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Original Research Article

Evaluation of Antihypertensive Effect of Aqueous Methanol Extract of *Caralluma tuberculata* N.E.Br in Sprauge Dawley Rats

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Abstract

Purpose: *To evaluate the phytochemical profile and antihypertensive effect of Caralluma tuberculata N.E.Br (AMECT).*
Methods: *The antihypertensive effect of the aqueous methanol extract of (AMECT) was evaluated in both normotensive and hypertensive rats. In normotensive rats, various doses (100, 300 and 500 mg/kg body weight, p.o.) were administered at 0, 1, 3 and 6 hr intervals. Anti-hypertensive activity of the crude extract was investigated in three experimental hypertensive models, viz, egg-fed diet, glucose-induced and cadmium-induced hypertensive rats. Cardiovascular parameters, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) and heart rate (HR) were measured by tail cuff method using non-invasive blood pressure apparatus (NIBP) attached. AMECT was also investigated for its phytochemical profile.*
Results: *The results indicate that AMECT produced a dose-dependent, significant ($p < 0.05$) decrease in SBP, DBP, MBP, and HR ($p < 0.01$) of normotensive rats, when compared to control groups, at all test doses. The 500 mg/kg dose produced a highly significant effect (mm Hg, $p < 0.001$) in SBP (85.9 ± 7.2), DBP (71.86 ± 12.1), MBP (75.1 ± 11.7) and HR (238.08 ± 8.3 beats/min), in comparison to 100 and 300 mg/kg doses; therefore, 500 mg/kg was selected for antihypertensive test in egg-fed, glucose-induced and cadmium-treated hypertensive rats. Significant ($p < 0.05$) antihypertensive and negative chronotropic effects were observed in hypertensive models compared to their respective normal controls. Phytochemical analysis revealed the presence of tannins, alkaloids, phenolic compounds, cardiac glycosides and flavonoids.*
Conclusion: *The findings indicate that Caralluma tuberculata possesses significant anti-hypentensive activity in rats.*

Keywords: *Phytochemical profile, Antihypertensive, Cardiovascular, Caralluma tuberculata N.E.Br, Blood pressure*

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INTRODUCTION

Hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through blood vessels. [1]. Hypertension has been defined by the World Health Organization as a persistent

increase of systemic blood pressure > 140 mm Hg systolic or > 90 mm Hg diastolic, or both. Systemic hypertension is one of the most prevalent and serious causes of coronary artery and myocardial disease globally [2]. Hypertension remains a major health problem globally because of its impact on mortality and morbidity. According to World Health Organization (WHO) report, hypertension is estimated to cause 7.1 million premature deaths and 4.5 % of disease burden annually [3].

Most antihypertensive drugs have been evaluated for a number of specific patient populations; these include Angiotensin converting enzyme (ACE) inhibitors, β -blockers, calcium channel blockers and diuretics in patients with associated diabetes, nephropathy, coronary and cerebrovascular disease, heart failure, and left ventricular hypertrophy [4]. The side effects of these synthetic medicines have also been reported. For example, dry cough is a common side-effect of ACE inhibitors and is a major limiting factor of their use [5].

To treat hypertension, plants derived drugs have been used, such as *Allium sativum*, reserpine and rescinnamine from *Rauwolfia serpentina*, rhomitoxin from *Rhododendron molle*, protoveratrine A and B from *Veratrum album* and tetrandrine from *Stephenia tetradra* [6-8].

Caralluma of the family Asclepiadaceae is a genus of about a hundred species, distributed in Africa, Spain, Saudi Arabia, Middle East, Pakistan and India. In Pakistan, it is represented by two species viz., *Caralluma edulis* and *Caralluma tuberculata* [9].The local names of *Caralluma tuberculate* in different languages like Caralluma in English, Chunga in Urdu and Pamankay in Pushto. *Caralluma tuberculata* N.E.Br has been claimed traditionally to have several biological activities. The shoots of *Caralluma tuberculata* N.E.Br. have anti-hypertensive, anti-diabetic and anti-pyretic activity [10]. The aim of this study is to investigate the scientific basis for the traditional use of AMECT in hypertension treatment.

EXPERIMENTAL

Equipment

The equipment included in study were non-invasive blood pressure (NIBP) measuring apparatus (model no. ML125, AD Instruments, Australia), Power Lab Data Acquisition System (model no. ML865, AD Instruments), restrainers, Chart 5.0 software (AD Instruments), weighing balance (Shimadzu Corporation, Japan) and Herbal Grinder (SQW-100DFL, Shandong Sanqing Stainless Steel Equipment Co., Ltd. China).

Chemicals and drugs

The chemicals and drugs used were glucose 10 %, cadmium chloride, egg feed diet, normal saline (0.9 % NaCl) and distilled water. All chemicals were purchased from Sigma Chemical Co (St Louis, MO, USA).

Animals and housing conditions

Both adult male and female Sprague-Dawley rats (170-350 g) were used. Each of these animals was housed in controlled environment (23-25 °C) at animal house and provided human care in accordance with the National Institute of Health (NIH) guide for the care and use of laboratory animals. The study protocol was approved by the institutional Animal Ethics committee Faculty of Pharmacy, University of Sargodha (Approval no.30-B12 IEC UOS). Experiments comply with the declarations of National Research Council [11].

Collection and identification

A total of 5 kg of fresh plant was collected from the hilly area of Malakand district, Pakistan during the month of November 2012 and was authenticated by Dr Ameen Shah, a taxonomist in the Department of Biological sciences, University of Sargodha, Sargodha. A voucher specimen (no. AO-12) was deposited in the herbarium of the Faculty of Pharmacy, University of Sargodha for future reference.

Extraction procedure

The *Caralluma tuberculata* N.E.Br. was washed to remove any contaminants. Only shoots were used for study and then dried under shade at room temperature. The dried plant material was grounded into a course powder form by using china herbal grinder. Aqueous methanol (70:30) extract of the plant was prepared using cold maceration process. The plant material was then soaked in 3 L of 70 % aqueous methanol and kept for a total of 3 days (72 h) at room temperature, with occasional shaking. After 3 days, it was filtered through a porous cloth, the filtrate was collected, and the plant material was again soaked in 3 L of water for 3 days, twice. At the end, all of the three filtrates were combined, filtered through muslin cloth and Whatman qualitative Grade 1 filter paper. The filtrate of the extract was evaporated under reduced pressure

in rotary evaporator at 50 °C. This aqueous methanol extract was then air-dried to obtain a solid mass. The crude extract was dark brown in color [12].

Determination of extract yield

The percentage yield of the extract was determined gravimetrically using the dry weight of extract (x) and soaked samples material (y) as follows:

Percentage yield = x/y ×100 [13]

Assessment of hypotensive effect in normotensive rats

After an initial preliminary screening the dose with better results was used to study hypotensive effects in normotensive rats. Animals were divided into three groups of n=4 animals each. Group I, Group II and Group III were treated with 100 mg, 300 mg and 500 mg/kg of aqueous methanol extract respectively. The blood pressure (BP) of normotensive rats was noted at 0, 1, 3 and 6 h by using non-invasive blood pressure apparatus via the tail of rats (NIBP) [14]. For the test, the animals were placed in NIBP restrainer. The appropriate cuff with sensor was mounted on their tails and warmed to about 33–35 °C. The tail cuff was inflated to a pressure well above the expected SBP and slowly released during which the pulse rate was recorded by the BP analyzer. The SBP and MBP were read from the pulse tracings. Heart rate was also recorded. The DBP of both control and treated groups were calculated from SBP and MBP as in Eq (1) [15].

DBP = (3MBP – SBP)/2 …….(1)

Assessment of antihypertensive effect

Egg-feed diet-induced hypertensive model

Sprague Dawley Rats of either sex weighing 200-300 g were randomly assigned into two groups of n=4 animals each. Group 1 served as a control and was treated with a specially prepared egg-feed diet in order to produce cholesterol-induced hypertension. The diet was prepared by the addition of 12 eggs yolk to 500 g standard diet. The feed so prepared was dried in sunlight for 3 days. Animals were fed on this diet for 9 consecutive days [14]. Group II (treated group) was treated with egg feed diet and aqueous methanol extract 500 mg/kg for nine (9) consecutive days orally. Animals in both groups were given normal saline instead of tap water *ad libitum*. BP and heart rate of each of these groups were measured at day 0, 3, 6 and day 9. The onward steps were followed like the previous experiment [15].

Glucose-induced hypertensive model

Sprague Dawley rats of either sex were randomly divided into two groups (n = 4). Group I served as control and received 10 % glucose solution instead of tap water for 21 consecutive days. Animals in group II was given 10 % glucose solution and aqueous methanol extract for 21 consecutive days orally. Animals were fed on standard diet while tap water was given *ad libitum*. BP and heart rate of each of these groups were measured at 0,3,6,9,12,15,18 and 21 day. The next steps were followed like previous experiment [15,16].

Cadmium-induced hypertensive model

The selected rats of either sex were randomly divided into two groups of n=4 animals in each group. Group I served as cadmium control and received cadmium chloride (1 mg/kg, i.p.) dissolved in 0.9 % saline daily for 2 weeks to induce hypertension [14]. Animals in group II were given cadmium chloride (1 mg/kg, i.p.) and aqueous methanol extract for two weeks. Animals were fed on standard diet while tap water was given *ad libitum*. BP and heart rate of each of these groups were measured at 0, 3, 6, 9, 12 and 15 days. The subsequent steps were repeated like previous one [15].

Preliminary phytochemical screening

The phytochemical screening of AMECT was analyzed for the presence of different phytochemical groups such as saponins, flavonoids, cardiac glycosides, tannins, phenolic compounds, steroids, terpenoids, alkaloids using standard procedures [17].

Statistical analysis

The results were expressed as means ± standard error of mean (S.E.M) and statistical analysis was carried out by Student's t-test for all the experiments except for screening of 100, 300 and 500mg/kg doses for which one-way ANOVA followed by post- hoc Dunnett test was applied using Graph Pad Prism 5.0. $P < 0.05$ was considered statistically significant.

RESULTS

The extract yield was 12 %.

Hypotensive effect of AMECT

Normotensive rats

In normotensive rats, AMECT at all doses showed a significant decrease in SBP ($p < 0.05$) and MBP ($p < 0.05$) at 1st hour. Similarly, a highly significant reduction in DBP ($p < 0.001$) and MBP was observed at 3rd hour. The extract also exhibited a significant decrease in SBP ($p < 0.05$) at 1st and 3rd hour. However, at 6th hour, AMECT at all doses produced a non-significant fall in SBP, DBP and MBP. Moreover, the extract revealed a highly significant decrease in HR ($p < 0.01$) at 1st and 3rd hour, while a slightly significant reduction in heart was observed at 6th hour. A maximum decrease in all parameters was observed at 500 mg/kg (p.o.) dose as compared to 100 and 300 mg/kg doses (Tables 1 and 2).

Egg-feed diet-induced hypertensive rats

After initial screening in normotensive rats, the 500 mg/kg dose produced a significant effect as compared to 100 and 300 mg/kg, therefore 500 mg/kg was selected for antihypertensive study in hypertensive models. In egg feed-induced hypertensive rats, AMECT (500 mg/kg) exhibited a significant ($p < 0.01$) reduction in SBP, MBP, DBP and HR at 3, 6 and 9 days (Table 3), when compared with control.

Glucose-induced hypertensive rats

In glucose-induced hypertensive rats, AMECT exhibited a highly significant decrease ($p < 0.001$) in SBP, DBP, MBP and HR at 3, 9, 12, 15, 18 and 21 days when compared with control (Table 4).

Cadmium-induced hypertensive rats

In cadmium induced hypertensive rats, AMECT exhibited a highly significant decrease ($p < 0.001$) in SBP, DBP, MBP and HR at 3, 6, 9, 12 and 15 days when compared with control (Table 5).

Phytochemical profile

The phytochemical profile of AMECT indicate the presence of various secondary metabolites including saponins, flavonoids, cardiac glycosides, tannins, phenolic compounds, steroids, terpenoids and alkaloids (Table 8).

Table 1: Effect of AMECT on the blood pressure of normotensive rats

Time (h)	SBP (mmHg)			DBP(mmHg)			MBP(mmHg)		
	100 mg/kg	***300 mg/kg***	***500 mg/kg***	***100 mg/kg***	***300 mg/kg***	***500 mg/kg***	***100 mg/kg***	***300 mg/kg***	***500 mg/kg***
0	134 ±4.4	135.4 ±9.03	129.5 ±3.7	111.93 ±6.7	119.3 ±8.6	113.1 ±8.5	119.2 ±6.0	124.4 ±8.7	118.6 ±6.9
1	110.4 ±2.5**	102.9 ±12.5**	104.6 ±5.4**	100.13 ±2.2*	93.33 ±6.4*	75.31 ±5.5*	103.6 ±2.36*	97.2 ±6.55*	80.6 ±6.3**
3	111 ±8.6**	98.9 ±17.5**	85.9 ±7.2***	97.83 ±7.9*	87.6 ±9.0*	71.86 ±12.1*	102.2 ±8.15**	91.6 ±8.78**	75.1 ±11.7***
6	126.2 ±4.8	126.5 ±3.18	119.3 ±6.9	108.3 ±7.24	103.6 ±7.3	100.6 ±1.49	114.1 ±6.38	109.6 ±6.8	106.6 ± 1.2

Results are expressed as mean ± SEM (n = 4). ***Key****: * p < 0.05, ** p < 0.01, *** p < 0.001; n.s. = not significant, compared with. control (0)*

Table 2: Effect of AMECT on heart rate (HR) of normotensive rats

	HR (beat/min)		
Time (h)	***100 mg/kg***	***300mg/kg***	***500 mg/kg***
0	353.03±9.07	368.30±1.92	352.48±1.46
1	303.64±1.63**	273.97±7.65**	238.08±8.37**
3	286.37±0.69**	284.40±7.90**	247.83±2.12**
6	324.74±2.06*	298.75±2.43*	261.32±12.18*

Results are expressed as mean ± SEM (n = 4). ***Key****: * p < 0.05, ** p < 0.01, *** p < 0.001; n.s. = not significant, compared with. control (0)*

Table 3: Effect of AMECT on the blood pressure and heart rate (HR) of egg-feed diet-induced hypertensive rats

	SBP (mmHg)		DBP(mmHg)		MBP(mmHg)		HR (Beat/min)	
Days	***C G***	***T G***	***C G***	***T G***	***C G***	***T G***	***C G***	***T G***
0	127.3 ±4.0	111.4 ±4.8	120.6 ±2.6	100.1 ±3.1	118.8 ±0.7	105.5 ±5.3	343.2 ±1.4	383.2 ±0.4
3	155.6 ±3.2	100.6 ± 1.7**	150.7 ±2.9	91.4 ±1.8**	157.3 ±1.9	94.3 ±1.7**	352.7 ±1.3	377.7 ±0.3**
6	168.8 ±1.7	90.9 ±8.6**	160.3± 0.7	77.6 ±5.3**	165.4 ±2.3	76.2 ±6.2**	394.2 ±1.4	369.2 ±0.7**
9	177.5 ±3.5	93.8 ±5.7**	167.9 ±1.4	87.6 ±5.0**	173.5 ±1.8	90.3± 5.2**	369.7 ±1.1	359.1 ±0.6**

Results are expressed as means ± SEM (n = 4). ***Key:*** ** p < 0.05, ** p < 0.01, vs. control group (egg-feed group); treated group: egg-feed diet; + AMECT (500 mg/kg); C = Control, G = group and T = treated*

Table 4: Effect of AMECT on blood pressure of glucose-induced hypertensive rats

Days	SBP (mmHg)		DBP(mmHg)		MBP(mmHg)	
	G C	***T G***	***G C***	***T G***	***G C***	***T G***
0	132.7 ±6.7	136.2 ±3.43	117.1 ±0.9	121.9 ±1.6	128.4 ±9.2	126.8 ±1.5
3	139.2 ±1.9	107.9 ±2.1***	134.2 ±1.7	101.7 ±5.8***	136 ±2.0	104.8 ±5.7***
6	149.9 ±2.4	104.3 ±2.1***	140.5 ±0.6	98.8 ± 5.6***	142 ±1.4	101.6 ±5.3***
9	152.9 ±1.5	102.8 ±6.2***	145.5 ±2.8	88.6 ±6.4***	147 ±0.9	93.1 ±6.5***
12	158.9 ±2.6	111.6 ±5.2***	149.6 ±3.3	95.9± 8.4***	151 ±0.8	100.1 ±6.3***
15	163.5 ±1.4	94.6 ±6.1***	155.8 ±0.8	83.0 ±6.6***	160 ±1.8	86.9 ± 6.1***
18	168.2 ±1.8	91.7 ± 3.5***	160.9 ±1.6	80.3 ± 3.1***	165 ±1.9	83.2 ±3.8***
21	172.9 ±1.6	85.5 ±6.8***	165.4 ±3.0	73.7 ± 6.6***	170 ±2.5	77.7 ±6.7***

Results are expressed as mean ± SEM (n = 4). ***Key:*** ****p < 0.001) compared to control group (Glucose-induced group); treated group = glucose + AMECT (500mg/kg). G = Glucose, C = Control and T = Treated.*

Table 5: Effect of AMECT on the heart rate (HR) of glucose-induced hypertensive rats

HR (beat/min)	
GC	***TG***
352.9 ±3.9	344.1 ±5.0
359 ±7.2	272.8 ±9.1***
363.7 ±6.1	298.1 ±3.9***
381.1 ±2.7	277.7 ±8.5***
387.8 ±4.1	255.9 ±2.7***
377.1 ±9.9	229.2 ±5.8***
352.2 ±9.3	235.5 ±7.8***
377 ± 1.4	216.1 ±7.9***

Results are expressed as mean ± SEM (n = 4). ***Key:*** ****p < 0.001) compared to control group (Glucose-induced group); treated group = glucose + AMECT (500mg/kg). G = Glucose, C = Control, and T = Treated*

DISCUSSION

From thousands of years medicine and natural products have been closely interconnected through the use of traditional medicine. Despite competition from other drug discovery methods, natural products are still providing their fair share of new clinical candidates [18].

Plants of the apocynaceae family are rich in alkaloids or glycosides, especially in the seeds and latex. Some species are valuable sources of medicine, insecticides, fibers, and rubber [19]. An aqueous methanol extract prepared from the shoots of *Caralluma tuberculata* N.E.Br was used to explore the potential effects on certain anti-hypertensive parameters by performing both *in vivo* and *in vitro* experiments.

Table 6: Effect of AMECT on the blood pressure of cadmium-induced hypertensive rats

Days	SBP (mmHg)		DBP(mmHg)		MBP(mmHg)	
	C* C	***T G***	***C* C***	***T G***	***C* C***	***T G***
0	119.5 ±0.8	131.5 ±1.05	116.2 ±1.2	113.4 ±2.1	117.3 ±0.7	121.1 ±0.8
3	144.2 ±0.6	101.3 ±4.2***	139.6 ±0.5	92.1 ±5.9***	141.5 ±0.4	96.3 ±4.3***
6	155.0 ±0.6	98.6 ±0.8***	149.4 ±2.3	89.6 ±3.1***	151.5 ±0.5	92.1 ±2.1***
9	166.6 ±0.6	107.3 ±4.7***	160.8 ±0.8	93.4 ±3.6***	161.6 ±0.4	99.3 ±1.0***
12	175.9 ±1.9	99.4 ±3.1***	170.6 ±3.1	88.8 ±5.9***	172.4 ±1.7	92.4 ±5.1***
15	170.6 ±.5	89.4 ±3.1***	165.1 ±3.2	78.5 ±5.2***	167.6 ±1.8	77.4 ±4.9***

Results are expressed as means ± SEM (n = 4); ***Key:*** *where:* *** *p < 0.001 compared to control (Cadmium induced group). Treated group: Cadmium + AMECT (500 mg/kg). (Where C*= Cadmium-induced, C= Control, T= Treated Group).*

Table 7: Effect of AMECT on HR of glucose-induced hypertensive rats

HR(beat/min)	
C* C	***T G***
387 ±1.27	353.3 ±1.4
407.3 ±5.3	318.5 ±9.5***
425.1 ±3.4	275.4 ±3.1***
424.8 ±2.9	523.5 ±8.4***
425.2 ±2.2	215.5 ±3.2***
442.1 ±2.4	229.7 ±3.7***

Results are expressed as mean ± SEM (n = 4). ***Key:*** *where: *** p < 0.001 compared to control (cadmium-induced group).* ***Treated group:*** *cadmium + AMECT (500 mg/kg); C* = cadmium-induced, C = control, T= treated group*

In normotensive rats, the hypotensive effect of AMECT was determined at various doses by using NIBP. The results indicate that the extract produced a dose-dependent decrease in SBP, DBP, MBP and heart rate of normotensive rats, with maximum effect at 500 mg/kg. Hence this dose was selected for antihypertensive study in egg feed, glucose and cadmium induced hypertensive rats. In hypertensive models, the extract exhibited a significant decrease in SBP, DBP, MBP and heart rate of rats.

Previously, it has been reported that saturated fats present in egg yolk cause hypercholesterolemia, which is a major risk factor for cardiovascular diseases like hypertension. Cholesterol rich diet and high glucose intake have also been linked to dyslipidemia which is considered a major risk factor for hypertension [20,21]. The study shows that egg feed is rich in cholesterol also induced hypertension in rats [16]. The hypholipidemic activity of *Caralluma tuberculate* has previously been reported by Abdel-Sattar *et al* [22]. In rats, glucose-induced hypertension has been linked with increased reactive oxygen species production as well as reduction in nitric oxide (NO) levels [19,20]. It has been reported that plants rich in polyphenols have antioxidant effect which minimizes endothelial dysfunction through increased NO formation, decreased LDL formation, increased prostacyclin formation, increased EDHF mediated vasorelaxation and decreased endothelin-1 production. Thus, polyphenols' beneficial vasorelaxation effects have been attributed to exert blood pressure reduction in rats [25]. Moreover, studies show that cadmium exerts its hypertensive effects by interacting with calcium channels as a partial agonist and producing direct contractile effect on vascular smooth muscle [26]. The hypertensive effect of cadmium exposure results from complex actions on both vascular endothelial cells and vascular smooth muscle cells [27]. This study provides evidence concerning the significant effects of *Caralluma tuberculate* in ameliorating hypertension, vascular dysfunction in rats after cadmium exposure.

Decrease in blood pressure produced by AMECT was much higher in hypertensive rats than in normotensive rats. This is in agreement with

Table 8: Phytochemical profile of the extract

Secondary metabolite	Observation	Relative presence
Alkaloids	Coloured ppt present	+ + + +
Tannins	Dark green solution/or blue-black precipitate	+ + + +
Phenols	Blue-black precipitate	+ + + +
Flavonoids	Yellow solution that turns to colourless	+ + + + +
Saponins	Persistent froth	+ + + +
Cardiac glycosides	Reddish brown layer formed at interface	+ + + + +
Steroids	Blue green ring	+ + +
Terpenoids	Reddish brown coloration	+ + + +

Key: *Very high level = + + + + +; High level = + + + +; Moderate level = + + +*

previous findings that hypertensive rats appear to have a stronger response to hypotensive agents [28].

Thus, the antihypertensive effect of AMECT in egg feed, glucose and cadmium induced hypertensive rats might be due to certain hypolipidemic, antioxidant, vasodilator and depressor activities of the plant extract. In another study, the aqueous methanol extract significantly caused a reduction in the SBP, DBP, MBP, heart rate and body weight of normotensive rats at 14, 21 and 28 days. These results indicated that the aqueous methanol extract has both antihypertensive and hypotensive effects. Since decrease in heart rate leads to reduced blood pressure, decrease in heart rate might also have contributed to the antihypertensive effect of the extract [29].

The phytochemical profile of the extract revealed that it contains certain biologically active compounds. It has been well established that cardiac glycosides are involved in antihypertensive effects. Similarly, plant species containing certain alkaloids, phenols and flavonoids have been reported to exhibit antihypertensive activity [30]. Hence, the antihypertensive activity of the extract might also be due to the presence of these phytochemical constituents.

CONCLUSION

Caralluma tuberculata extract exerts significant antihypertensive activity in rats and this appears to be due to the various bioactive compounds in the plant. Thus, there is need for activity-directed fractionation of this extract to isolate the active principle(s) in order to elucidate their exact mechanisms of action.

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