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Mitigating Cadmium Nephrotoxicity: The Therapeutic Potential of Nicotinamide as a PARP Inhibitor

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Introductions

Nephrotoxicity refers to the harmful effects of substances, typically medications or chemicals, on the kidneys, potentially resulting in conditions such as acute kidney injury (AKI) or chronic kidney disease (CKD) (Stevens *et al*., 2006). It is a major concern in clinical settings, especially with the use of certain antibiotics, chemotherapy agents, and nonsteroidal anti-inflammatory drugs (NSAIDs). The mechanisms of nephrotoxicity include direct tubular cell toxicity, inflammation, oxidative stress, and disruption of renal hemodynamics (Cekmen *et al*., 2013). Early detection and monitoring are crucial to prevent irreversible kidney damage and ensure patient safety.

The kidney filters around 120 mL of plasma per minute, a process regulated by intraglomerular pressure. This pressure is influenced by the afferent and efferent arterioles. Afferent arteriole pressure is affected by circulating prostaglandins, while efferent arteriole pressure and intraglomerular pressure are influenced by angiotensin II-mediated vasoconstriction (Lucas *et al*., 2019). Consequently, NSAIDs like diclofenac, angiotensin II receptor blockers (ARBs) like valsartan, and angiotensin-converting enzyme inhibitors (ACEIs) like captopril can worsen intraglomerular pressure and decrease the glomerular filtration rate (GFR). Cyclosporine and tacrolimus also induce afferent arteriole vasoconstriction in a dose-dependent manner (Setia *et al*., 2020).

Acute kidney injury (AKI) is characterized by a sudden decline in kidney function, which is often reversible but can lead to long-term consequences like CKD and increased cardiovascular risk (Makris *et al*., 2016). AKI can be caused by reduced kidney perfusion, systemic inflammation, and nephrotoxic

drugs, particularly in patients with chronic renal damage, advanced age, diabetes mellitus, or heart failure (Gameiro *et al*., 2018).

Chronic kidney disease (CKD) is a global health issue characterized by decreased filtration function, proteinuria, and structural abnormalities. These lead to waste accumulation, fluid retention, and potentially kidney failure requiring dialysis or transplantation (Chen *et al*., 2019). CKD is marked by oxidative stress, inflammation, and reduced antioxidant defence, which result in fibrosis, tubular atrophy, and interstitial inflammation.

Cadmium

Cadmium is a very toxic pollutant in industrial and environmental settings which can lead to serious health issues like cancer, kidney damage, and respiratory problems. Ingesting cadmium orally can result in acute poisoning, which is identified by symptoms like feeling sick, throwing up, and experiencing stomach discomfort (Rahimzadeh *et al*., 2017). Continued exposure to small amounts of cadmium over time can lead to lasting health problems such as kidney damage, osteoporosis, and bone fractures. Cadmium has the ability to imitate vital metals such as zinc, which can cause imbalances in calcium, zinc, and iron levels (Jolly *et al*., 2023). The harmful impacts of cadmium are due to its capacity to produce reactive oxygen species, reduce antioxidants, and attach to metallothionein proteins, resulting in cellular harm and apoptosis (Smereczański *et.al*., 2023; Brzóska *et al*., 2023). The usual treatment for cadmium poisoning includes providing supportive care like gastrointestinal decontamination and kidney dialysis, along with using chelating agents to eliminate the metal from the body. Cadmium enters the environment through both natural and anthropogenic sources. Natural sources include weathering of rocks and volcanic eruptions. Cadmium is naturally present in Earth's crust, with an average concentration of about 0.1 mg/ kg, and is widely distributed in sedimentary rocks and marine phosphates. Natural phenomena like weathering and volcanic eruptions can release cadmium into the environment, contributing to its presence in soil, water and air. Cadmium can enter aquatic ecosystems via industrial effluents, atmospheric deposition, and agricultural runoff. In water, it binds to suspended particles or sediments, affecting its distribution and uptake by aquatic organisms However, human activities significantly contribute to cadmium pollution. Industrial processes, such as metal refining, battery production, and pigment manufacturing, release large amounts of cadmium into the air (Trinchella *et al*., 2006). Additionally, the application of cadmium-containing pesticides and fertilizers

contaminates soil and water resources. Coal combustion and municipal waste incineration also contribute to atmospheric cadmium**.** Industrial processes like metal processing, coal burning and petroleum combustion release cadmium into the atmosphere, soil and water resources leading to environmental pollution (Genchi *et al*., 2020). Human exposure to cadmium can occur through various routes, including occupational exposure in primary metal industries, consumption of contaminated food, and smoking. Cadmium exposure can lead to adverse health effects in humans, affecting multiple organ systems and causing toxicity, bone disease, kidney dysfunction, and cardiovascular issues. (Gonick *et al*., 2008). Cadmium contamination in drinking water is a significant health concern due to the potential to cause adverse effects even at low exposure levels. The WHO has set a guideline of 0.003mg/L for cadmium in drinking water, based on an allocation of 10% of provisional tolerable weekly intake (PTWI) to drinking water, based on kidney effects. The Canadian government has set a maximum contamination limit of 0.005mg/L for cadmium in drinking water. Data derived from five Canadian cities showed concentrations of cadmium in drinking water to be less than 0.000044mg/L (Adam *et al*., 2019). The Australian National Health and Medical Research Council has established a guideline value of 0.002 mg/L for cadmium in drinking water. European Union directive includes a value of 0.005mg/L for cadmium in drinking water (Wasyluk *et al*., 2021). A study in Kamrup district, Assam, India revealed heavy metal contamination of drinking water, including cadmium. this concentration poses a threat to drinking water safety due to increasing industrial discharge into the environment (Chakrabarty *et al*., 2011). In western Uttar Pradesh, India found that concentration of cadmium in underground water sources exceeded the permissible limit set by WHO. The study indicated that the drinking water samples contained cadmium concentrations higher than the regulatory threshold, posing a risk of cadmium toxicity to the population in the region (Indrees *et al*., 2018). Groundwater samples collected from various locations in Chennai showed elevated level of levels of cadmium, with concentrations in some areas being 15 times higher than WHO standards. The study highlighted the vulnerability of Chennai to heavy metal contamination in groundwater with heavy metals, including cadmium (Kumar *et al*., 2018; Somasundaram *et al*., 1993). A report by The Energy and Resources Institute (TERI) states that nearly 718 districts in India have contaminated groundwater with heavy metal, including cadmium. According data generated in 2024, the state with highest level of cadmium in drinking water is Tamil Nadu (Elangovan *et al*., 2011). The water quality monitoring station at Todarpur on the Sukheta River recorded the maximum cadmium concentration of 12.57µg/L in December 2020, exceeding the limits set by WHO. (Csaba Vörös *et al*., 2021). The current status of cadmium contamination in drinking water in Punjab, India is concerning, according to a study published in the International Journal of Engineering

Research and Application in 2017, the concentration of cadmium in drinking water samples from the Malwa region of Punjab exceeded the permissible limits set by the Bureau of Indian Standards (BIS) .The study found that the cadmium concentration in all the samples was higher than the BIS standard of 0.005mg/L, with the highest concentration observed in the district of Muktsar at 0.97mg/L (Kubier *et al*., 2019).Another study published in the Journal of Environment Sciences and Health, Part B , in 2020 reported that the concentration of cadmium in drinking water samples from Sutlej river was higher than the permissible limits set by WHO , the study found that the concentration of cadmium in water was higher along the transboundary during both the pre-monsoon and post-monsoon seasons, with the likelihood of cancer risk due to ingestion of cadmium through water being higher in areas (Setia *et al*., 2020).

Fate of cadmium in body

The process of oral cadmium absorption in rats is intricate and includes multiple factors. Research has indicated that cadmium is taken in from the gastrointestinal tract into the bloodstream and then carried to different organs, such as the kidneys and liver . It is estimated that the daily absorption of cadmium from the intestines amounts to approximately 0.36%-0.54% of the total dose of cadmium consumed orally. This intake is important because it impacts how the toxic substance is spread and removed from the body, potentially causing harmful effects like kidney and liver damage (Ohta *et al*., 2000). After being exposed to cadmium, it builds up in liver cells and can surpass metallothionein's ability to bind to it, leading to liver histopathological alterations. In addition, chronic cadmium exposure can result in kidney dysfunction and changes in bone metabolism, with varying impacts depending on the level and length of exposure. Furthermore, rats exposed to cadmium experience disruptions in the metabolism of zinc, copper, iron, and calcium, resulting in notable organ-specific accumulations and excretion patterns that are observed during periods of recovery. The excretion of orally administered cadmium in rat bodies varies depending on the dose and exposure duration. Studies have shown that after oral cadmium exposure, more than 70% of the total dose is excreted in faeces within the first five days, indicating low absorption rates **(**Bagchi *et al*., 1996). Furthermore, urinary excretion of metallothionein, a sensitive indicator of cadmium exposure, increases linearly with the concentration of cadmium in drinking water over a two-year period (Ohta *et al*., 2000). Additionally, the toxic effects of cadmium on renal function and bone metabolism are dose-dependent, with higher doses leading to renal dysfunction, hepatic damage, and lower decreased bone mineral density (Bomhard *et al*., 1996). These findings highlight the

importance of understanding the excretion patterns of cadmium in rat bodies to assess its toxicological impact accurately. Cadmium administration in the leads to increased levels of oxidative stress markers, affecting both neuronal shape and cognitive functions (Trevino *et al*., 2022). Sudden exposure to Cadmium results in a rise in metallothionein production in the liver and kidneys, impacting how Cadmium is spread and gathered in these body parts. Moreover, exposure to Cadmium activates phospholipase A2 enzymes in the brain, causing changes in phospholipids and an increase in pro-inflammatory cytokines and apoptotic factors. Furthermore, metallothionein-like Cadmium binding protein is essential for safeguarding the testes from Cd toxicity by upregulating in response to Cd accumulation and initiating protective mechanisms in the testicular tissues (Ohta *et al*., 2000).

Cadmium-induced Cardiotoxicity

Cadmium toxicity produces gradual hypertension and raised cardiac output to increased stroke volume but does not affect the heart rate in rats (Klinova *et al*., 2021) Cadmium also revealed its effects in another study in which it was found that the mean blood pressure was reduced with exposure to cadmium. These changes in haemodynamics point to the direction that cadmium has detrimental effects on the cardiovascular system. Cadmium increases the amount of collagen, areas of necrotic myocardial fibres and hypertrophy of heart tissue. Morphological changes involving cardiomyocytes include shrinkage and disintegration of the mitochondria and an increase in the size of intracytoplasmic vacuoles. Cadmium exposure has been elicited to be associated with functional impairments and following structural abnormalities may explain the observed changes. (Klinova et al., 2021). Cadmium affects the cardiovascular system, in particular, it causes lipid peroxidation and raises the level of reactive oxygen species in cardiomyocytes. This oxidative damage results in the impaired function of the cell and also causes cell death. This work also revealed that Cadmium up-regulates Bcl-2 while downregulating Bax in rats' heart tissue.

Cadmium-induced Hematotoxicity

Orally ingested cadmium affects gastrointestinal absorption of iron and its utilisation can lead to anaemia if adequate iron is not taken through the diet. Cadmium toxicity has been reported in some studies among humans suffering from dietary chronic cadmium intake. It was mentioned before that decreases in the number of red blood cells were detected in rats orally administered with cadmium in a dose-dependent manner. This anaemia is ascribed to the toxic effects of cadmium on the cells; it

interacts with free radicals and alters the red blood cell membranes and the haemoglobin by membrane lipid peroxidation and haemoglobin oxidation. (Asagba *et al*., 2007)

Cadmium-induced Musculoskeletal effects

Oral cadmium exposure has a considerable musculoskeletal impact. Studies reveal that exposure to cadmium affects rat bone mineralisation and positively influences bone loss in aged animals. Cadmium can stimulate the rate of bone resorption, changes in osteoclast activity and calcium absorption and damage the kidneys, which means osteoporosis can develop. Therefore, chronic administration of cadmium chloride (in the concentration of 40 mg/L in drinking water for 6 weeks) can negatively affect the membrane fluidity of mesenchymal stem cells isolated from rats' bones, and thus, bone health. This cadmium exposure diminishes the proliferation capacity of mesenchymal stem cells, affecting their viability, destroying cytoplasm, and impacting metabolic/antioxidant enzymes. (Guadalupe *et al*., 2015)

Cadmium-induced Hepatotoxicity

Cadmium is a heavy metal that causes severe hepatic injuries and toxic manifestations in the body. Literature has revealed that cadmium induces oxidative stress, which results in elevated lipid peroxidation, reduced antioxidant enzyme activity and liver function derangement. For instance, a study showed that cadmium treatment increased the level of lipid peroxidation marker (TBARS) and reduced the levels of the antioxidant enzymes such as SOD, CAT, GPx and GSH in the liver tissue of rats (Sarkar *et al*., 1995). Another study showed the cadmium regulates liver fibrosis and cirrhosis. Cadmium not only induces hepatotoxicity but also affects liver function by modulation of cellular signalling pathways and cellular processes (Niture *et al*.,2021). Cadmium has also been found to affect liver energy metabolism, resulting in differences in the weight of the liver, liver index, and liver function (Sarkar *et al*., 1995).

Cadmium-induced Nephrotoxicity

Cadmium is an issue of great concern because it is non-biodegradable and has long biological half-life causing its build up in the kidneys which are the main target organs of cadmium (Prozialeck *et al*., 2021). Chronic cadmium exposure significantly damages the renal tissues and triggers a pathologic response involving oxidative stress, inflammation, and apoptosis. Such findings reveal that absolute kidney weight and cadmium concentration in the renal tissues of Cd-treated rats are higher than the

sham and/or vehicle-treated ones, suggesting impaired kidney function (Almeer *et al*., 2019). The histopathological studies show that cadmium causes several structural aberrations in the kidney such as vacuolization, congested glomerules, reduction and necrosis in the size of glomerulus, alarming disruption in the lining of the tubules along with vascular congestion. These changes are associated with a rise in the levels of Kidney Function markers: KIM-1, metallothionein, lipid peroxidation, NO, TNF-α, IL-1β and Bax and caspases (Almeer *et al*., 2019). In addition, acute and chronic Cd exposure cause a stepwise increase of renal damage which is a direct relationship between exposure dose and renal toxicity. This includes swollen glomeruli, renal tubules that have become narrowed, epithelial cell death and extensive infiltration of inflammatory cells. Similar to the nephron, mitochondria in renal tubular epithelial cells also demonstrate swelling and deformation along with vacuolation (Almeer *et al*., 2019). Regarding the biochemical alterations, cadmium leads to enhanced levels of the serum MDA and SOD1, while it decreases SOD2 and CAT levels, reflecting redox status disturbance. Moreover, the levels of Bcl-2 is down-regulated while Bax displayed a dose-dependent up-regulation and the Bax/Bcl-2 ratio increases significantly indicating enhanced apoptosis in the kidney (Almeer *et al*., 2019).

PARP [Poly (ADP-ribose) polymerase]

PARPs are a group of enzymes that have essential functions in different cellular processes like DNA damage repair, transcription, innate immunity, and controlling signaling pathways . PARPs facilitate the movement of ADP-ribose from NAD+ to target proteins and poly-nucleic acids, resulting in either mono-ADP-ribosylation (MARylation) or poly-ADP-ribosylation (PARylation) (Wu *et al*., 2020). Post-translational modifications play a crucial role in regulating chromatin structure, replication, recombination, and DNA repair. Recent research has brought attention to the role of PARPs in natural immune reactions, indicating their potential as targets for various diseases such as cancer, infections, and inflammatory conditions. Moreover, PARP inhibitors have displayed potential in the treatment of cancer by regulating PARP function, especially in DNA damage response and nucleosome remodelling processes (Chaitanya *et al*., 2010). The PARP family consists of 17 members, with 10 being potential members, that exhibit significant diversity in structure and function inside the cell. The family is divided into three categories according to their patterns and roles: Group 1 (PARP 1-5) contains a conserved glutamate residue (Glu988) and is functional, while Group 2 (PARP 6-8, 10-12, and 14-16) are potential mono-(ADP-ribose) polymerases and are not functional. Members of Group 3 (PARP 9 and 13) lack the PARP signature motif for NAD+ binding and do not possess Glu988, suggesting they are not functional.

The PARP family consists of four domains: a DNA-binding domain, a caspase-cleaved domain, an auto-modification domain, and a catalytic domain. The catalytic region is accountable for facilitating poly (ADP-ribose) synthesis, which plays a role in both DNA repair and cellular apoptosis. The most researched member of the family is PARP-1, which has a key function in DNA repair and cell death. The family is also engaged in transcription, spermatogenesis, epigenetics, and differentiation (Jubin *et al*., 2016; Suskiewickz *et al*., 2023). PARP involvement in kidney injury includes causing kidney lesions, affecting kidney energy metabolism, supporting inflammatory responses, and playing a key role in inducing reperfusion injury in different tissues and organs, such as the kidneys (Wang *et al*., 2018; Deshpande *et al*., 2021; Yoon *et al*., 2015). Activation of PARP can worsen side effects like anaemia in individuals with chronic kidney disease and cancer. Moreover, activation of PARP1 caused by acute kidney injury from ischemia can result in interstitial fibrosis, an important structural aspect of chronic kidney disease (CKD), by mechanisms that include inflammation, activation of myofibroblasts, proliferation of fibroblasts, and deposition of extracellular matrix (Yoon *et al*., 2015). PARP inhibitors have displayed potential in shielding against kidney damage caused by ischemia-reperfusion and other nephrotoxic situations (Deshpande *et al*., 2021).

Below is an overview of the PARP inhibitors ranging from the initial generation to the latest, third generation.

Table no 1

PARP inhibitor	**Chemical name**	**Use**
First generation PARP inhibitors		
Nicotinamide	Pyridine-3-carboxamide	PARP inhibitor, reduce oxidative stress and inflammation.
3-Aminobenzamide	3-Aminobenzamide	A weak PARP inhibitor. Angiogenesis.
Second-generation PARP inhibitors		
PD128763	3,4-dihydro-5-methylisoquinolin-1(2*H*)-one	Originally developed by Warner-Lambertan and characterized as a cytoprotective agent and a

		chemosensitizer and radiosensitizer
DPQ	3,4-Dihydro-5[4-(1-piperindinyl) butoxy]-1(2H)-isoquinoline	Anti-inflammatory
NU1025	2-(4-hydroxyphenyl) benzamidazole-4-carboxamide	Inhibitors of topoisomerase I and II
Third-generation PARP inhibitors, FDA-approved PARP inhibitors		
Olaparib	4-[[3-[4-(cyclopropanecarbonyl) piperazine-1-carbonyl]-4-fluorophenyl] methyl]-2H-phthalazin-1	Olaparib was the first PARPi to be approved as first-line maintenance monotherapy in the US based on the results of the Phase III SOLO1 trials.
Niraparib	2-[4-[(3S)-piperidin-3-yl] phenyl] indazole-7-carboxamide	Niraparib reduced the risk of disease progression or death in patients with newly diagnosed ovarian cancer, irrespective of whether the patients had compromised or functional DNA repair mechanisms.
Talazoparib	(11S,12R)-7-fluoro-11-(4-fluorophenyl)-12-(2-methyl-1,2,4-triazol-3-yl)-2,3,10-triazatricyclotrideca-1,5(13),6,8-tetraen-4-one	Talazoparib is a new PARP inhibitor that has been recently approved for use in patients with metastatic breast cancer.
Veliparib	2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide	DNA damage repair, Anti-cancer

Role of PARP in kidney

PARP-1 is the founding and best-studied member of the PARP family. Activation of PARP-1 is important in the DNA damage response and repair of single-strand DNA breaks. Overactivation of PARP-1 due to excessive DNA damage can lead to regulated necrosis pathways, cell death, and tissue damage in the kidney. PARP inhibitors can prevent this overactivation of PARP-1, thereby alleviating ischemia-reperfusion injury (IRI) in the kidney (Devalaraja *et al*., 2009). PARP-1 activation in the kidney after IRI can lead to poly (ADP-ribosylation) of the glycolytic enzyme GAPDH. This modification inhibits GAPDH activity, compromising anaerobic glycolysis and exacerbating ATP depletion in the proximal tubular cells. PARP inhibitors can prevent the poly (ADP-ribosylation) of GAPDH, restoring its activity and ATP levels, thereby protecting against IRI-induced kidney injury. PARP overactivation can deplete cellular NAD+ levels, which are essential for various cellular functions. PARP inhibitors can prevent the depletion of NAD+ and maintain the activity of NAD+-dependent enzymes, such as sirtuins, which can also help alleviate IRI-induced kidney damage (Devalaraja *et al*., 2009). PARP inhibition can affect the intrarenal immune microenvironment, influencing the trafficking and subtypes of leukocytes, as well as the levels of cytokines and chemokines. Early PARP inhibition may improve the intrarenal immune response and facilitate recovery after IRI, but late PARP inhibition may have detrimental effects on the healing process (Suskiewickz *et al*., 2023).

PARP1 hyperactivation is a critical mechanism in the development of programmed necrosis in the kidney. When DNA damage occurs, PARP1 is activated to initiate the repair process. However, excessive DNA damage can lead to the overactivation of PARP1, which can result in the depletion of cellular NAD+ and ATP, ultimately causing cell death and tissue damage. In the kidney, PARP1 overactivation has been linked to the development of acute kidney injury and chronic kidney disease (Arruri *et al*., 2021). The overactivation of PARP1 can also trigger the release of AIF from mitochondria, leading to programmed necrosis. This process is mediated by the activation of calpains and the depletion of intracellular ATP. The inhibition of PARP1 has been shown to alleviate pathological kidney lesions, improve kidney energy metabolism, and inhibit inflammatory responses (Wang *et al*., 2018).

PARP is the primary molecule that causes NAD+ levels to decrease following exposure to DNA-damaging agents and gamma radiation. This results in constant depletion of NAD+ and consumption of ATP in cells with unresolved DNA damage, ultimately leading to programmed necrosis. Exhaustion of

NAD+ and opening of mitochondrial pores are important stages in cell death caused by PARP1. Replenishing NAD+ aids in restoring mitochondrial membrane potential and hinders AIF movement from mitochondria to the nucleus. Activation of PARP1 leads to quick mitochondrial dysfunction, leading to the release of AIF and cytochrome c. Overstimulation of PARP1 causes a decline in mitochondrial energy production due to the breakdown of poly ADP-ribose into AMP, which hinders ADP from binding to the adenine nucleotide transporter, exacerbating the energy shortage. (Formentini *et al*., 2009)

Activation of PARP1 leads to the liberation of AIF from mitochondria, initiating a cellular demise pathway independent of caspase activation (Yu *et al*., 2009) The study found that AIF release relies heavily on PARP1, while PARP1-induced cell death depends on AIF. Therefore, PAR serves as a signal for cell death by inducing the liberation of AIF when PARP1 is activated, and cells without AIF have a higher likelihood of surviving PARP1-induced cell death (Yu *et al*., 2009). The liberation of AIF from mitochondria is necessary for PARP1-induced cell death, known as "parthenatos," and is not reliant on calpain activation. The translocation of AIF to the nucleus is essential for cell death induced by compounds like arsenic trioxide, involving increased ROS production and elevated PARP1 function, a phenomenon that can be reduced by PARP1 inhibitors. These results show that when PARP1 is activated by ROS, it leads to the liberation of AIF and triggers a cell death process that is independent of caspases. Furthermore, upon AIF translocation to the nucleus, it results in chromatin condensation and DNA fragmentation. Reducing AIF levels can increase cell resistance to necrosis caused by DNA alkylating agents, indicating AIF's role in cell death through the PARP pathway (Hong *et al*., 2013).

Rats treated with Alpha Lipoic acid against cadmium-induced nephrotoxicity attenuation of Caspase-9, Caspase-3 and PARP1. (Chen *et.al*., 2018). Thus cleavage of PARP1 by caspase is the emblem of apoptosis. study concludes that PARP inhibition offers protective effects on kidney grafts by reducing poly-ADP-ribosylation and oxidative stress, enhancing anti-apoptotic signalling, and shifting kinase pathways toward cytoprotection (Kalmar *et al*., 2013). PARP-1 plays a detrimental role in ischemic kidneys by inhibiting glycolysis through the poly(ADP-ribosylation) of GAPDH. This inhibition contributes to energy depletion and cell death during ischemic renal injury. inhibition of PARP with 3-AB attenuates ischemic renal injury in rats. PARP inhibition preserves renal function and reduces histological damage in this model of ischemia-reperfusion injury (Martin *et al*., 2000).

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