European Journal of Public Health Studies
ISSN: 2668 - 1056
ISSN-L:2668 - 1056
Available on-line at: www.oapub.org/hlt

DOI: 10.46827/ejphs.v8i3.225 Volume 8 | Issue 3 | 2025

ROLIPRAM AND PDE4 INHIBITION AS PROMISING THERAPEUTICS IN INFLAMMATION

E. Mammadov[1],
S. İmamverdiyev[2],
R. Naghiyev[2i],
O. Isayev[2]
[1]Ege Hospital,
Baku, Azerbaijan
[2]Azerbaijan Medical University,
Baku, Azerbaijan

Abstract:
Ischemia-reperfusion injury (IRI) remains a significant clinical challenge due to the complexity of its pathophysiology, which encompasses oxidative stress, inflammation, and regulated cell death. The evidence reviewed in this study highlights the promising role of Rolipram as a potential therapeutic agent for mitigating ischemia-reperfusion (I/R)-induced tissue damage. By increasing intracellular cAMP levels, Rolipram modulates key molecular pathways, including NF-κB, MAPK, and CREB, leading to a reduction in pro-inflammatory cytokine production, an inhibition of oxidative stress, and an enhancement of cellular survival mechanisms. Future research should aim to address these limitations through the use of advanced delivery systems, isoform-selective inhibitors, and well-controlled clinical trials. Nevertheless, the current evidence base supports the ongoing investigation of Rolipram as a multifunctional therapeutic candidate with the potential to significantly improve outcomes in ischemia-reperfusion injury.

Keywords: reactive oxygen species, ischemia–reperfusion injury, inflammation, rolipram

1. Introduction

Ischemia of vital organs can result in serious outcomes such as myocardial infarction (MI) and cerebral infarction, both of which may cause irreversible tissue damage. Prolonged lack of oxygen and nutrients disrupts cellular metabolism, ultimately leading to cell death. This pathological process not only compromises organ function but also significantly increases morbidity and mortality rates (19). Ischemia-reperfusion injury (IRI) is a pathological condition in which the restoration of blood flow following a period

[i] Correspondence: email eminmammadov107@gmail.com

of ischemia paradoxically exacerbates tissue damage and impairs organ function. This phenomenon is associated with a range of clinical conditions, including acute myocardial infarction, stress ulcers, pancreatitis, intestinal ischemia, intermittent claudication, acute tubular necrosis, post-shock liver failure, and multisystem organ failure (4). The reintroduction of oxygen and nutrients triggers a cascade of harmful events such as oxidative stress, calcium overload, mitochondrial dysfunction, and intense inflammatory responses, all of which contribute to further cellular injury. I/R injuries involve multiple pathological mechanisms, including various forms of cell death (apoptosis, necrosis, and ferroptosis), oxidative stress, inflammation, disruption of the blood-brain barrier (BBB), extracellular matrix (ECM) remodeling, angiogenesis, cardiomyocyte hypertrophy, and fibrosis. These interconnected processes contribute to the progressive deterioration of tissue structure and function, complicating recovery and therapeutic interventions. (19)
The pathophysiology of IRI is highly complex, involving multiple interrelated mechanisms. Oxidative stress and the inflammatory response play central roles in the progression of tissue damage. During the IRI, numerous factors such as proinflammatory cytokines and reactive oxygen species (ROS) are generated, contributing to cellular dysfunction and injury (6). IRI is a multifactorial inflammatory condition associated with significant morbidity and mortality, often leading to acute organ dysfunction. Its complex pathogenesis poses major challenges for effective clinical management and underscores the need for targeted therapeutic strategies (1,16). ROS are a group of highly reactive and potentially harmful oxidant molecules, including superoxide anion, hydroxyl radical, singlet oxygen, and hydrogen peroxide, which are produced within living cells. These elements are implicated in both the synthesis and degradation processes that are vital to the maintenance of cellular homeostasis. Under normal physiological conditions, ROS act as critical regulators of cell signaling and energy metabolism. However, in the context of IRI, excessive ROS generation leads to oxidative stress by interacting with cellular lipids, proteins, and DNA, thereby amplifying tissue damage (6). This oxidative imbalance has been demonstrated to disrupt mitochondrial function, enhance inflammatory responses, and contribute to endothelial dysfunction, thereby exacerbating the initial injury. The targeting of ROS-mediated pathways has been identified as a potential strategy for reducing tissue damage in I/R-related conditions. One of the key outcomes of oxidative stress is lipid peroxidation, a process in which ROS attack polyunsaturated fatty acids in cell membranes, leading to structural damage and loss of membrane integrity. Among the by-products of lipid peroxidation, malondialdehyde (MDA) is one of the most mutagenic aldehydes formed. MDA has been identified as a reliable biomarker for oxidative stress and sustained cellular damage, as its accumulation is indicative of ongoing lipid degradation and the extent of oxidative injury. Elevated MDA levels are frequently observed in conditions involving ischemia-reperfusion injury, neurodegenerative diseases, and inflammatory disorders (17).

An overproduction of ROS, especially superoxide anions (O_2^-), disrupts cellular redox homeostasis and initiates oxidative stress. Superoxide acts as a primary initiator in a chain of radical-driven reactions, ultimately leading to the excessive accumulation of secondary ROS such as hydrogen peroxide (H_2O_2) and hydroxyl radicals (•OH).

Superoxide dismutase (SOD), a metalloenzyme and key component of the endogenous antioxidant defense system, catalyzes the dismutation of superoxide into hydrogen peroxide and molecular oxygen. This enzymatic reaction serves as a critical early defense mechanism to limit ROS-mediated cellular injury and preserve oxidative balance (12). I/R injury has been shown to elicit a complex and tightly regulated sterile inflammatory response, which, although critical for initiating tissue repair, can also contribute to secondary tissue damage and organ dysfunction. Inflammation, under physiological conditions, serves as a protective mechanism against invading pathogens. This process involves the activation and recruitment of innate immune cells, such as neutrophils and macrophages (15). These cells are responsible for the clearance of pathogens through the process of phagocytosis, and they also produce a range of mediators (7). Concurrently, antigen presentation activates lymphocytes, thereby triggering adaptive immune responses and further amplification of cytokine and chemokine signaling cascades. In the setting of I/R, inflammation occurs in the absence of microbial invasion and is thus defined as sterile inflammation. This process is initiated by damage-associated molecular patterns (DAMPs) released from necrotic or stressed cells, which activate pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) on resident immune and endothelial cells. The ensuing signal transduction leads to the rapid mobilization of neutrophils, production of proinflammatory cytokines (e.g., TNF-α, IL-1β, IL-6), chemokines (e.g., CXCL1, MCP-1), and endothelial activation (14). These events culminate in increased vascular permeability, leukocyte adhesion and transmigration, and further propagation of oxidative and inflammatory injury, forming a central component of the pathophysiology of I/R-induced organ damage (7).

Despite the extensive research that has been carried out in this field, the clinical management of I/R injury remains suboptimal due to several critical limitations in existing therapeutic strategies. The majority of contemporary interventions concentrate on a limited number of pathways, including oxidative stress, inflammation, or apoptosis, without adequately addressing the multifactorial and dynamic nature of I/R pathophysiology. Antioxidants, for instance, frequently fail to achieve effective intracellular concentrations or suffer from poor bioavailability and timing-related challenges, thereby limiting their efficacy in neutralizing ROS at the initiation of reperfusion. In a similar way, anti-inflammatory agents have been shown to suppress necessary immune functions or to exhibit systemic side effects that restrict their clinical application. Furthermore, a significant number of experimental therapies that demonstrate potential in preclinical models, including ischemic preconditioning, cytokine inhibitors, and mitochondrial-targeted agents frequently fail to translate into clinical benefit due to differences in species physiology, comorbidities, and therapeutic windows. A further significant challenge pertains to the inability to selectively target injured tissues while sparing healthy ones, resulting in off-target effects. Consequently, there is an urgent need for multimodal and precisely timed interventions that integrate the regulation of oxidative stress, immune activation, and cellular metabolism to effectively mitigate I/R-induced damage.

Rolipram is described as a selective inhibitor of phosphodiesterase-4 (PDE4), an enzyme that plays a critical role in intracellular signaling by hydrolyzing the phosphodiester bonds of secondary messenger molecules such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). This enzymatic activity results in the reduction of cAMP/cGMP bioavailability and signaling activity. Inhibition of PDE4 leads to an increase in intracellular cAMP levels, which mediates anti-inflammatory, immunomodulatory, and neuroprotective effects.

Rolipram has shown therapeutic promise in the regulation of inflammatory responses, prevention of neurological disorders, and management of various cardiovascular diseases. The suppression of pro-inflammatory mediators such as TNF-α and IL-6 via PDE4 inhibition is particularly important in protecting tissues from inflammatory damage. (Kim Hüang) PDE4 is predominantly found in immune and neural cells and specifically hydrolyzes cAMP. An elevation in intracellular cAMP suppresses the synthesis of chemokines such as TNF-1 and IL-2, as well as the expression of cell adhesion molecules, contributing to a dampened immune response through cAMP-dependent signaling cascades.

Although limited, existing studies on human eosinophils suggest that the pharmacological effects of PDE4 inhibitors in these cells mirror those observed in guinea pig eosinophils. Rolipram effectively inhibits superoxide anion generation and significantly reduces leukotriene C_4 (LTC_4) synthesis, chemotaxis, and CD11b adhesion molecule expression in response to platelet-activating factor (PAF) and C5a stimulation. Studies involving murine macrophages have demonstrated that rolipram enhances the synthesis of IL-10, a key immunoregulatory cytokine that inhibits the production of TNF-α and IL-6, thereby maintaining immune homeostasis. This mechanism supports rolipram's potential as a therapeutic agent in chronic inflammatory diseases. In murine models of chronic arthritis, the anti-inflammatory effect of rolipram has been shown to play a dominant role, indicating its potential for long-term immunoregulation.

Rolipram has exhibited notable efficacy against various inflammatory processes. For instance, in rodent models, it significantly reduced endogenous TNF-α secretion. Intraperitoneal administration of rolipram also attenuated LPS-induced TNF-α expression and mRNA levels in the brain. In Wistar rats, rolipram reduced inflammatory responses in an LPS-induced anterior uveitis model and significantly lowered systemic levels of E-selectin, TNF-α, and IL-6. In general, these results highlight rolipram's anti-inflammatory effects on both neural and immune cells, primarily through the elevation of intracellular cAMP levels.

The present review is intended to provide a comprehensive analysis of preclinical studies investigating the effects of Rolipram in various models of IRI, including cardiac, cerebral, renal, and gastrointestinal systems. The investigation focuses on the anti-inflammatory, antioxidant, and anti-apoptotic mechanisms, with a particular emphasis on molecular targets such as NF-κB, TNF-α, and IL-1β.

2. Material and Methods

The process involved three fundamental steps: firstly, formulating the hypothesis; secondly, identifying significant literature by employing suitable techniques and standards for inclusion; and thirdly, synthesizing and structuring the data collected prior to presenting the outcomes.

2.1 Defining the research question

The objective of this review is to evaluate the therapeutic potential of Rolipram in the context of IRI, a pathological process characterized by oxidative stress, inflammation, and regulated cell death following the restoration of blood flow after a period of ischemia. Rolipram has emerged as a promising pharmacological agent due to its ability to elevate intracellular cAMP levels, which in turn modulates key signaling pathways involved in inflammation, oxidative damage, and cellular survival.

2.2 Identifying relevant references by using appropriate search methods and inclusion criteria

The current literature review was conducted using electronic databases, including PubMed, Scopus, Web of Science (WoS), and Google Scholar. A systematic search was conducted by independent researchers to identify relevant articles addressing the research question. In the case of any discrepancies arising during the selection process, these were resolved through consultation with a third author who served as an arbitrator. The resolution of any further disagreements was achieved through group discussions involving an additional researcher. The final manuscript was subjected to a comprehensive review process, resulting in approval by all authors.

In line with the established eligibility criteria, the literature search was restricted to cross-sectional epidemiological studies, systematic reviews, and meta-analyses published in English between 2020 and 2025. The search strategy employed utilized Boolean operators, such as "AND", to combine relevant Medical Subject Headings (MeSH) and keywords across all database fields.

2.2.1 Search query: "Rolipram" and “ischemia-reperfusion injury”

The resulting records were then imported into EndNote v.20 (Thomson ResearchSoft, Stanford, CA, USA) for the purpose of citation management and the identification and removal of duplicates. Subsequently, a comprehensive review of each reference was conducted to determine its relevance. Non-academic sources, including newspapers, internet websites, and magazines, were excluded from the study. Following the screening process, a total of 9 records were retained for further analysis.

3. Results

The present manuscript utilizes a desktop analysis approach, with a particular emphasis on the reliability of the information sources. In view of the novelty of the topic, a total of 9 relevant academic papers were identified and analyzed.

The study by Bozkurt et al. (2024) investigates the therapeutic potential of Phosphodiesterase 4 (PDE4) inhibition via rolipram in mitigating ovarian ischemia-reperfusion (OIR) injury in rats. The authors of the study demonstrate that OIR elevates inflammatory markers (TNF-α, IL-6, NF-κB, MAPK) and reduces AQP5 and cAMP levels, while rolipram has been shown to reverse these effects in a drug-dependent way. The findings from both molecular and histopathological analyses support the conclusion that PDE4 inhibition has a protective effect, which is achieved through the regulation of AQP5 expression and inflammatory signaling. These research outcomes underscore AQP5 as a prospective molecular target in the therapeutic approach to OIR injury. (3)

The study conducted by Lu aims to investigate the therapeutic potential of rolipram in the context of sepsis. Although previously unproven for this particular purpose, rolipram was found to significantly improve outcomes in murine models of sepsis, including E. coli infection, cecal ligation and puncture (CLP), and LPS injection. The pharmaceutical treatment was found to have a dual effect on the immune system, reducing both organ damage and pro-inflammatory cytokine levels while enhancing anti-inflammatory responses. These outcomes were likely achieved through the inhibition of the MAPK and NF-κB pathways (14). The results suggest that rolipram may offer a promising, versatile treatment strategy for sepsis. (8)

In their study, Zhong et al. critically highlighted the pressing need for effective pharmacological strategies in the management of stroke, given its high mortality, disability, and recurrence rates. Traditional therapeutic interventions, such as thrombolysis, are constrained by narrow therapeutic windows and associated bleeding risks. This has given rise to a renewed interest in neuroprotective alternatives. PDE4, particularly the PDE4D isoform, has emerged as a promising target due to its role in synaptic plasticity, metabolic regulation, and neuroprotection following ischemic injury. It is hypothesised that PDE4 inhibitors may offer innovative and safer therapeutic options for stroke patients by supporting neuronal recovery and minimizing secondary brain damage. (20)

The present study by Nashtahosseini et al. explores the role of cytokine signaling in diabetic peripheral neuropathy (DPN), emphasizing oxidative stress and inflammatory pathways. Rolipram has been demonstrated to be efficacious in the reduction of oxidative stress markers (ROS and lipid peroxidation) and the inhibition of inflammation by decreasing TNF-α and COX2 production. These results suggest that rolipram could be a promising therapeutic option, capable of mitigating peripheral nerve damage through regulation of inflammatory and oxidative mechanisms in diabetic neuropathy. (11)

Varona et al. investigate PDE4 as a potential therapeutic target in abdominal aortic aneurysm (AAA), a condition characterized by excessive inflammation and oxidative

stress. Utilizing an angiotensin II-infused mouse model, the authors demonstrate that PDE4B expression is elevated in inflammatory cells of both experimental and human AAAs. The study demonstrated that the treatment of rolipram significantly prevented aneurysm formation, reduced vascular inflammation and oxidative stress, and preserved vascular integrity. These outcomes provide evidence to support the hypothesis that PDE4B inhibition via rolipram could be a promising therapeutic strategy for the prevention of AAA progression. (18)

The study by Maher et al. explores the possible therapeutic effects of the PDE4 inhibitor rolipram in reversing cognitive deficits caused by sleep deprivation in mice. The researchers demonstrated that prolonged sleep deprivation significantly impaired memory consolidation and reduced cyclic AMP (cAMP) levels in the hippocampus. The efficacy of rolipram in restoring cognitive function was demonstrated by its ability to engage both the protein kinase A (PKA)-dependent pathway and the exchange protein directly activated by cAMP (Epac)-dependent pathway. These outcomes suggest that rolipram could be a promising pharmacological strategy to address cognitive impairments associated with sleep disorders by simultaneously modulating multiple intracellular cAMP signaling mechanisms. (10)

The study by Bhatt et al. evaluates the therapeutic effects of PDEIs against arsenic-induced neurotoxicity in rats. PDEIs are a class of pharmaceuticals which inhibit phosphodiesterase enzymes. The study specifically focuses on two PDEIs: rolipram and vinpocetine. Chronic exposure to arsenic has been demonstrated to result in significant impairment to brain function, increased oxidative stress, and reduced antioxidant capacity. Treatment with rolipram and vinpocetine led to a significant reduction in oxidative damage, enhancement of antioxidant enzyme activity, and an increase in the expression of CREB and phosphorylated CREB (P-CREB) in the hippocampus. (2)

The present review by Ma et al. addresses the therapeutic potential of targeting cyclic AMP (cAMP) signaling via PDE4 inhibition for liver diseases, particularly alcoholic liver disease (ALD) and metabolism-associated fatty liver disease (MAFLD). PDE4 inhibitors have demonstrated significant potential in reducing hepatic inflammation, enhancing lipid metabolism, and alleviating insulin resistance. Furthermore, PDE4 inhibition has demonstrated a beneficial impact on liver fibrosis through the suppression of hepatic stellate cell activation. While encouraging preclinical results have been observed, the inconsistent outcomes of clinical trials highlight the necessity for further investigation to substantiate the efficacy of PDE4 inhibitors as therapeutic modalities for liver disease. (9)

The review by Fan et al. systematically evaluates the anti-inflammatory and vasculoprotective properties of PDE4 inhibitors, with a particular focus on rolipram. Rolipram has been demonstrated to significantly reduce pulmonary inflammation and tissue damage in pneumococcal pneumonia. This effect is achieved through the upregulation of the anti-inflammatory mediator annexin A1 (AnxA1) and the suppression of pro-inflammatory cytokines (TNF-α, IL-6). Furthermore, it has been demonstrated to have protective effects in models of sepsis by inhibiting MAPK and NF-κB signaling pathways, enhancing IL-10 production, and reducing the secretion of

inflammatory cytokines (IL-1β, IL-5, IL-6, IL-12, TNF-α). Furthermore, rolipram has been evidenced to alleviate endotoxin-induced cardiac dysfunction by increasing the expression of dual specificity phosphatase 1 (DUSP1) and mitigating fibrosis by modulating macrophage polarization and cytokine release. Taken together, these data underscore the therapeutic significance of PDE4 inhibition in inflammatory and vascular diseases. (5)

4. Discussion

The results of this review demonstrate the significant therapeutic potential of Rolipram in reducing the adverse effects of IRI in various organ systems. The preclinical data demonstrate that Rolipram has anti-inflammatory, antioxidant, and anti-apoptotic activity, primarily through the elevation of cAMP levels and subsequent modulation of key molecular pathways such as NF-κB, MAPK, and CREB. A number of studies have identified the protective role of Rolipram in reducing oxidative stress and inflammatory cytokine production (e.g., TNF-α, IL-6), both of which are central to the pathogenesis of IRI. The observations reported by Bozkurt et al. concerning ovarian IRI, and those of Varona et al. concerning abdominal aortic aneurysm models, provide particularly significant evidence of the capacity of Rolipram to modulate inflammatory markers and preserve tissue structure (3, 18). Furthermore, the observed increase in anti-inflammatory mediators, including IL-10 and annexin A1, suggests that Rolipram not only suppresses harmful immune activation but also supports regulatory processes that maintain immune homeostasis. The potential of Rolipram to protect neurons was demonstrated in studies of ischemic stroke and sleep deprivation models. These studies showed that Rolipram enhanced cognitive performance and neuronal resilience by restoring cAMP signaling and modulating PKA and Epac pathways. This observation is consistent with the literature on diabetic peripheral neuropathy and arsenic-induced neurotoxicity, thereby further substantiating the comprehensive efficacy of PDE4 inhibition in attenuating neural oxidative damage and inflammation. Despite these encouraging results, it is crucial to acknowledge the limitations that mitigate the immediate clinical relevance of Rolipram. Firstly, the majority of existing data are derived from animal models, which may not accurately reflect human pathophysiology. The existence of species-specific differences in PDE4 isoform expression, pharmacokinetics, and immune responses poses significant barriers to the translation of research findings into clinical practice. Secondly, while Rolipram demonstrates strong efficacy in experimental settings, its known side effects – particularly nausea and gastrointestinal discomfort associated with PDE4 inhibition – may limit its tolerability in humans, as observed in early clinical trials.

Furthermore, the optimal timing and dosage of Rolipram remain as significant challenges. The dynamic nature of IRI, with distinct early and late pathological phases, necessitates a nuanced understanding of when and how to deliver therapy to maximize benefit while minimizing off-target effects. In this context, the development of isoform-selective PDE4 inhibitors or targeted delivery systems (e.g. nanoparticle-based carriers)

may enhance therapeutic specificity and safety. An additional factor that must be considered is the organ-specific variation in response to Rolipram. While consistent anti-inflammatory and antioxidant benefits are observed across cardiac, renal, cerebral, and hepatic models, the degree of protection and the molecular mechanisms involved appear to vary. This underlines the necessity for organ-specific studies to determine optimal therapeutic regimens and elucidate signaling pathways that differ.

The present review supports the growing scientific view that multimodal agents, such as Rolipram, which simultaneously target oxidative stress, inflammation, and cell death pathways, represent a promising class of therapeutics for IRI. However, there are still significant clinical translation gaps. Future research should concentrate on well-designed clinical trials, long-term toxicity studies, and combination strategies that combine Rolipram with drugs targeting complementary pathways such as mitochondrial protection, endothelial repair, or immune modulation.

5. Conclusion

IRI remains a significant clinical challenge due to the complexity of its pathophysiology, which encompasses oxidative stress, inflammation, and regulated cell death. The evidence reviewed in this study highlights the promising role of Rolipram as a potential therapeutic agent for mitigating I/R-induced tissue damage. By increasing intracellular cAMP levels, Rolipram modulates key molecular pathways, including NF-κB, MAPK, and CREB, leading to a reduction in pro-inflammatory cytokine production, an inhibition of oxidative stress, and an enhancement of cellular survival mechanisms.

Preclinical models across multiple organ systems – including the brain, heart, kidneys, liver, and ovaries – demonstrate consistent protective effects of Rolipram, suggesting broad therapeutic applicability. Nevertheless, despite the encouraging results, significant challenges persist in translating these findings into clinical practice. These include species-specific responses, adverse side effects, limited human data, and the need for precise dosing and timing strategies.

Future research should aim to address these limitations through the use of advanced delivery systems, isoform-selective inhibitors, and well-controlled clinical trials. Nevertheless, the current evidence base supports the ongoing investigation of Rolipram as a multifunctional therapeutic candidate with the potential to significantly improve outcomes in ischemia-reperfusion injury.

Financial Support Statement
None.

Ethics Statement
As this is a literature search without the collection of primary data, a formal ethical approval is not required. We will disseminate our results in the form of an open-access publication and international conferences.

Conflict of Interest Statement
The authors declare no conflict of interest.

About the Author(s)
Dr. Emin Məmmədov is a urologist-andrologist, with medical training from Azerbaijan Medical University and specialist certification from Çukurova University in Adana, Turkey. He also holds the prestigious European Board of Urology (FEBU) diploma and specializes in advanced urological surgery.
Professor Sudeyif B. İmamverdiyev is an esteemed urologist-scientist at Azerbaijan Medical University, where he established the university's Urology Hospital in 1975 and has led the Urology Department since 1990. He is a corresponding member of the Azerbaijan National Academy of Sciences and the accomplished author of numerous innovations and rationalization proposals in surgical methodology.
Dr. Rauf N. Naghiyev is an Associate Professor (Teaching Assistant) in the Department of Urology at Azerbaijan Medical University, specializing in laparoscopic nephrectomy and other minimally invasive urological surgeries. He has co-authored peer-reviewed studies assessing outcomes of laparoscopic partial and radical nephrectomies, contributing to the advancement of urological surgical practices.
Associate Professor Orxan Isayev is a medical doctor specializing in histology, embryology, and cytology at Azerbaijan Medical University. Educated at AMU (2005–2011) and later trained in oncology research during his doctoral studies at Heidelberg University (2012–2014), he has co-authored multiple peer-reviewed studies on cancer stem cells and pancreatic cancer mechanisms.

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