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Nephroprotective Potential of Sinigrin Against Gentamicin Induced Kidney Damage in Wistar Rats: A Preclinical Evaluation

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Abstract

Background: Oxidative stress is pivotal in the etiopathogenesis of renal damage instigated by drugs, and it is reported that compounds with antioxidant potential can attenuate the drug-induced renal toxicity. Sinigrin, a constituent glucosinolate of *Brassica nigra* seeds, has proven antioxidant, anti-inflammatory and cytoprotective activity, proposing its potential use in mitigating drug induced oxidative damage. **Aim:** The present study evaluates the ameliorative potential of sinigrin against gentamicin induced oxidative renal damage. **Methods:** Adult Wistar albino rats were divided into five groups. Gentamicin 80 mg/kg body weight was given intraperitoneally for 8 days to induce nephrotoxicity. Sinigrin, the test drug, was given orally at doses of 10, 15, and 25 mg/kg starting 3 days prior to and continued for 8 days along with gentamicin. The serum sample was collected for biochemical estimation of creatinine, urea, uric acid, Blood Urea Nitrogen (BUN), and Malondialdehyde (MDA). The kidney sections were examined for histopathological evaluation. The findings are expressed as mean ± SEM, subjected to one-way ANOVA followed by Tukey's test analysis. A *p*-value of <0.05 was deemed significant. **Results:** Pretreatment and co-administration of sinigrin with gentamicin attenuated the elevations in serum urea, uric acid, creatinine, BUN, and MDA. Histopathological findings corroborated with the biochemical evidence. Sinigrin showed signs of tubular regeneration, mitigating gentamicin induced renal tubular necrosis. **Conclusion:** The findings imply that pretreatment and co-administration of sinigrin have a noteworthy protective effect in an animal model of gentamicin-induced renal damage, and more research on the underlying mechanism of action is required.

Major Findings: Sinigrin markedly mitigated gentamicin-induced oxidative damage in rat kidneys demonstrated by improvements in biochemical parameters and histological findings. These findings confirm sinigrin's nephroprotective potential and warrant further study of its mechanism.

Keywords: Gentamicin, Murine Model, Nephroprotective, Oxidative Stress, Sinigrin

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1. Introduction

Drug induced nephrotoxicity is a frequently encountered iatrogenic complication in therapeutics and there is an exponential increase in drug related Acute Kidney Injury (AKI) with special emphasis on antimicrobial agents[1]. Aminoglycoside antibiotics, more commonly gentamicin, a common arsenal to

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combat gram-negative bacterial infections owing to their high efficacy is offset by its potential to cause dose-dependent renal damage[2-6]. The renal toxicity associated with gentamicin therapy is observed in 10-20% of therapeutic regimens and hitherto has posed a serious threat in the guise of AKI, causing significant morbidity[2,7,8]. Gentamicin instigated renal toxicity is now being used as a recognized screening model to evaluate possible protective or regenerative strategies in drug induced AKI.

It is common knowledge that gentamicin induced renal toxicity occurs due to its transport and aggregation within the tubule cells in the proximal part of the nephron. The characteristic features of renal toxicity include biochemical alterations like raised creatinine and Blood Urea Nitrogen (BUN) in the serum, along with histological changes evidenced by tubular interstitial damage, glomerular lesions, such as congestion, glomerular hypertrophy or atrophy, accumulation of amorphous substance in mesangial matrix and other intraglomerular alterations which result in low Glomerular Filtration Rate (GFR)[9,10]. Reactive Oxygen Species (ROS) production, inflammation, oxidative damage that affects cellular membranes and inadequate renal antioxidant status are key active instigators of pathogenic effects in the renal tubules and glomeruli induced by gentamicin[11]. Literature analysis of various earlier studies has positively linked antioxidant and anti-inflammatory features of chemical entities with their renoprotective effects in experimental models of renal damage incited by gentamicin[12-15].

Sinigrin is a vital glucosinolate, (analogous to the glucosides) obtained from the plants of *Brassicaceae* family, particularly in black mustard seeds (*Brassica nigra*). Sinigrin is broken down by a myrosinase mediated reaction into allyl isothiocyanate, which mediates a varied physiological action. Sinigrin exhibits significant antitumor and antioxidant actions. It protects against inflammation and helps to defend the body against bacterial and fungal infections. Its role in the repair of wounds has also been established. It is also used as a nutraceutical for various therapeutic and prophylactic indications[16].

Medicinal plants are a rich storehouse of complex phytoconstituents with curative properties. Renal damage induced by free oxygen radicals can be mitigated with the use of natural antioxidants and the phytocompound sinigrin, with known biological actions, can prove to have protective effects against gentamicin induced renal injury. This might enable us to improvise and advance our present knowledge on pharmacotherapeutic strategies to tackle drug induced AKI. There is insufficient data on the therapeutic potential of sinigrin though this compound has various biological activities. Further scientific exploration of the full gamut of pharmacotherapeutic actions and mechanism of action of sinigrin are warranted. Therefore, the current work intended to review the actions of sinigrin on biochemical and histopathological parameters in an *in-vivo* model of gentamicin induced renal damage.

2. Materials and Methods

The protocol was approved by the Institutional Animal Ethics Committee. (Approval no-KMC/MNG/IAEC/08-2020). Adherence was maintained to the guidelines set by the Committee for the Control and Supervision of Experiments on Animals.

2.1 Experimental Animals

Thirty adult Wistar albino rats of either sex, weighing 150-200grams, inbred in the institutional central animal house were used for the study. Animals were housed in clean polypropylene cages under standard environmental conditions (22± 30C, 55 ± 5% humidity and a 12 h light/ dark cycle) and fed with standard rodent diet and water *ad libitum*. Prior to starting the experimental procedure, the animals were accustomed to the study conditions for a week.

2.2 Drugs and Chemicals

Normal saline, gentamicin sulphate injection, and sinigrin (sinigrin hydrate, analytic grade) were procured from Sigma Aldrich Chemicals Pvt Ltd.

2.3 Experimental Procedure: Gentamicin Induced Nephrotoxicity

The study was conducted over 11 days. Five treatment groups with six animals each were housed in individual cages. The treatment groups are outlined in Table 1. Group 1(Normal control) received normal

saline orally; Group 2(disease control) is treated with intraperitoneal (i.p.) gentamicin, 80 mg/kg body weight (b.w) for 8 days[12]. Groups 3,4 and 5(Test groups) received oral administration of sinigrin at doses 10, 15, and 25 mg/kg b.w respectively with the aid of oral gavage needles, along with gentamicin 80 mg/kg b.w. administered i.p[7]. Sinigrin administration began 3 days prior to the initiation of gentamicin treatment.

2.4 Sample Collection and Estimation of Biochemical Parameters

The blood samples from the animals were obtained after a 24-hour fasting period that followed the last administration of the drug. Collection of blood sample was through retro orbital venous plexus into sterile vacutainers following application of 0.5% Proparacaine Hydrochloride drops for anesthesia. The blood specimens were spun in a centrifuge for 15 minutes at 3000 rpm to isolate the serum for biochemical analysis. The animals were euthanized, and the kidneys were dissected for histopathological evaluation. The estimation of serum urea, creatinine, uric acid, and BUN levels in the sample serves as an indicator of renal damage. They were estimated using standardized test kits obtained from Agappe Diagnostics Ltd. The estimation of serum Malondialdehyde (MDA) by using the thiobarbituric acid (TBA) method will determine the extent of oxidative stress[18].

2.5 Histopathological Examination

The renal tissues preserved in a neutral buffered 10% formalin solution underwent dehydration with alcohol and clearing with xylol. After processing in paraffin, sections of 5mm in size were cut. They were stained with Hematoxylin-Eosin (H and E) for light microscopy observation to identify and analyze the morphological changes due to gentamicin induced nephrotoxicity. The histopathological scoring was based on the extent and severity of tubular injury. The scoring system was adopted by Gilbert et al: Score 0:Normal, Score 1:Areas of focal granulovacuolar epithelial cell degeneration and granular debris in tubular lumens with or without evidence of tubular epithelial cell desquamation of small foci (<1% of total tubule population), Score 2:Tubular epithelial necrosis and desquamation easily seen but involving less than half of cortical tubules, Score 3:More than half of proximal tubules showing desquamation of necrosis but involved tubules easily found, Score 4:Complete or almost complete tubular necrosis[12].

2.6 Statistical Analysis

The results are expressed as mean ± standard error of mean (SEM). SPSS version 25(IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) was used for statistical analysis. To compare the variations in the parameters evaluated between the groups, a one-way ANOVA followed by Tukey's post hoc test was applied. A value of p less than 0.05 was indicative of statistical significance.

3. Results

3.1 Biochemical Impact of Sinigrin on Renal Function

Estimation of serum biomarkers revealed a significant increase in serum levels of urea (144.10±34.70 mg/dl), creatinine (2.58±0.35 mg/dl), uric acid (2.21±0.30 mg/dl) and BUN (51.70±18.07 mg/dl) following administration of gentamicin in group 2(disease control) for 8 days in comparison to group 1(normal control). Co-administration of the test drug, sinigrin at doses 10, 15 and 25 mg/kg b.w with gentamicin in groups 3, 4 and 5 resulted in reduction in the serum

Table 1. Treatment schedule

Groups	Drugs	Dose
Group1 (Normal Control)	Normal Saline	1ml/kg b.w once daily
Group 2 (Disease control)	Gentamicin	80mg/kg b.w once daily
Group 3 (Test 1)	Sinigrin + Gentamicin	10mg/kg b.w+80mg/kg b.w once daily
Group 4 (Test 2)	Sinigrin + Gentamicin	15mg/kg b.w +80mg/kg b.w once daily
Group 5 (Test 3)	Sinigrin + Gentamicin	25mg/kg b.w+80mg/kg b.w once daily

levels of urea (82.98±9.22 mg/dl, 71.78±4.74 mg/dl, 65.43±7.05 mg/dl) creatinine (0.98± 0.14 mg/dl, 0.73±0.14 mg/dl, 0.53±0.07 mg/dl) uric acid (0.88±0.65 mg/dl, 0.60±0.08 mg/dl, 0.38±0.79 mg/dl) and BUN (28.80±3.03 mg/dl, 23.21±0.50 mg/dl, 18.06±0.42 mg/dl) as compared against group 2-disease control. Sinigrin at 25 mg/kg b.w with gentamicin, elicited a prominent attenuation ($p < 0.05$) in concentrations of all the renal biomarkers indicative of nephrotoxicity. The serum urea reduced to 65.43±7.05 mg/dl, creatinine to 0.53±0.07 mg/dl, uric acid to 0.38±0.79 mg/dl, and BUN to 18.06±0.42 mg/ dl in the group treated with 25 mg/kg b.w of sinigrin compared to disease control. The results are depicted in Table 2.

A significant rise in serum MDA level (111.35±18.38 mmol/l) was observed in Group 2 (disease control) treated with gentamicin, suggesting oxidative stress linked to gentamicin induced kidney toxicity in comparison to Group 1(normal control). Co-administration of sinigrin with gentamicin at doses 10, 15 and 25mg/kg b.w in groups 3,4 and 5 resulted in the decrease in the MDA levels, with group 3 showing 75.06±6.71mmol/l, group 4 had 68.93±6.14mmol/l and group 5 exhibited a significant decrease to 57.20±9.44 mmol/l compared to Group 2 (disease control) as depicted in Table 2.

3.2 Histopathological Evaluation

The histopathological scores obtained by evaluating the sections of the kidneys from various groups are expressed in Table 3. The renal tissue from the normal control animals, which received normal saline, exhibited normal tubular architecture and intact glomeruli, with an Acute Tubular Necrosis (ATN) score of 0 (Figure 1). The Group 2 (disease control) treated with gentamicin alone showed acute kidney damage, which was evident by extensive tubular necrosis with granular casts, glomerular and interstitial infiltration, and congestion

Table 2. Effect of sinigrin on biochemical parameters

Groups	Treatment	Parameters				
		Urea (mg/dl)	Creatinine (mg/dl)	Uric acid (mg/dl)	BUN (mg/dl)	MDA (mmol/l)
Group 1 Normal control	Normal saline 1ml/kg	25.03±1.50	0.56±0.04	0.55±0.05	11.63±0.69	48.45±14.04
Group 2 Disease control	Gentamicin (80mg/kg)	144.10±34.70$^{\#}$	2.58±0.35$^{\#}$	2.21±0.30$^{\#}$	51.70±18.07$^{\#}$	111.35±18.38$^{\#}$
Group 3 Test 1	Sinigrin (10mg/kg)	82.98±9.22	0.98±0.14*	0.88±0.65*	28.80±3.03	75.06±6.71
Group 4 Test 2	Sinigrin (15mg/kg)	71.78±4.74*	0.73±0.14*	0.60±0.08*	23.21±0.50	68.93±6.14
Group 5 Test 3	Sinigrin (25 mg/kg)	65.43±7.05*	0.53±0.07*	0.38±0.79*	18.06±0.42*	57.20±9.44*

BUN-Blood urea nitrogen, MDA-Malondialdehyde. Values are expressed as mean ± SEM $^{\#}p < 0.05$ when compared to normal control group.
**p< 0.05 when compared to gentamicin treated group.

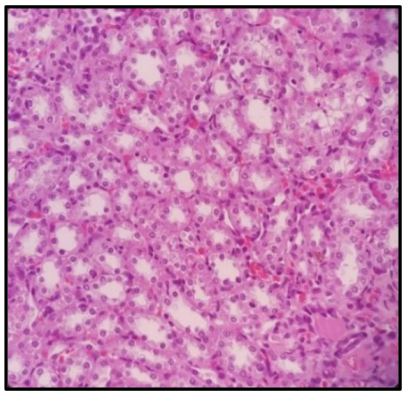


Figure 1. Kidney sections of control (normal saline) group showing normal renal structure (Glomeruli and tubules). ATN Score-0 (H and E 200X).

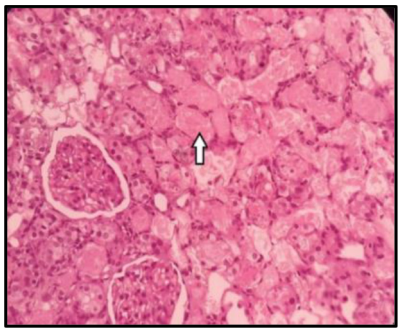


Figure 2. Kidney sections from gentamicin treated group revealed that more than half of the proximal tubules exhibited extensive epithelial desquamation, accompanied by the presence of granular casts within the tubular lumen. ATN Score-3 (H and E 200X).

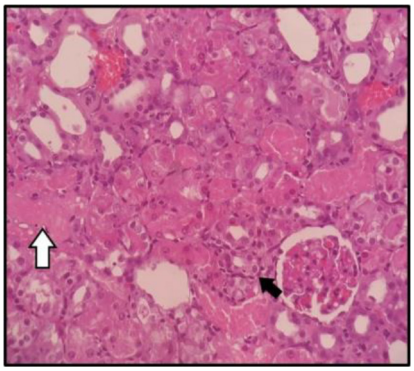


Figure 3. Kidney sections from the group treated with sinigrin (10 mg/kg) and gentamicin displayed tubular epithelial necrosis with granular casts (indicated by white arrows), involving less than half of the cortical tubules. Evidence of tubular regeneration was observed in the lower region of the image (black arrows). ATN Score-2 (H and E 200X).

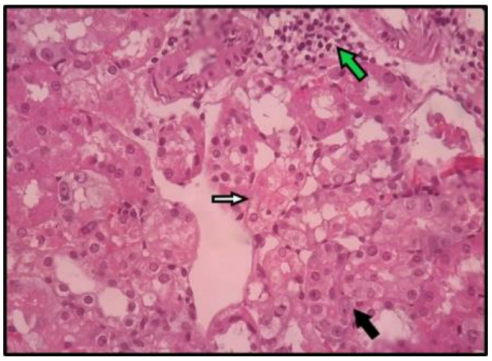


Figure 4. Kidney sections of sinigrin 15 mg/kg with gentamicin treated group showing tubular cells showing granulovacuolar degeneration (white arrow), regenerative changes (black arrow) and interstitial lymphocytic infiltration (Green arrow). ATN Score-1 (H and E 200X).

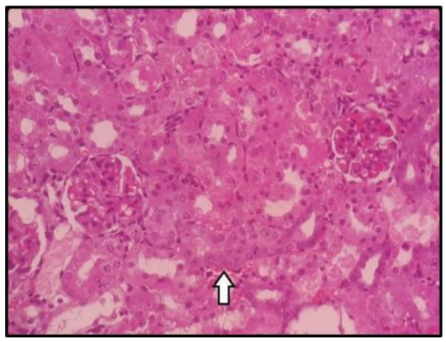


Figure 5. Kidney sections of sinigrin 25 mg/kg with gentamicin treated group showing normal looking tubules with few showing regenerative change (white arrow), without necrosis or granular casts in tubular lumen. ATN Score-0 (H and E 200X).

corresponding to an average ATN score of 3 (Figure 2). Treatment with 5 10, 15, and 25 mg/kg b.w sinigrin along with gentamicin in groups 3, 4, and 5, resulted in dose-dependent histological improvements. Sinigrin administered at 10mg/kg b.w-group 3 showed few focal areas of tubular necrosis with granular casts and signs indicating regeneration of tubules with an ATN score of 2. (Figure 3). Further improvement was observed at 15mg/kg b.w-group 4 and 25 mg/kg b.w-group 5 doses, with kidney sections showing evidence of tubular regeneration, absence of necrosis and casts, and resolving interstitial injury, corresponding to average ATN scores of 1 and 0, respectively (Figures 4 and 5). These findings provide evidence for the nephroprotective properties of sinigrin in mitigating renal damage caused by gentamicin.

Table 3. Histological evaluation of renal tissue following gentamicin and sinigrin treatment in rats

Histopathological Feature	Normal control	Gentamicin	Sinigrin (10mg/kg)	Sinigrin (15mg/kg)	Sinigrin (25mg/kg)
Glomerular infiltration	Absent (-)	3+	2+	2+	Absent (-)
Interstitial congestion	Absent (-)	3+	2+	1+	1+
Interstitial infiltration	Absent (-)	3+	1+	1+	Absent (-)
Tubular regeneration	Absent (-)	Absent (-)	Absent (-)	1+	2+
ATN score	0	3	2	1	0

ATN- Acute Tubular Necrosis

4. Discussion

This study attempts to evaluate the beneficial actions of sinigrin in renal damage induced by gentamicin in a murine model. Gentamicin demonstrates potent efficacy against Gram-negative bacterial infections; however, the risk of toxicity to kidney structure and function limits its utility. The renal impairment was apparent in this experiment with gentamicin, 80mg/kg/day b.w injected intraperitoneal for eight days as indicated by raised serum urea (144.10±34.70 mg/dl), creatinine (2.58±0.35 mg/dl), uric acid (2.21±0.30 mg/dl) and BUN (51.70±18.07 mg/dl) compared to the control group. The alterations in the biochemical parameters were further supported by histological examination. The presence of extensive tubular necrosis with granular casts, glomerular and interstitial infiltration and congestion in the gentamicin treated group indicated and corroborated with earlier studies that describe gentamicin induced nephrotoxicity[12-15].

Pretreatment and co-administration of sinigrin with gentamicin significantly mitigated the increase in serum urea, creatinine, uric acid and BUN levels observed in the gentamicin treated group. The treatment with sinigrin at 10, 15, and 25 mg/kg progressively reduced elevated serum levels of urea (82.98±9.22 mg/dl, 71.78±4.74 mg/ dl, 65.43±7.05 mg/dl) creatinine (0.98±0.14 mg/ dl, 0.73±0.14 mg/dl, 0.53±0.07 mg/dl) uric acid (0.88±0.65 mg/dl, 0.60±0.08 mg/dl, 0.38±0.79 mg/ dl) and BUN (28.80±3.03 mg/dl, 23.21±0.50 mg/dl, 18.06±0.42 mg/dl) respectively indicating improvement in kidney function correlated with increasing doses. The improvements in biochemical parameters corroborated with the histopathological findings which showed evidence of renal tubular regeneration, absence of necrosis and casts in tubular lumen and resolving interstitial inflammation particularly at larger dose of sinigrin (25 mg/kg b.w). These results demonstrate that sinigrin confers a protective effect against gentamicin-induced kidney toxicity in a dose-dependent manner promoting recovery of both renal function and tissue structure. The gradual improvement in renal biomarkers with histological signs emphasizes the sinigrin's role in preserving the renal integrity.

Oxidative stress is widely acknowledged as a major contributing factor in the development of kidney damage caused by gentamicin. In this study a marked elevation of serum MDA levels (111.35±18.38 mmol/l) was observed in the gentamicin treated animals when compared to the normal saline treated control group. There was no significant difference in serum MDA levels between the control group and the group treated with sinigrin. Pretreatment and co-administration of sinigrin at 10,15 and 25 mg/kg b.w with gentamicin provided protection by significantly decreasing the MDA levels to75.06±6.71mmol/l, 68.93±6.14mmol/l, and 57.20±9.44 mmol/l respectively. Taking the above results into consideration, we find that sinigrin has nephroprotective potential. The present study adds to the evidence from the earlier study on the extract of *Brassica nigra* having antioxidant and anti-inflammatory activity demonstrating nephroprotective activity[19].

Renal oxidative stress, renal inflammatory cascades, and an increase in related pathogenic signalling pathways are the main mechanisms responsible for gentamicin-induced nephrotoxicity[3,20]. Therefore, various necrotic and apoptotic pathways result in low cell viability attributed to gentamicin and this may explain the effectiveness of antioxidants and agents with anti-inflammatory properties in attenuating the renal damage induced by the drug.

Naturally sourced phytochemicals contribute to protecting the body from oxidative stress and inflammatory responses. Glucosinolates and their hydrolysis products are considered as indirect antioxidants as they modulate metabolizing enzymes, providing protection against oxidative stress[21]. Sinigrin, a bioactive glucosinolate found in cruciferous vegetables, is recognized for its diverse biological effects, including antioxidant and anti-inflammatory properties. Its metabolic activation to Allyl Isothiocyanate (AITC) is primarily responsible for these effects. Different studies have documented these properties of AITC. Results from a study by K. Ippoushi et al., showed that sinigrin had a suppressive effect on NO production observed in rats administered lipopolysaccharide (LPS)and the impact was attributed to AITC inhibiting induction of iNOS expression by LPS in rats[22,23]. Erkekoglu *et al.,* illustrated that AITC can modulate of antioxidant status by neutralizing the reactive oxygen species and enhancing cell viability, thus illustrating its protective role in HepG2 cells against cytotoxic and genotoxic effects[24]. Nuclear erythroid 2-related factor 2 (Nrf2) and nuclear factor kappa-light-chain-enhancer of activated

B cells (NF-κB) have a central role in oxidative stress and inflammation. Treatment with sinigrin reduce the production of Tumor Necrosis Factor- α (TNF-α) and interleukin -6 (IL-6), in activated macrophages which induce inflammation and the possible mechanism as described by H.W. Lee et al. is its ability to cause down regulation of p38 and c-Jun N-terminal kinase (JNK) phosphorylation, suppression of NF-κB activation and NLRP3 inflammasome[25]. Nrf2 transcription factor leads to up regulation of antioxidant genes in states of oxidative stress and Isothiocyanates (ITCs) increase their activity[26] and are also known to assist activity of natural antioxidants like tocopherols and enhance synthesis of glutathione which is a direct antioxidant[27].

As inflammatory response follows oxidative stress as a compensatory mechanism to overcome the oxidative damage, the plant derived bioactive components with antioxidant profile can act via varied mechanism as discussed earlier which may be responsible for their health benefits observed in oxidative stress induced chronic diseases. Therefore, sinigrin and its active metabolite AITC could be of potential use in affording nephroprotection via their antioxidant, cytoprotective and anti-inflammatory actions. Considering this we propose that the nephroprotective activity seen with sinigrin in this study could have been due to the above properties, but future explorations are needed to meticulously investigate the molecular processes involved and validate these assumptions.

5. Conclusion

To conclude, the current data in this study contributes experimental evidence of the renoprotective effects of sinigrin when administered by the oral route in an experimental murine model of gentamicin induced damage to the kidney. We further suggest that the observed nephroprotection could be linked to its antioxidant and anti-inflammatory activity.

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Author Contribution

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