is one of the most common complaints for which patients seek advice and help from health professionals. Pain is not simple or easily defined-in fact; it is not one phenomenon, but several. Pain today is most appropriately defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. The etiology of chronic pain is seldom all psychological or all physical. Commonly, there is little association between the extent of injury and the amount of pain complains [2].

Inflammation is the reaction of the living tissues to injury; it comprises systemic response (involving nervous and hormonal adjustments, and proliferation of the lymphoreticular system); and local response (pain, redness, warmth and swelling). The three important aspects of inflammation that render themselves readily to measurement are erythema (local vasodilation), edema (increased capillary permeability) and formation of granulation tissue. Compounds claimed to possess anti-inflammatory activity can be evaluate either by their ability to reduce one or more of these phenomena in experimentally induced inflammation or by testing their anti-inflammatory activity in experimental arthritis produced in animals [3].

Many Indian medicinal plants are reported to be useful in diabetes, pain and inflammation. However, search for new drug continue. *Alangium Salvifolium* belongs to the family Alangiaceae. It is commonly known as sage leaved alangium, stone mango, hill sack tree and ancole fruit plant in English, nalla oodaga, oodaga chettu, aankolam and urgu in Telugu. It is a deciduous shrub or tree. It is commonly distributed in most parts of Chittoor district of Andhra Pradesh like Tirupati, Talakona, Chandragiri and Aragonda. The root bark is used for snake bite, cutaneous troubles, anthelmintic, astringent, purgative, diaphoretic and colic. Leaves are used in diabetes and the fruits are used as astringent, tonic and laxative, whereas the seeds are used in hemorrhage. *Pavonia Zeylanica* belongs to the family Malvaceae. It is commonly known as karubenda, china mutharapulagam, peramuthi and chittimulli in Telugu. It is very commonly distributed in farm fields, wastelands and rare in forest fringers, throughout the Chittoor district of Andhra Pradesh. Whole plant is used as febrifuge and anthelmintic [4].

An extended literature review shows that an Anti-arthritic activity of bark extracts of Alangium Salvifolium Wang [5] and Anti-fertility activity of the stem bark of Alangium Salvifolium Wang in wistar female rats [6] has been reported. Larvicidal efficacy of medicinal plant extracts against Anopheles Stephensi and Culex quinquefasciatus [7] for Pavonia Zeylanica has been reported. However the aqueous plant extracts are not scientifically explored for its anti-diabetic, analgesic and anti-inflammatory activity. Hence an effort has been made to screen the plants for anti-diabetic, analgesic and anti-inflammatory activities.

MATERIALS AND METHODS

Collection of Plant Material

The proposed plants material of fresh stem and leaves of Alangium Salvifolium and Pavonia Zeylanica were collected from Tirupati, Chittoor district of Andhra Pradesh, India. The species of the proposed study was identified and authentified by Dr.K.Madhava Chetty, Asst.Professor of Dept.of Botany, Sri Venkateswara University, Tirupati, Andhra Pradesh, India. Voucher specimens were deposited at Dept. of Pharmacognosy for further reference.

Extraction and phytochemical screening

The shade dried powder of the stem and leaves of plants was packed well in Soxhlet apparatus and was subjected to continuous hot extraction with distilled water after defatting with hexane until the completion of extraction. The extracts evaporated to dryness and kept in a desiccators till experimentation.

The extract was subjected to qualitative chemical investigation for the identification of different phytoconstituents like sterols, glycosides, saponins, alkaloids, flavonoids, carbohydrates, tannins and proteins [8-10].

Animals

Wistar albino rats of either sex weighing between 200-250gms were used for the evaluation of antidiabetic and anti-inflammatory activity. Male albino mice (20-30gm) were used for the evaluation of analgesic activity. The animals were maintained on the suitable nutritional and environmental conditions throughout the experiment as per the rules and regulations of the Institutional animal ethics committee. Experimental protocols for the pharmacological and toxicity studies were reviewed and approved by the Institutional animal ethical committee (1423/PO/a/11/CPCSEA).

Toxicity Study

An acute toxicity study was performed to determine LD_{50} using different doses of the extracts according to the method described under OECD guidelines [11].

Effect of AEAS and AEPZ on Blood Glucose Levels in Normoglycemic rats [12, 13]

Animals were divided into six groups of six rats in each group.

Group-I: Animals received 1% NaCMC 2ml/kg body wt. per orally.

Group-II: Animals received AEAS 400mg/kg body wt. per orally.

Group-III: Animals received AEAS 800mg/kg body wt. per orally

Group-IV: Animals received AEPZ 400mg/kg body wt. per orally.

Group-V: Animals received AEPZ 800mg/kg body wt. per orally.

Group-VI: Animals received standard drug Glibenclamide 0.5mg/kg body wt. per orally.

In this study the entire groups of animals were fasted overnight and administered with respective drugs as per the mentioned dosage schedule. Blood glucose levels were determined at 0, 1, 2, 3 and 4 hours, after drug administration.

Effect of Blood Glucose Levels on Glucose fed Hyperglycemic Rats (Oral Glucose Tolerance Test)

The animals were divided into six groups of six rats in each group.

Group-I : Animals received glucose at a dose of 2gm/kg body wt. per orally.

Group-II: Animals received AEAS 400mg/kg body wt. in 1% NaCMC and glucose solution at a dose of 2gm/kg body wt. per orally.

Group-III: Animals received AEAS 800mg/kg body wt. in 1% NaCMC and glucose solution at a dose of 2gm/kg body wt. per orally.

Group-IV: Animals received AEPZ 400mg/kg body wt. in 1% NaCMC and glucose solution at a dose of 2gm/kg body wt. per orally. .

Group-V: Animals received AEPZ 800mg/kg body wt. in 1% NaCMC and glucose solution at a dose of 2gm/kg body wt. per orally.

Group-VI: Animals received standard drug Glibenclamide 0.5mg/kg body wt. and glucose solution at a dose of 2gm/kg per orally.

In this study, the entire group of animals were fasted and treated with above dosage schedule orally. AEAS, AEPZ and glibenclamide were administered half an hour before administration of glucose solution. Blood glucose levels were determined at 0, 1, 2, 3 and 4 hours, after glucose administration.

Experimental induction of diabetes

For the induction of diabetes in rats, Streptozotocin solution (70mg/kg body wt. citrate buffer P^H4.5) is injected intraperitoneally. A rest period of two days is allowed for the blood glucose level to stabilize. During this period the animals used to have free access to both food and water. Blood sugar levels of the animals are determined, 48 hours after injection of STZ. The animals having blood glucose level more than 200mg/dL were selected for the experimentation.

Effect of AEAS and AEPZ on Blood Glucose Levels in Streptozotocin Induced Diabetic Rats

Different groups of rats were used to study the effects of AEAS and AEPZ. The rats were divided into seven groups each consisting of six rats.

Group-I: Normal control animals received 2ml/kg of 1% NaCMC per orally for 15 days.

Group-II: Streptozotocin induced diabetic animals received 1% NaCMC 2ml/kg per orally for 15 days.

Group-III: Streptozotocin induced diabetic animals received AEAS 400mg/kg per orally for 15 days.

Group-IV: Streptozotocin induced diabetic animals received AEAS 800mg/kg per orally for 15 days.

Group-V: Streptozotocin induced diabetic animals received AEPZ 400mg/kg per orally for 15 days.

Group-VI: Streptozotocin induced diabetic animals received AEPZ 800mg/kg per orally for 15 days.

Group-VII: Streptozotocin induced diabetic animals received the standard drug Glibenclamide 2.5mg/kg per orally for 15 days.

All the group of animals received the treatment for 15 days. Blood samples were collected one hour after the drug administration and the day 5^{th}, 10^{th} and 15^{th} to determine the blood glucose level. For glucose determination, blood was obtained by snipping tail with sharp razor [14]. Then the blood glucose levels were determined by using Haemo-Glucotest (20-800R) glucose strips. This method, which permits the measurement of blood glucose levels with minimum injury to rat, was previously validated by comparison with glucose oxidase method [15].

Evaluation of Analgesic activity

Fasted normal mice were divided into six groups of six mice in each group.

Acetic acid induced abdominal writhing test

The divided animals were grouped as follows for acetic acid induced abdominal writhing test [16,17].

Group I: Control received 2ml/kg of 1% NaCMC.

Group II: Test animals received AEAS 400mg/kg body weight in 1% NaCMC p.o.

Group III: Test animals received AEAS 800mg/kg body weight in 1% NaCMC p.o.

Group IV: Test animals received AEPZ 400mg/kg body weight in 1% NaCMC p.o.

Group V: Test animals received AEPZ 800mg/kg body weight in 1% NaCMC p.o.

Group VI: Standard group animals received Aspirin at an oral dose of 100mg/kg.

Animals were treated with above scheduled doses 60 min before acetic acid administration. The total number of writhing after intra peritoneal administration of 0.1ml/10gm of 0.6% solution of acetic acid was recorded for 30 min, starting 5 min after the injection. For the purpose of scoring, a writhe is indicated by stretching the abdomen with

simultaneous of at least one hind limb. The percentage inhibition of writhing by an analgesic is calculated according to the following formula:

$$\text{Percentage inhibition} = \frac{\text{Average writhes in control group} - \text{Average writhes in test group}}{\text{Average writhes in control group}} \times 100$$

2.5.2 Hot Plate method

Thirty six mice were weighed and the basal reaction time by observing hind paw licking or jump response (whichever appears first) in animals when placed on hot plate maintained at constant temperature (55°C) was taken. The animals were divided into six groups of six rats each [18,19].

Group I: Control received 2ml/kg of 1% NaCMC.

Group II: Test animals received AEAS 400mg/kg body weight in 1% NaCMC p.o.

Group III: Test animals received AEAS 800mg/kg body weight in 1% NaCMC p.o.

Group IV: Test animals received AEPZ 400mg/kg body weight in 1% NaCMC p.o.

Group V: Test animals received AEPZ 800mg/kg body weight in 1% NaCMC p.o.

Group VI: Standard group animals received Aspirin at an oral dose of 100mg/kg.

After administration of the above scheduled drugs, the reaction time was measured in seconds at 0 min (before drug challenge), 15, 30, 60 and 120 minutes.

2.6 Evaluation of Anti-inflammatory activity

Anti-inflammatory activity was determined in albino rats of either sex. The rats were divided into six groups of six animals each.

2.6.1 Carrageenan induced rat paw edema method

One hour after oral administration of the extracts and standard drug, edema was induced to all the groups by subcutaneous injection of 0.1ml of 1% solution of Carrageenan in 0.9% w/v saline on the plantar surface of the left hind paw of rats [20,21].

Group I: Control received 2ml/kg of 1% NaCMC.

Group II: Test animals received AEAS 400mg/kg body weight in 1% NaCMC p.o.

Group III: Test animals received AEAS 800mg/kg body weight in 1% NaCMC p.o.

Group IV: Test animals received AEPZ 400mg/kg body weight in 1% NaCMC p.o.

Group V: Test animals received AEPZ 800mg/kg body weight in 1% NaCMC p.o.

Group VI: Standard group animals received Indomethacin10mg/kg p.o.

The paw is marked with ink at the level of lateral malleolus and immersed in the mercury column of a Plethysmometer for measuring the paw volume. The paw volume was measured immediately after the Carrageenan injection and then at 3,6,12 and 24 hour. The percentage inhibition of inflammation was calculated by using the following formula:

$$\text{Percentage inhibition of inflammation} = \frac{A - B}{A} \times 100$$

Where, A and B denotes mean increase in paw volume of control and drug treated animals respectively.

2.7 Statistical analysis

Data obtained from pharmacological experiments were expressed as mean±SEM. The data were statistically analyzed by one way ANOVA followed by Dunnett's test.

RESULTS AND DISCUSSION

The preliminary phytochemical studies indicated the presence of alkaloids, flavonoids, terpenoids, tannins and carbohydrates. In acute toxicity study, the AEAS and AEPZ did not produced lethality up to the dose level of 5000mg/kg.

Effect of AEAS and AEPZ on blood glucose levels in normoglycemic rats showed the significant decrease in the blood glucose level at the doses of 800mg/kg. The results were shown in table-1. The mean blood glucose level maintained at 89.83 to 92.16 mg/dL at dose of 400mg/kg AEAS and 90.66 to 84.00 mg/dL at dose of 800mg/kg AEAS. The

mean blood glucose level decreased from 89.17 to 90.83 mg/dL at dose of 400mg/kg AEPZ and 92.00 to 83.00 mg/dL at dose of 800mg/kg AEPZ.

Table 1: Effect of AEAS and AEPZ on Blood Glucose Level in Normoglycemic Rats

Groups		Blood Glucose Level (mg/dL)				
		0 hour	1 hour	2 hours	3 hours	4 hours
I	Normal	90.16±1.08	88.67±1.28	87.16±2.40	85.00±2.32	91.17±2.24
II	AEAS 400mg	89.83±2.07	87.16±2.17	85.00±2.38	82.83±1.83	92.16±1.76
III	AEAS 800mg	90.66±1.98	87.00±1.53	84.00±1.39	77.67±1.69*	84.00±1.46
IV	AEPZ 400mg	89.17±1.80	87.50±1.73	87.16±2.27	83.16±1.78	90.83±2.09
V	AEPZ 800mg	92.00±1.95	89.33±1.80	79.33±1.40*	75.33±1.71**	83.00±1.75*
VI	Standard	89.50±2.45	85.50±1.65	77.00±1.73**	71.50±2.04**	80.50±2.81**

Values are expressed as Mean±SEM (n=6). * p<0.05, ** p<0.01. Statistical significant test for comparison was done by ANOVA , followed by Dunnett's test. The blood glucose values of group II to VI are compared with group I.

Effect of blood glucose levels on glucose fed hyperglycemic rats (Oral Glucose Tolerance Test) results were shown in Table-2. The mean blood glucose level decreased from 82.16 mg/dL to 84.50 mg/dL at dose of 400mg/kg AEAS and 84.33 mg/dL to 77.50 mg/dL at dose of 800mg/kg AEAS. The mean blood glucose level decrease from 86.00 mg/dL to 82.16 mg/dL at dose of 400mg/kg AEPZ and 87.67 mg/dL to 76.67 mg/dL at dose of 800mg/kg AEPZ.

Table 2: Effect of Blood Glucose Levels on Glucose fed Hyperglycemic Rats (Oral Glucose Tolerance Test)

Groups		Blood Glucose Level (mg/dL)				
		0 hour	1 hour	2 hour	3 hours	4 hours
I	Glucose	83.83±1.92	144.83±2.52	113.50±4.14	101.17±3.52	86.00±3.39
II	AEAS 400mg	82.16±1.85	144.50±2.67	132.33±3.90*	92.66±3.65	84.50±2.10
III	AEAS 800mg	84.33±1.52	150.33±2.66	135.00±4.97**	88.17±3.50*	77.50±1.41*
IV	AEPZ 400mg	86.00±2.30	141.00±2.48	130.17±3.82*	91.16±3.64	82.16±2.24
V	AEPZ 800mg	87.67±2.52	152.17±3.12	133.83±4.31**	86.33±3.01*	76.67±1.61*
VI	Standard	79.50±1.41	154.83±2.57	131.33±3.05*	82.83±3.08**	71.66±2.20**

Values are expressed as Mean±SEM (n=6). * p<0.05, ** p<0.01. Statistical significant test for comparison was done by ANOVA , followed by Dunnett's test. The blood glucose values of group II to VI are compared with group I.

In the effect of AEAS and AEPZ on blood glucose levels in streptozotocin induced diabetic rats, the blood glucose levels were measured in first to seventh groups of the experimental rats in initial and at the 5, 10 and 15 days of treatments are given in table-3. STZ induced diabetic rats showed significant increase in the level of blood sugar. Oral administration of AEAS and AEPZ showed the significant decrease on blood sugar level in 10 to 15 days of treatment. The blood glucose level of diabetic animals significantly reduced from 295.33 mg/dL to 286.17 mg/dL at dose of 400mg/kg AEAS and 268.00 mg/dL to 227.00 mg/dL at dose of 800mg/kg AEAS. The mean blood glucose level decrease from 296.16 mg/dL to 282.33 mg/dL at dose of 400mg/kg AEPZ and 270.50 mg/dL to 196.83 mg/dL at dose of 800mg/kg AEPZ. These results were comparable with 2.5mg/kg of glibenclamide which shows significant reduction of blood glucose level from 267.66 mg/dL to 150.16 mg/dL on 15th day.

Table 3: Effect of AEAS & AEPZ on Blood Glucose in Streptozotocin Induced Diabetic Rats

Groups		Blood Glucose Level (mg/dL)			
		Initial	Day 5	Day 10	Day 15
I	Normal Control	78.83±1.19	84.83±3.16	82.50±2.42	81.00±1.51
II	Diabetic Control	276.50±2.23	279.00±4.52	306.33±3.15	312.67±1.45
III	AEAS 400mg	295.33±6.82	291.83±3.72	289.66±3.60*	286.17±3.93**
IV	AEAS 800mg	268.00±4.47	264.16±4.73	256.00±3.80**	227.00±3.94**
V	AEPZ 400mg	296.16±6.64	290.00±4.75	287.33±4.01*	282.33±4.80**
VI	AEPZ 800mg	270.50±5.23	262.66±3.99*	232.83±4.42**	196.83±4.72**
VII	Standard	267.66±4.89	255.16±3.09**	219.67±5.15**	150.16±5.71**

Values are expressed as Mean±SEM (n=6). * p<0.05, ** p<0.01. Statistical significant test for comparison was done by ANOVA , followed by Dunnett's test. The blood glucose values of group III to VII are compared with group II.

The results of analgesic effect of AEAS and AEPZ in acetic acid induced writhing in mice were shown in Table-4. The number of writhes were significantly lower than the control group and the maximum inhibition is seen at AEPZ 800mg i.e., 52.94%. Standard drug has produced as protective effect and exhibited 74.84% of inhibition.

Table 4: Effect of AEAS and AEPZ by Acetic acid induced writhing in mice

Groups		Number of Writhing	Percentage of Inhibition
I	Control	51.00±3.11	--
II	AEAS 400mg	45.33±1.71	11.12%
III	AEAS 800mg	29.66±2.29**	41.84%
IV	AEPZ 400mg	40.16±2.36*	21.25%
V	AEPZ 800mg	24.00±1.98**	52.94%
VI	Standard	12.83±2.49**	74.84%

Values are expressed as Mean±SEM (n=6). * p<0.05, ** p<0.01, *** p<0.001 Statistical significant test for comparison was done by ANOVA, followed by Dunnett's test. The number of writhings of group II to VI are compared with group I.

The result of the hot plate method (Table-5) revealed that the reaction time for mice was significantly increased in a dose dependent manner. The reaction time significantly increases at a dose of AEPZ 800mg/kg i.e., 12.83 min at 120 min. The reaction time shown by the standard drug is 14 min.

Table 5: Analgesic effect of AEAS & AEPZ in mice by hot plate method

Groups		Reaction time (Seconds)				
		0 min	15 min	30 min	60 min	120 min
I	Control	6.50±0.76	6.66±0.71	7.00±0.78	7.33±0.49	7.50±0.56
II	AEAS 400mg	6.16±0.48	6.50±0.43	7.17±0.47	8.66±0.33	9.33±0.50*
III	AEAS 800mg	7.00±0.36	7.66±0.49	8.16±0.31	9.50±0.42*	12.67±0.42**
IV	AEPZ 400mg	6.50±0.62	6.83±0.40	7.50±0.43	9.33±0.49*	10.83±0.60**
V	AEPZ 800mg	7.33±0.56	8.00±0.45	9.33±0.42*	11.00±0.36**	12.83±0.31**
VI	Standard	6.67±0.49	8.66±0.49*	10.17±0.47**	12.67±0.61**	14.00±0.44**

Each value represents the mean±SEM, n=6. * p<0.05, ** p<0.01, Statistical significant test for comparison was done by ANOVA , followed by Dunnett's test. Groups II to VI are compared with group I.

The percentage inhibition of edema values of Carrageenan induced rat paw edema is given in table-6. The inhibition was higher at a dose of AEAS 800mg i.e., 60.32%. However the standard drug has exhibited the percentage inhibition of edema was 73.81%.

Table 6: Anti-inflammatory effect of AEAS and AEPZ on Carrageenan Induced Rat Paw Edema

Groups		Mean paw volume (ml)					Percentage inhibition at 24 hour
		0 hour	3 hour	6 hour	12 hour	24 hour	
I	Control	0.80 ± 0.09	1.43 ± 0.14	1.46 ± 0.12	1.36 ± 0.12	1.26 ± 0.12	-----
II	AEAS 400mg	0.86 ± 0.10	1.18 ± 0.07	1.16 ± 0.06	1.00 ± 0.07*	0.90 ± 0.09*	28.57%
III	AEAS 800mg	0.90 ± 0.08	1.10 ± 0.08	1.00 ± 0.10**	0.83 ± 0.08**	0.50 ± 0.07**	60.32%
IV	AEPZ 400mg	0.83 ± 0.08	1.23 ± 0.06	1.20 ± 0.07	1.10 ± 0.04	0.93 ± 0.04*	26.19%
V	AEPZ 800mg	0.86 ± 0.07	1.06 ± 0.06*	1.06 ± 0.08*	0.93 ± 0.10*	0.56 ± 0.09**	55.55%
VI	Standard	0.81 ± 0.08	1.00 ± 0.10*	0.96 ± 0.11**	0.70 ± 0.12**	0.33 ± 0.06**	73.81%

Values are expressed as Mean±SEM (n=6). * $p<0.05$, ** $p<0.01$. Statistical significant test for comparison was done by ANOVA, followed by Dunnett's test. The mean paw volumes of group II to VI are compared with group I.

CONCLUSION

The results of the pharmacological studies clearly demonstrates that the aqueous extracts of stem and leaves of *Alangium Salvifolium* and *Pavonia Zeylanica* has significant anti-diabetic activity in streptozotocin induced diabetic rats. Thus the present study supports the traditional folklore.

A variety of chemical agents have been used for producing pain. The intra peritoneal administration of noxious chemical substances to mice produces peritoneal irritation, which elicits a writhing response. Many chemical agents have been reported to produce writhing but acetic acid and phenylbenzoquinone are the two most commonly used irritants. In hot plate method a cut off period of 15 sec was observed to avoid damage to the paws.

Experimentally induced paw edema is one of the most commonly used methods employed for the evaluation of anti-inflammatory agents. Many phlogistic agents have been used for the induction of edema, among them Carrageenan been found to be the most suitable agent and provides a good predictive value for anti-inflammatory potential of a novel compound. The results of the present study confirm that aqueous extract of stem and leaves of Alangium Salvifolium and Pavonia Zeylanica has an analgesic and anti-inflammatory activities.

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