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Review article

Kynurenic acid and its analogues

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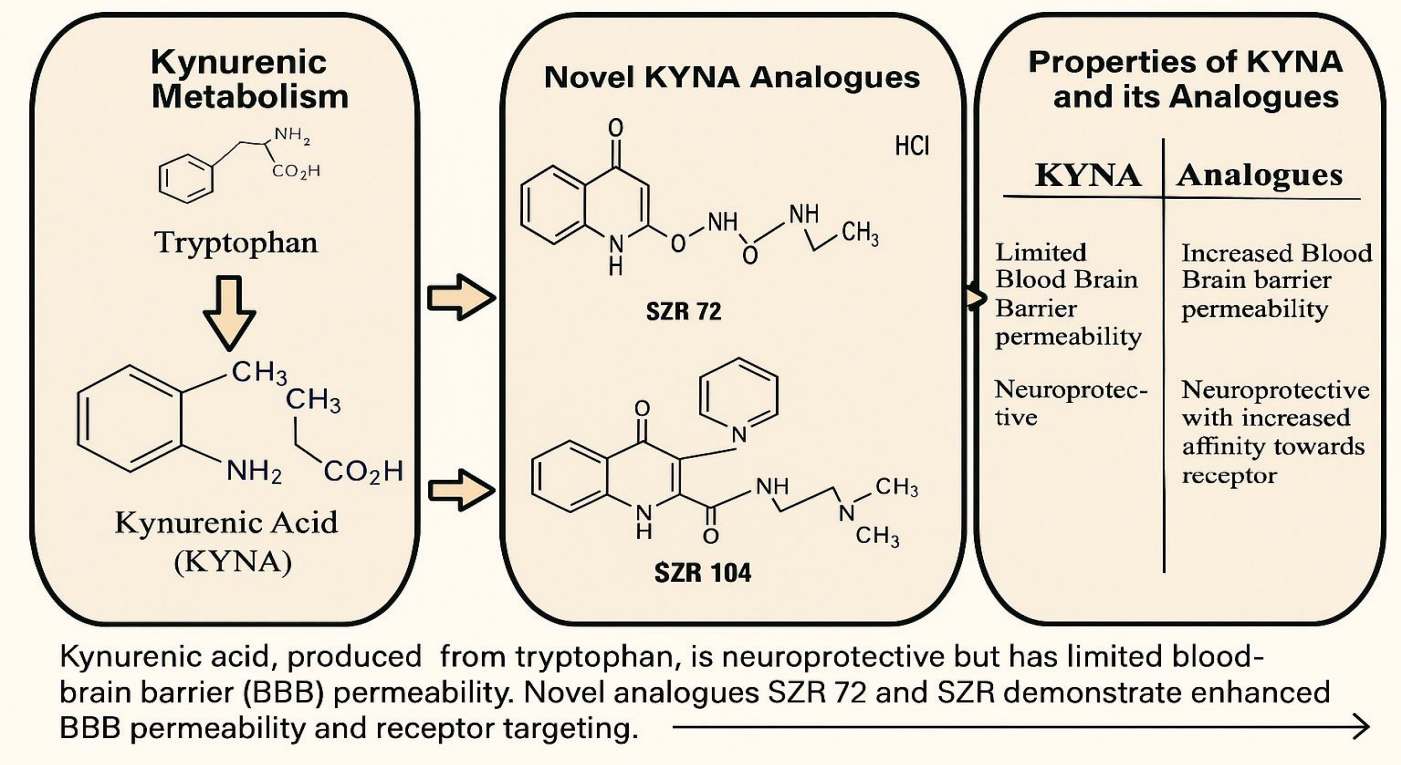
ABSTRACT

Tryptophan serves as a rate-limiting essential amino acid and a distinctive building block of peptides and proteins. Many immune system cells are known to be regulated by tryptophan metabolites. Kynurenic acid, an endogenous byproduct of tryptophan metabolism, functions as a wide-spectrum inhibitor of excitatory amino acid receptors and may serve as a protective agent in neurological disorders. Nevertheless, kynurenic acid's efficacy as a neuroprotective drug is considerably constrained by its restricted ability to traverse the blood–brain barrier. Thus, there is a huge demand for novel kynurenic acid analogues that may easily pass through the blood–brain barrier. The production of kynurenic acid is discussed in this article, as well as an overview of the primary novel kynurenic acid analogues, along with their molecular structures and modes of action.



Keywords: Kynurenic acid, Tryptophan metabolites, Neuroprotective agent, Kynurenic acid analogue, N-methyl-D-aspartate.

INTRODUCTION

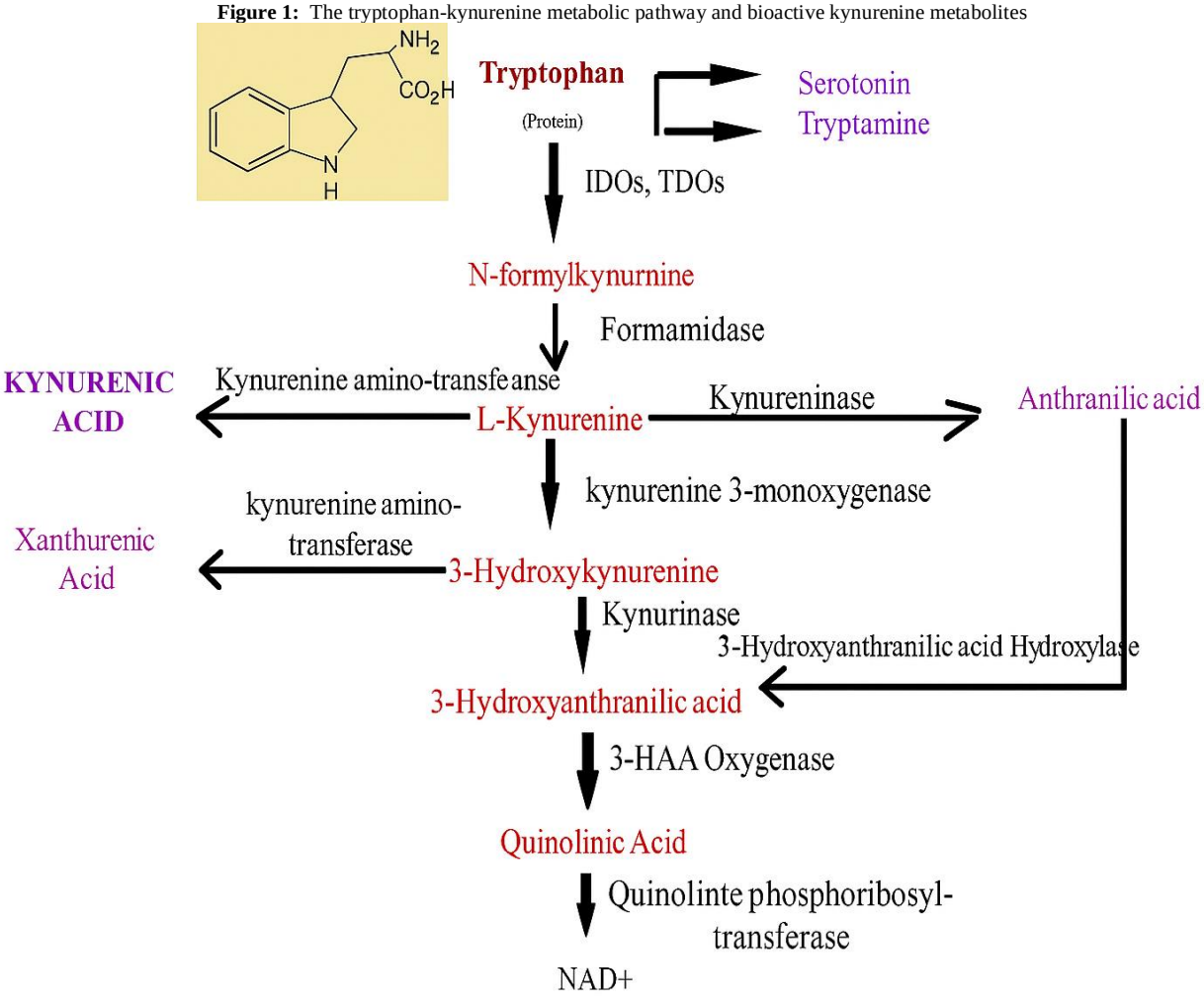
More than 150 years have passed since the discovery of kynurenic acid (KYNA) and the following elucidation of its chemical structure and biosynthesis, which set off a chain of discoveries that ultimately had a big impact on neurology. Originating from the essential amino acid Tryptophan (TRP), KYNA was the first of a class of substances known as "kynurenines" that are associated to metabolism [1]. Additionally, via exerting agonistic effects on the aryl hydrocarbon receptor (AhR), a transcription factor implicated in xenobiotic metabolism, KynA controls the immunological response [2]. In recent years, there has been a major gain in information regarding the role of metabolites of the kynurenic acid synthesis pathway in both the neurological system and as potential causes of a number of serious brain illnesses.

The kynurenine pathway and receptors

In both humans and animals, astrocytes and neurones produce KYNA, a neuroprotective endogenous tryptophan metabolite, through the kynurenine pathway [3]. All three ionotropic excitatory amino acid receptors— N-methyl-D-aspartate receptors (NMDARs), kainite receptors, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPARs)— are inhibited to roughly the same extent at high micromolar doses by KYNA, a competitive, broad-spectrum glutamate receptor antagonist. KYNA can also non-competitively inhibit α7-nicotinic acetylcholine receptors and also act as an agonist at the orphan G-protein-coupled receptor GPR35[4]. The levels of KYNA in the body and brain are influenced by ageing, stress, inflammation, and genetic diversity. KYNA has also been linked to a number of neuropsychiatric and neurodegenerative diseases [5,6,7]. Additionally, compared to cerebral fluid, KYNA is more abundant in urine, pancreatic mucus, serum, and breast milk. It has since been discovered to have an impact on the peripheral immunological and digestive systems [8,9].

Enzymes such as tryptophan 2, 3-dioxygenase (TDO) and indoleamine 2, 3-dioxygenase (IDO), which catalyse the degradation of tryptophan to formyl kynurenine, are responsible for the Kynurenine pathway's initial stage. IDO is an extrahepatic cytokine-inducible enzyme, while TDO is mostly expressed in the liver. Formyl kynurenine form amidase catalyses the subsequent stage of kynurenine production. Nicotinamide adenosine dinucleotide (NAD+) is the primary byproduct of kynurenine metabolism. Using kynurenine, kynurenine aminotransferase produces KYNA, a physiologically active substance [1,10].

Figure 1: The tryptophan-kynurenine metabolic pathway and bioactive kynurenine metabolites



KYNA Synthesis

Increasingly, recent research findings indicate that the brain's higher KYNA level is protective [11]. Although KYNA has a poor blood–brain barrier (BBB) penetration rate, there are several ways to raise the brain's concentration of KYNA in an experimental setting [12]. Tryptophan degradation along the Kynurenine Pathway is an important immune response regulator, particularly as a counter-regulatory mechanism during inflammation.[13] Tryptophan 2,3-dioxygenase (TDO) and indolamine 2,3-dioxygenase (IDO) 1 and 2 are the three rate-limiting enzymes of KP. To keep TRP in a state of homeostasis, TRP positively regulates TDO [14,15]. Kynurenine 3-hydroxylase degrades L-kynurenine to quinolinic acid first, then kynurenines and 3-hydroxyanthranilic acid oxygenase. Quinolinic acid is then metabolised by quinolinic acid phosphoribosyl transferase into nicotinic acid mononucleotide and, lastly, to the active coenzyme nicotinamide adenine dinucleotide (NAD). The alternative potential of L-kynurenine degradation is the synthesis of KYNA via irreversible transamination of L-kynurenine or the formation of anthranilic acid by kynurenines, which is then hydroxylated to 3-hydroxyanthranilic acid. Additionally, the transaminase catalyses the creation of xanthurenic acid from 3-OH-kynurenine [16]. Moreover, hormones like cortisol, insulin, glucagon, or epinephrine control the production and function of TDO [17]. Interferon-γ (IFN-γ) and other inflammatory stimuli upregulate IDO1 and 2 [18,19.20]. The significance of KP activation is determined by the production of physiologically active metabolites such as kynurenine (KYN), kynurenic acid, quinolinic acid, and anthranilic acid, which mediate various immuno- and neuromodulator effects. Metabolites like KYNA and QUIN have been shown to influence neurological activities within the central nervous system. KYNA is a neuroprotective metabolite that acts as an antagonist for every ionotropic glutamate receptor, comprising NMDA, AMPA, and kainite receptors, in addition to the α7 nicotinic acetylcholine receptor (α7nAChR) [21,22].

KYNA: Mechanism of action in the brain

For a while, it was thought that a relationship between KYNA and the neurotransmitter NMDA receptor complex could have a physiological role in the functioning of the brain. However, it has been repeatedly proven that KYNA is a powerful antagonist of the glycine allosteric site of the NMDA receptor complex. KYNA has been linked to several neuropsychiatric and neurodegenerative disorders, with its concentrations in the brain and body altered through variables such as inflammation, stress, ageing, and genetic variation [5,23,24].

Research into KYNA's molecular mechanisms of action in the central nervous system has produced conflicting findings. At low concentrations, KYNA acts as a competitive inhibitor at the NMDA receptor's glycine-binding region and a noncompetitive antagonist at the -7 nicotinic receptor. However, at non-physiologic (millimolar) levels, KYNA has been found to bind rather non-selectively on a number of distinct receptor types [25]. Thus, in regions of the brain with neuronal damage and accompanying NMDA receptor hyperactivity, KYNA acts as a glutamate receptor antagonist, which contributes considerably to its neuroprotective effects [26]. Clinical trials using rationally designed structural variations of KYNA that are specifically bound to the NMDA receptor's glycine-binding domain are underway. Furthermore, KYNA competes with AMPA receptors for binding in the glutamate-binding region in the extracellular ligand-binding domain, resulting in a lower-affinity competitive antagonist [27].

With regard to KYNA's limited capacity to penetrate the blood-brain barrier (BBB), it cannot be utilised as a neuroprotective medication or systemically. This led to the development of various novel KYNA analogues, prodrugs, or derivatives [28].

KYNA in CNS

The central nervous system contains the majority of glutamate receptors. Electrophysiological research indicates that KYNA modulates the brain's neurotransmission [8].

Kynurenic acid analogues

SZR-72{N-(2-(diethyl amino) ethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide}-Amide derivative

SZR-104{N-(2-(dimethyl amino) ethyl)-3-(morpholinomethyl)-4-oxo-1,4dihydroquinoline-2-carboxamide} - Aminoalkylated amide derivative

SZRG-21{N-(2-(dimethyl amino) ethyl)-3-methyl-4-oxo-1,4-dihydroquinoline-2-carboxamide [21]

4-Cl-KYN (L-4-chlorokynurenine) - a prodrug converted in vivo to its active metabolite 7-Cl-kynurenic acid (7-Cl-KYNA)

These analogues can replicate KYNA's pharmacological properties, such as its antagonistic effects on glutamate receptors.

The synthetic analogues of KYNA include N-(2-(dimethylamino)ethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (SZR-72) is a derivative of KYNA amide; N-(2-(dimethylamino)ethyl)-3-(morpholinomethyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide (SZR-104) is a aminoalkylated amide derivative with the new function at C–3 position; and N-(2-(dimethylamino)ethyl)-3-methyl-4-oxo-1,4-dihydroquinoline-2-carboxamide (SZRG-21), which has an alkyl group in the C–3 position as a transitional derivative between SZR-72 and SZR-104. They can replicate KYNA's pharmacological properties, such as its antagonistic effects on glutamate receptors [29].

The neuroprotective substance L-kynurenine sulphate (KYNA-11) can pass the blood-brain barrier and converted to Excitatory Amino Acid (EAA) receptor antagonist KYNA through the

kynurenine aminotransferase enzyme, which is mostly found in glia and has the capacity to both release and absorb KYNA-11. Even in preclinical research, the usage of KYNA-11 is limited due to its significant conversion to the EAA receptor agonist Quinolyl acid (QUIN) upon systemic administration, despite the fact that we obtained good findings in terms of neuroprotection. Particularly in a sick organism, QUIN may pass the blood-brain barrier and have the opposite effect [8,30].

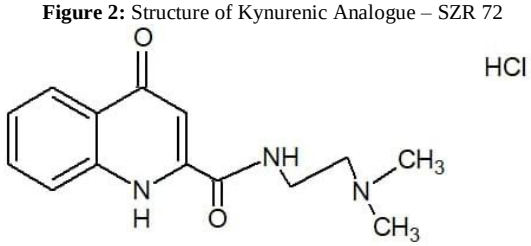
SZR-72

A promising derivative of KYNA, SZR-72, is being studied by many research teams. While KYNA is not very permeable, SZR-72 easily passes through the blood-brain barrier. SZR-72 successfully controlled mitochondrial respiration, and in sepsis, KYNA may help to re-establish microcirculation [31].

It is reported that treatment with the synthetic analogue SZR-72 and the endogenous tryptophan metabolite KYNA decreased the severity of experimental Acute Pancreatitis (AP) in a dose-dependent manner. This protective effect could be mediated by a number of methods. Both drugs increase the expression of the Heat Shock Protein 72 (HSP72) protein while decreasing pancreatic expression of the proinflammatory cytokine IL-1b.

Additionally, these substances restore haemodynamic characteristics, such as pancreatic microcirculation, and lessen metabolic acidosis. In AP, their activity appears to be unrelated to acinar N-methyl-D-aspartate receptor (NMDAR1). Moreover, SZR-72 inhibits neutrophil granulocyte activation [32].

Figure 2: Structure of Kynurenic Analogue – SZR 72



SZR 72

SZR-104

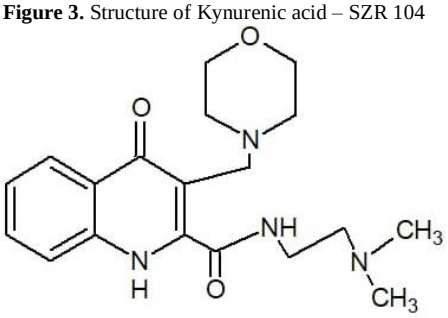
SZR104 was functioning via non-glutamatergic molecular pathways. KYNA and its synthetic substitute SZR104 serve as ligands for the AHR. SZR104's inhibitory effect on microglia activation and proliferation may be explained by its action on AHRs. The AHR complex's genetic processes may have induced the microglia's phenotypic shift, including reduced TNFα release and increased expression of tumour necrosis factor-stimulated gene-6 (TSG-6) [33,34].

SZR-104 has demonstrated the ability to alter immune systems and inhibit glutamate receptors, exhibiting actions similar to KYNA [34].

KYNA and SZR104 both have anti-inflammatory properties in vitro and in vivo, as evidenced by their substantial immunosuppressive capacities in an animal model of epilepsy and inhibiting phagocytosis in microglial cells [35]. Lipopolysaccharide (LPS) treatment in microglial cells also decreased the levels of the inflammatory marker proteins C-X-C motif chemokine ligand 10 (CXCL10) and also C-C motif chemokine receptor 1 (CCR1).

Histone H3 Lys site methylations appear to be crucial epigenetic indicators for inflammation. It's interesting to note that KYNA and its analogue SZR104 may influence KYNA signalling pathways, which may reduce neuroinflammation by triggering anti-inflammatory responses [36].

Figure 3. Structure of Kynurenic acid – SZR 104



SZR 104

SZRG-21

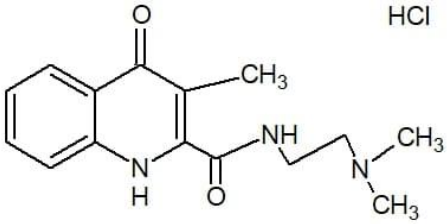
SZRG-21 exhibits an impact on motor activity and emotional behaviour.

BBB penetration - Proven efficacy in lowering cytokine levels in colitis models.

Impact on motor activity - Change motor activity and exploratory behaviours.

Emotional and behavioural modification affects psychological processes like motor-associated interest and emotions [2,3].

Figure 4: Structure of Kynurenic acid analogue- SZRG 21



SZRG 21

Cl-KYN

L-4-chlorokynurenine (4-Cl-KYN) was formulated as a prodrug that is immediately metabolised in vivo to its active derivative, 7-Cl-kynurenic acid (7-Cl-KYNA), a precise NMDAR antagonist at the glycine site [37]. 7-Chlorokynurenic acid (7-Cl-KYNA) is an effective and extremely specific competitive antagonist of the glycine B receptor, extensively utilised as a pharmacological probe to investigate the biology of the

NMDA receptor. In contrast to 4-Cl-KYN, 7-Cl-KYNA exhibits limited permeability across the blood-brain barrier, likely due to its polar characteristics and the absence of an active transport mechanism [38].

KYNA-1

Notably, the KYNA analogue 1 (KYNA-A1), N-(2-N, N-Dimethyl aminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride, exhibits a significantly greater inhibitory impact than KYNA on nitro glycerine-induced neuronal activation of second-order sensory neurones in the NTC (Nucleus Trigeminals caudles) [39]. KYNA-A1 also diminishes the quantity of cells exhibiting immunoreactivity for neuronal NOS (nNOS), calcitonin gene-related peptide (CGRP) discharge, and calmodulin-dependent protein kinase II alpha (CamKIIa) expression within the exact same nucleus [40,41]. NTG-induced hyperalgesia in the trigeminal region correlated with heightened transcriptional function of CGRP, nNOS, and cytokines in the trigeminal ganglia, cervical spinal cord, and medulla-pons, that was inhibited by KYNA-A1 injection. KYNA-A1 is a possible target of therapy for migraine therapy [42].

Table 1: Comparative Table of KYNA Analogues

Compound	Chemical Structure / Modification	Activity Profile	Mechanism of Action / Receptor Targets	Therapeutic Relevance
Kynurenic Acid (KYNA)	4-oxo-1,4-dihydroquinoline-2-carboxylic acid	NMDA (glycine site), AMPA, kainite, α7-nAChR	non-competitive antagonist at the glycine region of the NMDA receptor, interact with other receptors, such as the α7 nicotinic acetylcholine receptor and GPR35, influencing neurotransmission and inflammatory responses	Endogenous neuroprotectant; limited CNS use due to poor BBB penetration
SZR-72	C-3 side chain modification with a water-soluble cationic group	NMDA receptor glycine site antagonist; reduces TNF-α production; increases TSG-6 expression	Antagonist at NMDA receptor glycine site; modulates inflammatory pathways	Potential treatment for neuroinflammation and rheumatoid arthritis
SZR-104	N-(2-(dimethyl amino) ethyl)-3-(morpholino methyl)-4-hydroxyquinoline-2-carboxamide	Potent NMDA receptor antagonist; inhibits epileptiform activity; reduces TNF-α; increases TSG-6 expression	Antagonist at NMDA receptor; modulates microglial activation and inflammatory responses	Promising candidate for CNS disorders like epilepsy and neuroinflammation
SZRG-21	C-3 side chain modification	Modulates exploratory behavior; affects emotional components without impacting motor skills	Likely interacts with glutamatergic and cholinergic systems; exact targets not fully elucidated	Potential application in neuropsychiatric conditions
KYNA-1	Modified group at the 2-position of the quinoline ring	NMDA Receptor Antagonism, Tau Hyperphosphorylation	Enhanced neuroprotective properties compared to KYNA and has anti-inflammatory Effects	Investigated for its potential use in neurodegenerative diseases, such as tauopathies

CONCLUSION

In this review, we conclude that kynurenic acid is a naturally occurring compound formed during tryptophan metabolism. It plays an important role in the nervous system by acting as a broad-spectrum inhibitor of excitatory amino acid receptors, offering potential neuroprotective effects. However, its therapeutic application is significantly limited because it does not cross the blood–brain barrier efficiently. Novel kynurenic acid analogues that are structurally modified to improve their ability to enter the brain. These analogues not only retain the beneficial properties of kynurenic acid but also exhibit enhanced receptor targeting and biological activity. As a result, they hold great promise as future treatments for a variety of neurological disorders.

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