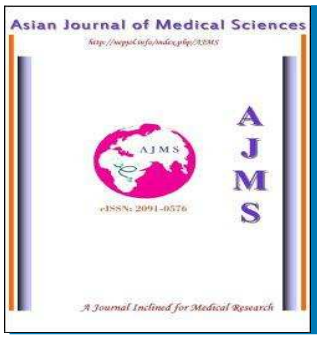

NEPHROPROTECTIVE EFFECTS OF CARVEDILOL AND *CURCUMA LONGA* AGAINST CISPLATIN-INDUCED NEPHROTOXICITY IN RATS

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"The efficacy of cisplatin in clinical use as a chemotherapeutic agent could be enhanced by co-treatment with nephroprotective agents."

ABSTRACT

Objective: Goal of this study is to investigate the effects of carvedilol (5 mg/kg, p.o), aqueous and methanolic extract of *Curcuma longa* (500mg/kg, p.o) against cisplatin induced renal damage in Wistar rats after a single intraperitoneal injection of 7.5mg^{-1}.

Methods: Wistar rats were randomly divided into 7 groups (n=10). Rats in group I were normal control received normal saline (5 ml/kg; i. p.) on day zero, while group VIa and VIb were vehicle control, received carboxymethyl cellulose (2.5 ml/kg; p.o.) and propylene glycole (2.5 ml/kg, p.o.) respectively from day 3 to 17. Renal toxicity was induced in rats of group II, III, IV and V by a single administration of cisplatin (7.5 mg/kg; i. p.) on day zero. Rats in group III, IV and V received a daily dose of carvedilol (5 mg/kg; p.o.), aqueous and methanolic extracts of *Curcuma longa* (500 mg/kg; p.o.) respectively from day 3 to 17, while group II served as cisplatin control.

Results: Post treated rats with carvedilol and aqueous and methanolic extracts of *Curcuma longa* for 15 days significantly increased body weight, decreased cisplatin induced abnormalities and mortality and decreased all the kidney marker such as serum urea nitrogen (SUN), serum creatinine (SCr), total proteins (TP), and uric acid (UA) increased by cisplatin, however, no appreciable improvement in hematological parameters were observed when compared with cisplatin control.

Conclusion: The results are indicative of nephroprotective effects of carvedilol as well as aqueous and methanolic extracts of *Curcuma longa*.

Key words: Cisplatin; Nephrotoxicity; Carvedilol; *Curcuma longa*.

INTRODUCTION

Cisplatin (cis-dichlorodiammineplatinum II) is a simple platinum complex, a widely used anti-neoplastic agent in the treatment of varieties of solid tumors however; the clinical usefulness of cisplatin has been seriously restricted because of its dose dependent nephrotoxic side effects.[1] Though several distinct hypothesized mechanisms have been projected for cisplatin toxicity in renal tubule cells, oxidative stress results from generation of free radicals by cisplatin mediated lipid peroxidation in kidney[2] are the main factor for its causation. Carvedilol is a non selective beta blocker with vasodilatory properties due to alpha-1 blockade. Interestingly it also possesses antioxidant and oxygen free radical scavenging properties.[3] Therefore, because of its unique properties the attempts are being made to know the effect of carvedilol as a synthetic agent on cisplatin induced nephrotoxicity model in rats. Unfortunately, synthetic agents are not without toxicity, so the consumption of botanicals as alternative medicine has been encouraged because they are relatively cheap, to their less frequent side effects and their significantly contribution to the improvement of human health in term of cure and prevention of various disorder compared to modern medicine.[4] *Curcuma longa Linn*. (Turmeric) belongs to family *Zingiberaceae* a yellow food color and ingredient in curry powder for a long time has been used in Asian traditional medicines as a stomach tonic, blood purifier and for the treatment of skin disease and wound healing.[5] Recently many studies revealed that *Curcuma longa* possesses anti-inflammatory, antioxidant, anticarcinogenic and hepatoprotective properties. Therefore an attempt is being made to study the effect of extract of rhizome of *Curcuma longa* in cisplatin induced nephrotoxicity in rats.

MATERIALS AND METHODS

Experimental animals

Wistar rats (150-200g) were procured from the Shree Farm, Maharashtra, India, and housed in a temperature-controlled condition (22±20 C) with 12:12 light: day cycle and maintained on standard rodent diet with ad libitum fresh drinking water throughout the experiment. All experimental procedures were conducted according to ethical principles for the evaluation of pain in conscious animals and to ethical guidelines of the CPCSEA. All animal experiments were duly approved by Institute Animal Ethics Committee.

Collection of plant material and preparation of extracts

The dried rhizomes of *Curcuma longa L*. were purchased from local market in Parbhani, Maharashtra, India in months of February, 2010 and 95% methanolic (20% w/v) and aqueous (10% w/v) extracts of rhizome of *curcuma longa* were prepared. The percent (%) extractability of rhizomes powder was calculated for both the extracts by following formula.

% extractability = Total amount of extract/ Total weight of powder taken for extract x 100

The final extract (methanol and water free) of rhizomes were preserved in refrigerator at 4^{o}C for further use.

Phytochemical studies

Phytochemical studies of methanolic and aqueous extract of *Curcuma longa Linn*. Rhizomes were carried out as per method described by Das *et al*.[6] and Tendale *et al*.[7] for presence of various phytochemicals.

Induction of nephrotoxicity

Cisplatin, 1 mg/ml (cytoplatin 50) was purchased from local Pharmacist, Parbhani, was injected intraperitoneally in rats, singly at dose rate of 7.5 mg/kg body weight by a sterile needle and syringe to experimentally induced nephrotoxicity, which was confirmed by various analysis such as biochemically.

Experimental protocol

Seventy Wistar rats were assigned randomly to 7 groups (each, n=10). Group I was normal control received normal saline (5 ml/kg, i. p.) as single dose on day zero. Group II, III, IV, and V received cisplatin (7.5 mg/kg, i. p.) as single dose on day zero. Group II was served as cisplatin control while group III, IV, and V received carvedilol (5 mg/kg, p.o. in 0.5% CMC), aqueous (500 mg/kg, p.o. in 0.5 % CMC) and methanolic extract of *curcuma longa* (500 mg/kg, p.o. in propylene glycol) from day 3 to day 17. Group-VIa and VIb received only0.5% CMC and propylene glycol (PG) respectively

(2.5 ml/kg, p.o.) from day 3 to day 17 and served as CMC and PG vehicle control. After the administration of last dose treatment, rats were sacrificed for the studies of cisplatin and different treatment groups for various parameters.

General observations and body weight

All the rats were continuously observed for behavioural and any other signs and appearance of any visible treatment related adverse reactions throughout the experimental period. Rats of all the groups were monitored regularly for alteration in body weight at every 3 days throughout the experimental periods. The per cent change in body was calculated as follows.

% change in body weight = Final body weight - Initial body weight/Initial body weight x 100

Mean survival time (MST)

The death pattern of animals due to cisplatin toxicity was calculated as described by Jagetia *et al*. [8] The MST was calculated from the animals dying during observation period of 18 days and those surviving 18 days periods. The MST of a group of animals is expressed as quotient obtained by dividing total number of days rats were observed by the total number of animals in the group.

Hematological studies

Fasting blood of 0.5 ml were collected from a rats on day zero and 24 hours after last treatment (day 18^{th}) from the retro orbital plexus and hematological parameters such as total erythrocyte count (TEC), total leukocyte count (TLC), hemoglobin (Hb), packed cell volume (PCV) and thromybocyte count were determined, by auto analyzer.

Biochemical studies

The blood sample of 2-3 ml after 24 hours fasting were collected from rats on day zero and 24 hours after last treatment (day 18th) in non heparinized tube from the retro orbital plexus. Serum was separated by centrifugation for 10 minutes at 3000 rpm and stored at -20^{o}C until analysis. The samples were analyzed for serum urea nitrogen (SUN) by modified Berthelot method, serum creatinine (SCr) by alkaline picrate method, uric acid (UA) by uricase/POD method, and total protein (TP) by Biuret method. The biochemical estimation were carried out by using Ambica Diagnostic reagent kits in autoanalyser slim (SEAC).

Statistical analysis

The data obtained from various parameters from all the groups were analyzed using Completely Randomized Block Design or one way ANOVA followed by Tukey test as post ANOVA analysis by using Assistat computer software. The treatment means were compared by critical differences by statistical method and all the values in test are expressed as mean $\pm$ SE.

RESULTS

Phytochemical studies

The phytochemical analysis of the aqueous and methanolic extracts of *Curcuma longa* rhizomes showed positive tests for reducing sugar, protein, glycosides, saponin and flavonoids in aqueous extracts, and positive tests for alkaloids, reducing sugar, phenolic compounds, flavonoids, saponine, protein, glycosides, tannin and curcuminoids in methanolic extracts.

Extractability

The extractability of aqueous and methanolic extracts of *Curcuma longa* rhizomes powder was observed to be 7.6 per cent and 8 per cent, respectively.

General observation

No animals from normal and vehicle control groups showed signs of any abnormalities during experimental period, while almost all the rats of cisplatin control group showed marked dullness and depression. 30% showed gastrointestinal disturbances manifested by severe foul smelling diarrhea, nervous abnormalities manifested by paralysis and circling movement in cisplatin control group. Rats treated with carvedilol also showed similar abnormalities as cisplatin control, however, the severity was at lesser proportion (10%). Moreover, rats treated with aqueous and methanolic extracts of *Curcuma longa* did not show signs of any abnormalities during experimental period.

Effect on body weight

Table 1 shows the effect of carvedilol, aqueous and methanolic extract of *Curcuma longa* on mean body weight and per cent change in body weight of different groups over the duration of study. All the animals in group II, III, IV and V which received cisplatin (7.5 mg/kg; i. p.) on day zero, showed marked reduction in body weight on day 3 when compared with normal

Table 1 Mean body weight (g) changes in different treatment groups.

Group No.	0th day (Mean ± SE)	3rd days (Mean ± SE)	% change	6th days (Mean ± SE)	% change	9th days (Mean ± SE)	% change	12th days (Mean ± SE)	% change	15th days (Mean ± SE)	% change	18th days (Mean ± SE)	% change
I	176.8 ± 4.56^{a}	183.6 ±4.47^{a}	3.86	192.0 ±4.65^{a}	8.61	199.8 ±4.92^{a}	10.05	206.1 ±5.07^{a}	16.64	212.4 ±4.98^{a}	20.24	219.2 ±5.13^{a}	24.07
II	174.6 ±4.56^{a}	165.4 ±3.92^{abc}	-5.13	157.7 ±4.00^{bc}	-10.03	152.5 ±4.12^{c}	-22.46	157.3 ±4.82^{c}	-9.73	162.9 ±3.88^{c}	-6.55	166.4 ± 4.82^{d}	-4.49
III	158.8 ± 4.39^{a}	150.8 ± 3.80^{c}	-5.03	150.4 ± 3.98^{c}	-5.34	154.8 ± 4.13^{c}	-2.62	163.3 ±4.90^{c}	2.73	171.0 ±3.98^{c}	7.64	177.8 ±4.90^{cd}	11.96
IV	161.8 ±4.20^{a}	153.0 ±8.82^{bc}	-5.37	156.0 ±3.99^{bc}	-3.46	164.0 ±4.50^{bc}	1.56	173.4 ±5.00^{bc}	7.35	183.3 ±4.00^{bc}	13.42	194.3 ±4.98^{bc}	20.18
V	178.4 ±5.96^{a}	168.5 ±3.96^{abc}	-5.63	173.8 ±4.08^{ab}	-2.41	182.5 ±4.98^{ab}	2.32	192.0 ±5.05^{bc}	7.67	200.5 ±4.96^{ab}	12.54	208.4 ±5.00^{ab}	17.06
VIa	168.6 ±4.98^{a}	175.2 ±4.10^{a}	4.68	181.8 ±4.60^{a}	7.92	188.1 ±4.87^{a}	11.66	194.8 ±5.06^{ab}	15.58	202.3 ±4.96^{ab}	20.13	209.8 ±5.10^{ab}	24.60
VIb	165.7 ±4.21^{a}	172.1 ±4.00^{ab}	3.92	180.1 ±4.60^{a}	8.83	185.6 ±4.90^{a}	12.22	182.4 ±4.98^{abc}	16.32	198.9 ±4.95^{ab}	20.27	206.5 ±5.00^{ab}	24.89
SMD	**19.65***	**19.26****		**20.03****		**21.18****		**25.70****		**21.47****		**22.07****	

Table 2 Mean survival time (MST) of different treatment groups.

Groups	Treatment groups	Number of survival / Total number of rats at 18th days	% Survival	MST (days)
I	Normal control	10/10	100	18
II	Cisplatin control (7.5 mg/kg; i. p.)	8/10	80	15.9
III	Cisplatin (7.5 mg/kg; i. p.) + carvedilol (5 mg/kg; p.o.)	9/10	90	17.1
IV	Cisplatin (7.5 mg/kg; i. p.) + aqueous extracts of *Curcuma longa* (500 mg/kg; p.o.)	10/10	100	18
V	Cisplatin (7.5 mg/kg; i. p.) + methanolic extracts of *Curcuma longa* (500 mg/kg; p.o.)	10/10	100	18
VIa	Carboxymethyl cellulose control	10/10	100	18
VIb	Propylene glycole control	10/10	100	18

MST – Mean survival time. Experiment was conducted for 18 days.

Table 3 Effect of carvedilol and *Curcuma longa* extract on various hematological parameters in cisplatin induced nephrotoxicity

Groups	TEC (10^6/mm3)		TLC (10^3/mm3)		Hb (g/dl)		PCV (%)		Thrombocytes (10^3/ml)	
	Day 0 Mean ±SE)	Day18 (Mean ±SE)	Day 0 (Mean ±SE)	Day18 (Mean ±SE)	Day 0 (Mean ±SE)	Day18 (Mean ±SE)	Day 0 (Mean ±SE)	Day18 (Mean ±SE)	Day 0 (Mean ±SE)	Day18 (Mean ±SE)
I	7.00 ±0.12	7.01 ±0.18^{a}	10.88 ±0.35	11.57 ±0.77^{ab}	11.83 ±0.46	11.79 ±0.31^{ab}	35.87 ±2.68	38.98 ±1.01^{ab}	410.70 ±6.73	422.80 ±12.07
II	7.34 ±0.19	5.20 ±0.08^{b}	11.01 ±0.42	11.16 ±0.65^{b}	12.75 ±0.24	9.76 ±0.30^{c}	39.25 ±0.31	33.71 ±1.00^{c}	423.30 ±11.27	441.70 ±15.48
III	7.20 ±0.17	5.74 ±0.10^{b}	10.57 ±047	10.76 ±0.48^{b}	12.32 ±0.22	10.33 ±0.31^{bc}	40.10 ±0.39	35.00 ±1.01^{bc}	409.60 ±10.74	438.20 ±12.80
IV	7.18 ±0.21	5.50 ±0.10^{b}	11.83 ±0.21	13.46 ±0.93^{ab}	11.88 ±0.23	10.31 ±0.31^{c}	38.73 ±0.98	33.08 ±1.00^{c}	417.60 ±12.33	435.50 ±13.61
V	7.21 ±0.16	5.80 ±0.11^{b}	11.37 ±0.23	14.70 ±0.99^{a}	11.78 ±0.26	10.60 ±0.31^{bc}	39.02 ±0.75	33.39 ±1.00^{c}	413.80 ±10.64	433.10 ±10.08
Via	7.10 ±0.11	7.12 ±0.20^{a}	10.42 ±0.38	10.51 ±0.33^{b}	12.19 ±0.17	12.39 ±0.49^{a}	37.88 ±0.87	38.95 ±1.03^{ab}	396.40 ±8.42	414.70 ±9.98
VIb	7.07 ±0.12	6.86 ±0.17^{a}	11.0 ±0.35	10.50 ±0.32^{b}	12.07 ±0.33	12.20 ±o.46^{a}	38.51 ±1.13	39.80 ±1.28^{a}	407.60 ±10.13	399.80 ±15.28
SMD	0.68 NS	0.74*	1.52 NS	3.24*	1.23 NS	1.47*	5.40 NS	4.42*	43.74 NS	54.68 NS

Mean value in column with different superscripts are significantly variable.
NS=Non-Significance SMD=Significant minimum difference *Significant (P<0.01)

control. Cisplatin control (group II) showed gradual decrease in body weight with maximum on day 9th (-22.46%) followed by gradual gain in body weight up to day 18th (-4.49%) when compared to day zero. In contrast, rats received carvedilol (5mg/kg), aqueous and methanolic extracts of *Curcuma longa* (500mg/kg) daily for 15 days showed increased body weight gradually but lesser extents than that of normal control.

Effect on MST

Table 2 shows the effect of carvedilol, aqueous and methanolic extract of *Curcuma longa* on MST of rats in different groups. Protection by carvedilol, aqueous and methanolic extracts of *Curcuma longa* against cisplatin were observed as evidenced by increased MST and decreased mortality when compared to cisplatin control groups.

Effect on hematological parameters

Table 3 shows the effect of carvedilol, aqueous and methanolic extract of *Curcuma longa* on various hematological parameters.

Cisplatin significantly decreased (P<0.01) TEC, Hb, and PVC but not TLC and thrombocytes count when compared with normal and vehicle control on day 18. Moreover, treatment with carvedilol, aqueous and methanolic extract of *Curcuma longa* did not cause any significant improvement in hematological parameters except TLC by methanolic extract of *curcuma longa* when compared to cisplatin control on day 18.

Effect on biochemical parameters

Table 4 shows effect of carvedilol, aqueous and methanolic extract of *Curcuma longa* on various biochemical parameters. All the biochemical parameters such as SUN, SCr, TP, and UA levels were significantly increased (P<0.01) in cisplatin control when compared to normal control group on day 18.

All biochemical parameters were significantly improved

Table 4 Effect of carvedilol and *Curcuma longa* extract on various biochemical parameters in cisplatin induced nephrotoxicity

Group	Serum urea nitrogen (SUN)		Serum creatinine (SCr)		Total protein (TP)		Uric acid (UA)	
	Day 0 (Mean ±SE)	Day 18 (Mean ±SE)	Day 0 (Mean ±SE)	Day 18 (Mean ±SE)	Day 0 (Mean ±SE)	Day 18 (Mean ±SE)	Day 0 (Mean ±SE)	Day 18 (Mean ±SE)
I	16.33± 0.38	16.60± 4.07^{b}	0.47± 0.06	0.52± 0.15^{c}	6.65± 0.29	6.80± 0.40^{b}	4.25± 0.51	4.38± 0.42^{c}
II	17.07± 0.41	75.02± 4.93^{a}	0.48± 0.06	3.87± 0.33^{a}	6.62± 0.23	9.21± 0.59^{a}	3.80± 0.53	7.68± 0.60^{a}
III	17.27± 0.34	26.38± 4.69^{b}	0.56± 0.05	1.21± 0.25^{b}	5.90± 0.18	7.47± 0.48^{ab}	4.04± 0.39	6.26± 0.51^{ab}
IV	16.37± 0.34	23.81± 4.48^{b}	0.51± 0.05	0.68± 0.17^{bc}	6.25± 0.22	6.56± 0.40^{b}	4.36± 0.55	2.80± 0.32^{c}
V	16.23± 0.26	20.35± 4.28^{b}	0.50± 0.04	0.59± 0.16^{bc}	6.39± 0.24	6.16± 0.40^{b}	4.03± 0.60	4.17± 0.40^{c}
Via	16.30± 0.35	16.60± 4.07^{b}	0.52± 0.07	0.52± 0.15^{c}	6.06± 0.22	6.19± 0.04^{b}	4.13± 0.54	4.18± 0.40^{c}
VIb	15.90± 0.38	16.42± 4.10^{b}	0.52± 0.06	0.54± 0.15^{c}	6.30± 0.24	6.62± 0.40^{b}	4.23± 4.41	4.54± 0.46^{c}
SMD	1.53 NS	17.61*	0.24 NS	0.65*	0.99NS	1.85*	2.16 NS	1.84*

Mean value in column with different superscripts are significantly variable. SMD=Significant minimum difference
NS=Non-Significance *Significant (P<0.01)

by treatment with aqueous and methanolic extract of *Curcuma longa* when compared with cisplatin control on day 18. However, carvedilol only caused significant improvement in SUN but not SCr, TP, and UA level when compared with cisplatin control on day 18

DISCUSSION

Cisplatin a very potent anticancer agent used for treatement of various solid tumors, however, the main dose limiting factor of cisplatin is nephrotoxicity, restrict its used beyond certain dose.[2]

In the present study, a single dose of cisplatin (7.5mg/kg, i. p.) resulted in severe kidney damage as revealed from significant increase in about five times and seven times in SUN, SCr level respectively in addition to significant increase in TP and UA as observed in previous studies.[9, 10] Decreased body weight, various abnormalities and mortalities and significant decrease in hematological parameters such as TEC, Hb and, PCV by cisplatin further supports possibility of kidney damage. The reduced body weight following cisplatin treatment may be attributed to the injured renal tubules and subsequently loss of ability of tubular cells to reabsorb water, leading to dehydration and loss of body weight or due to catabolic effects of

cisplatin. Moreover, the reduction in body weight of the animals in present study correlates with the decreased food intake during experimental period.

Decreased TEC, Hb, and PCV by cisplatin treated rats in present study might be due to myelosupressive effects of cisplatin.[11] The myelosupression and anemia are the most common problem encountered in cancer chemotherapy.[12] Erythropoietin secreted from kidney stimulates proliferation and differentiation of erythroid precursors in haemopoietic tissues.[13] Thus, lack of erythropoietin due to cisplatin induced kidney damage would have been the attributing factor for decreased TEC. No significant changes in TLC was observed in cisplatin treated rats in present study, which is against the previous finding [14] in which rats treated with single dose of cisplatin (16 mg/kg b.wt.) showed significant decrease in TLC levels when compared with normal control in 3 days study. However, our finding might be due to lower dose of cisplatin and longer duration to cause suppression of WBC stem cells as compared to above reference. The free radical such as reactive oxygen species (ROS) generation by cisplatin [15] which through binding to RBC membrane might cause oxidative damage resulting in decreased Hb levels. Furthermore, decreased TEC and Hb by cisplatin may be the attributing factor for decreased level of PCV in present study. Mild thrombocytopenia is one of the consequences of hematological toxicities by cisplatin [16], however; the observations in the present study are not in agreement with above report. This might be due to reversible appearance of thrombocytes to the normal levels by 18 days or inability of cisplatin to suppress platelets at dose (7.5 mg/kg) used in present study.

In our study, carvedilol (5mg/kg), aqueous and methanolic extracts of *Curcuma longa* (500mg/kg) administration for 15 days post cisplatin treatment significantly attenuated cisplatin-induced nephrotoxicity which was clearly manifested by improvement in the biochemical parameter and other abnormality and mortalities manifested by cisplatin. Although, the possible mechanism of its protection against cisplatin-induced nephrotoxicity was not studied in current study, it is possible that the protective effect might be attributed to its antioxidant and/or free radical scavenging activity as carvedilol and some of its metabolites are potent antioxidant activity has been attributed to its carbazole moiety.[17] Nephroprotective role of carvedilol has been demonstrated against cisplatin[18] and cyclosporine.[19] It is well established that curcumin of methanolic extract of *Curcuma longa* has a strong antioxidant capacity by preventing the production of free radicals.[20] The restoration of cisplatin induced loss in body weight by carvedilol, aqueous and methanolic extracts of *Curcuma longa* might be due to reduction in catabolic effects of cisplatin due to its antioxidant potential, however, increased feed consumption in present study could be the main attributing factor for weight gain. No significant increase in TEC, TLC, Hb, and thrombocytes was observed by carvedilol, aqueous and methanolic extracts of *Curcuma longa* treated rats in present study showed its lack of any appreciable effects in bone marrow especially erythroid precursor cells. Plant containing flavonoids and alkaloid in high concentration has been demonstrated for its nephroprotective role due to its antioxidant and/or free radical scavenging activity [21] and protective role of saponine against carbon tetrachloride induced liver and kidneys toxicity.[22] In the present study *Curcuma longa* contain curcumin, flavonoids, alkaloids, saponin, glycosides and many other active phytocomponents which might be responsible for present biological effects. In fact, further investigation is needed to know the nephroprotective effects of particular phytocomponents and its mechanism of action.

In conclusion, the results of the present study demonstrated that carvedilol and aqueous and methanolic extracts of *Curcuma longa* protects against cisplatin-induced kidney damage in rats and can be exploit it as nephroprotection. Not only carvedilol and curcumin of methanolic extract of *curcuma longa* which having strong antioxidant properties but there is need to give attention on other water soluble constituents of *Curcuma longa* which also having equally nephroprotective effect in cisplatin induced kidney damage.

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