IJMPR, 2026, 10(3), 52-58 **ISSN: 2319-5878**

INTERNATIONAL JOURNAL OF MODERN PHARMACEUTICAL RESEARCH

www.ijmpronline.com

Review Article

Impact Factor: 7.533

Coden USA: IJMPR3

A REVIEW ON THE PHARMACODYNAMICS, PHARMACOKINETICS, AND ANALYTICAL METHODS FOR ESTIMATION OF IGURATIMOD IN DOSAGE FORMS

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Article Received on: 05/02/2026 **Article Revised on: 25/02/2026** **Article Published on: 05/03/2026**

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https://doi.org/10.5281/zenodo.18885039

How to cite this Article: Mansi Patel[1]*, Pruthviraj K. Chaudhary, Dr. Khushbu Patel, Aachal Bhavsar, Jinal Goswami Dr. C. N. Patel (2026). A Review On The Pharmacodynamics, Pharmacokinetics, And Analytical Methods For Estimation Of Iguratimod In Dosage Forms. International Journal of Modern Pharmaceutical Research, 10(3), 52–58.

ABSTRACT

Iguratimod is a novel synthetic disease-modifying anti-rheumatic drug (csDMARD) primarily utilized for the treatment of rheumatoid arthritis. Distinguished by its multiple mechanisms of action immunomodulatory, anti-inflammatory, and bone-protective Iguratimod suppresses the production of key inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, and IL-17, and inhibits nuclear factor kappa B (NF-κB) activation. Furthermore, it modulates B and T cell function, decreases immunoglobulin production by B cells, and prevents bone resorption by inhibiting osteoclast differentiation. Analytical methods for the quantification of Iguratimod include official pharmacopoeia assays (HPLC, dissolution) and a range of reported approaches such as UV spectrophotometry, RP-HPLC, HPTLC, and LC-MS/MS. These validated techniques ensure the safety, efficacy, and quality of Iguratimod formulations. This review provides an overview of the mechanisms, pharmacokinetics, pharmacodynamics, clinical utility, and available analytical methods for Iguratimod as an anti-rheumatoid agent, highlighting its promise for broadening treatment options and improving outcomes in rheumatoid arthritis management.

KEYWORDS: Iguratimod, Rheumatoid arthritis, csDMARD, Anti-inflammatory, Immunomodulatory, Analytical method.

INTRODUCTION OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic autoimmune disease primarily affecting the joints. It causes pain, swelling, stiffness, and loss of function in the joints due to the immune system mistakenly attacking the synovium, which is the lining of the joints.

This leads to inflammation, the thickening of the synovium, and eventual damage to cartilage and bone within the joint.

The occurrence of RA is related to genetic, environmental, and immune factors. The goal of the treatment for patients with RA is clinical remission or low disease activity, ultimately preventing joint function damage.

RA differs from osteoarthritis, a common arthritis that often comes with age. RA affects the lining of your joints and damages the tissue that covers the ends of the bones in a joint. Eventually, this might cause your joints to not work as well. [1]

❖ SYMPTOMS

- joint pain,
- stiffness, and swelling,
- Low-grade Fever
- Fatigue
- loss of appetite
- Skin Issues

Anti-Rheumatoid drugs can be classified in to several categories (figure 1).[2]

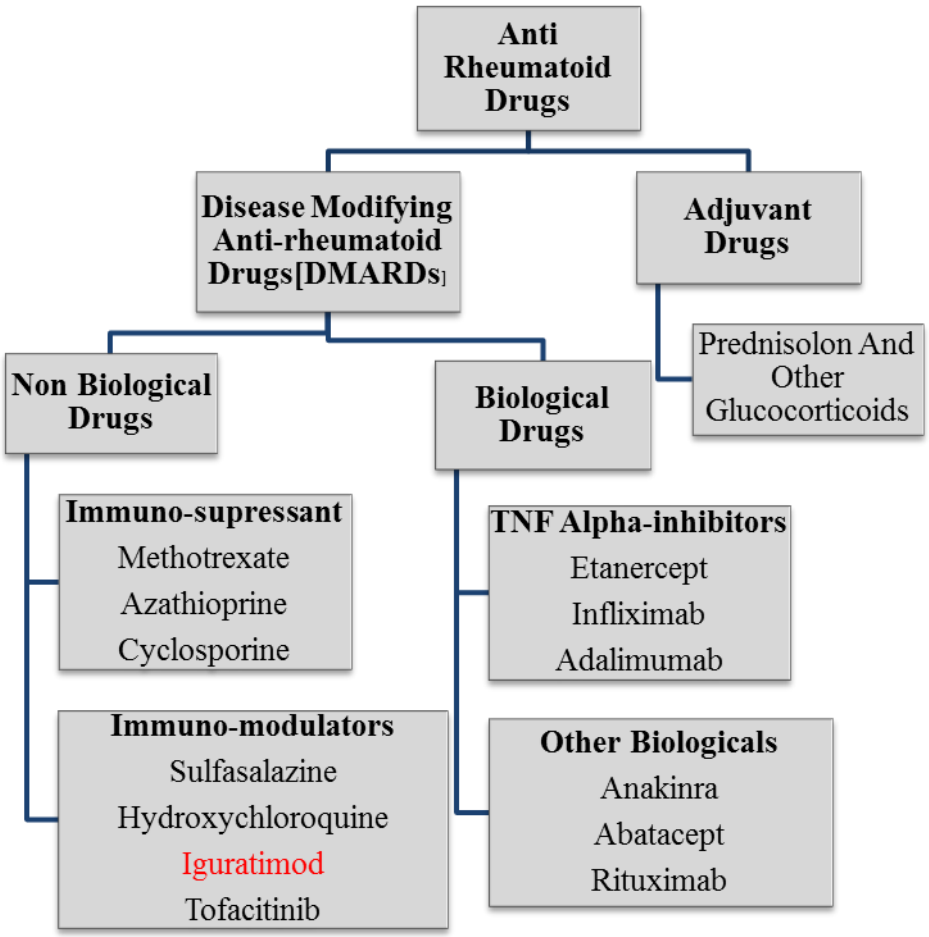

Figure 1: Classification Of Anti Rheumatoid Agents.

The mechanism of action of anti-rheumatic drugs varies depending on the class of drug. Here is a detailed overview:

1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs inhibit cyclooxygenase enzymes (COX-1 and COX-2), blocking the synthesis of prostaglandins. Prostaglandins are mediators of inflammation and pain, so NSAIDs reduce these symptoms but do not alter disease progression.

2. Conventional Synthetic DMARDs (csDMARDs)

- **Methotrexate:** The first-line DMARD. It increases adenosine release, which has anti-inflammatory effects, reduces neutrophil adhesion, inhibits leukotriene B4 synthesis, suppresses cell-mediated immunity, inhibits inflammatory cytokines (IL-1, IL-6, IL-8), and inhibits synovial collagenase gene expression.
- **Iguratimod:** Inhibits nuclear factor kappa-B (NF-κB): This suppression leads to decreased production of inflammatory cytokines like TNF-α, IL-1β, IL-6, IL-8, and IL-17, which are critical in the pathogenesis of rheumatoid arthritis and other autoimmune conditions.
- **Sulfasalazine:** Acts by preventing oxidative and nitrosative damage, mediating its anti-inflammatory effects.

3. Biologic DMARDs (bDMARDs)

TNF inhibitors (e.g., Etanercept, Infliximab, Adalimumab): Block tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine involved in joint damage.

- **Abatacept:** Blocks the co-stimulation of T-cells by binding to CD28 on T-cells, preventing activation and subsequent cytokine production.
- **Rituximab:** A monoclonal antibody against CD20 on B-cells, depleting B-cells which contribute to the inflammatory process.
- **Tocilizumab:** Blocks interleukin-6 (IL-6) receptors, inhibiting IL-6 mediated signaling involved in inflammation.

4. Glucocorticoids

Broadly suppress immune response and inflammation by modulating multiple inflammatory pathways.

Each drug targets different components of the immune and inflammatory pathways to achieve disease control and symptom relief in rheumatoid arthritis and other autoimmune conditions.[3-4]

PATHOPHYSIOLOGY

RA involves an autoimmune attack against the synovial membrane lining joints, leading to inflammation and destruction of cartilage and bone. The synovium

becomes hyperplastic, infiltrated by immune cells including CD4+ T cells, B cells, macrophages, neutrophils, and fibroblast-like synoviocytes (FLS). Activation of T cells, especially antigen-driven CD4+ cells, triggers chronic inflammation through cytokine production. B cells contribute by producing autoantibodies, presenting antigens, and secreting inflammatory cytokines. Macrophages serve as key effectors by producing pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), amplifying the inflammatory cascade. Neutrophils recruited to the joint release reactive oxygen species and damaging enzymes.[5]

INTRODUCTION OF IGURATIMOD

Iguratimod is a novel small-molecule conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) primarily used in the treatment of rheumatoid arthritis (RA). It has gained attention due to its unique mechanism of action that includes immunomodulatory, anti-inflammatory, and bone-protective effects.

Iguratimod suppresses the production of key inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukins (IL-1β, IL-6, IL-8, IL-17), and inhibits nuclear factor kappa B (NF-κB) activation, which plays a central role in inflammatory responses. Furthermore, it inhibits immunoglobulin production by B cells and promotes bone formation by stimulating osteoblastic differentiation while inhibiting osteoclastic activity, contributing to its efficacy in preventing joint damage and improving bone metabolism.

This multifaceted mode of action makes iguratimod a promising therapeutic agent, especially in patients who may not respond adequately to traditional DMARDs or biologic agents.

Due to its relatively recent introduction and distinct pharmacological profile, iguratimod has become an important subject in rheumatoid arthritis research, aiming to broaden treatment options and improve patient outcomes with a better safety profile compared to some biological therapies.[6-7]

HISTORY

Iguratimod is a synthetic disease-modifying anti-rheumatic drug (DMARD) first developed in Japan in the early 2000s, primarily for the treatment of rheumatoid arthritis. Following its initial discovery, Iguratimod underwent preclinical and clinical evaluation and was later approved for medical use in both Japan (2012) and China (2011). Its introduction provided a new treatment option for autoimmune conditions, and it is currently marketed under names such as Careram® and Iremod in these regions. While widely prescribed in Asia, Iguratimod is not yet approved for use in most Western countries.[8-9]

PHYSICOCHEMICAL PROPERTY

Iguratimod is a white to off-white crystalline powder with a molecular formula of $C_{17}H_{14}N_2O_6S$ and a molecular weight of approximately 374.37 g/mol. The drug exhibits a high melting point, ranging from 238°C to 242°C, and is virtually insoluble in water and ethanol, though it shows solubility in DMSO (dimethyl sulfoxide), DMF (dimethyl formamide), ACN (Aecetonitrile). Its density is predicted to be around 1.52 ± 0.1 g/cm³, and its partition coefficient (LogP) lies between 1.4 and 2.8, indicating moderate lipophilicity. Iguratimod has a predicted pKa of approximately 5.58.

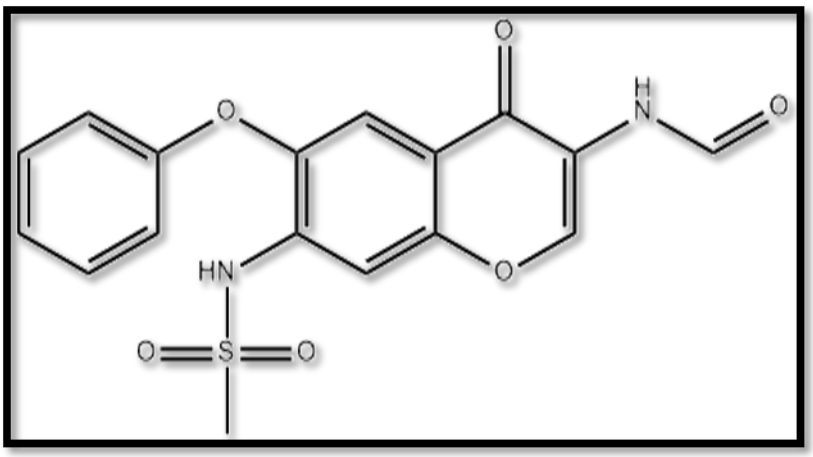

Figure2: Structure of Iguratimod.

MECHANISAM OF ACTION OF IGURATIMOD

Iguratimod (IGU) is a novel conventional synthetic disease-modifying antirheumatic drug (csDMARD) developed mainly in Japan and China for rheumatoid arthritis (RA). It provides disease modification through multiple mechanisms involving anti-inflammatory, immunomodulatory, and bone-protective effects.

➢ **Anti-inflammatory Actions**

Iguratimod inhibits the production of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), and granulocyte colony-stimulating factor (G-CSF). It selectively inhibits cyclooxygenase-2 (COX-2), reducing prostaglandin E2 synthesis, thereby decreasing inflammation and pain. Suppresses the release of bradykinin and other inflammatory mediators.

In synovial cells, Iguratimod lowers the expression of co-stimulatory molecules (CD54, CD58) important for antigen presentation and T cell activation.

➢ **Immunomodulatory Effects**

Inhibits B-cell function, reducing immunoglobulin (autoantibody) production. Suppresses T-cell proliferation, reducing the autoimmune response. Modulates nuclear factor-kappa B (NF-κB) signaling, a key transcription factor regulating inflammatory gene expression, by inhibiting its activation and nuclear translocation.

➢ **Bone Protective Properties**

Promotes osteoblast differentiation and bone formation by upregulating key factors and signaling pathways (e.g., p38 MAPK). Inhibits osteoclastogenesis by downregulating receptor activator of nuclear factor kappa-B ligand (RANKL), thus preventing bone resorption. Prevents cartilage degradation by inhibiting matrix metalloproteinases (MMPs).

Iguratimod inhibits protein citrullination and inflammation in rheumatoid arthritis (RA) by downregulating the sodium bicarbonate cotransporter 2 (NBCe2). This novel mechanism was elucidated in a recent study involving RA patients.

NBCe2 Role: NBCe2 is expressed highly in peripheral blood neutrophils of RA patients and is linked with increased protein citrullination, a post-translational modification implicated in generating autoantigens and driving inflammation in RA.

Bicarbonate Influence: Increased bicarbonate concentration elevates NBCe2 expression and citrullinated protein levels in neutrophils, promoting inflammation.

TNF-α Effect: Tumor necrosis factor-alpha (TNF-α), a major inflammatory cytokine in RA, further stimulates NBCe2 expression.

Iguratimod Action: Iguratimod reduces NBCe2 expression in neutrophils, thereby decreasing protein citrullination and subsequent inflammation.

Comparative Efficacy: The inhibitory effects of Iguratimod on NBCe2 expression, neutrophil activity, cytokine secretion (IL-6, TNF-α), and cell migration are comparable to established RA treatments such as methotrexate and dexamethasone.[10]

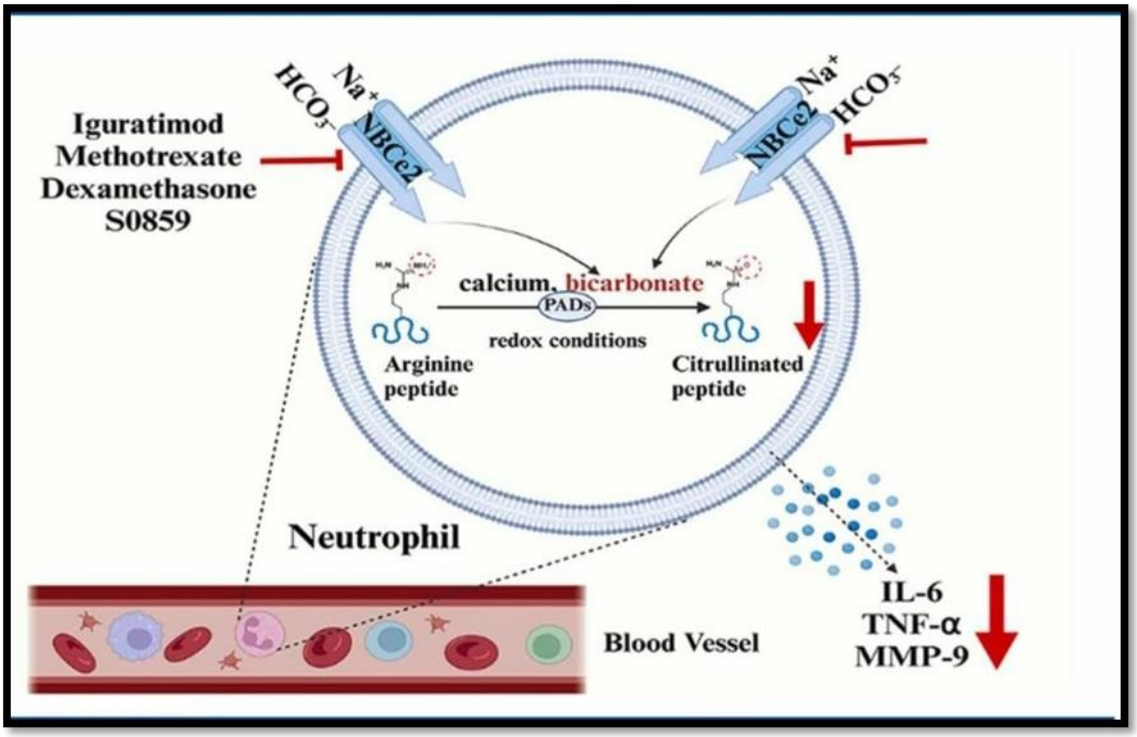

Figure 3: Mechanismof Action of Iguratimod.

PHARMACOKINETICS

Iguratimod is well absorbed orally, with a Tmax of approximately 3.6 to 5.9 hours in humans and rats, respectively. Food intake can increase its peak plasma concentration (Cmax) and reduce Tmax, indicating enhanced absorption without significantly affecting overall exposure (AUC) or elimination half-life (t1/2). The volume of distribution (Vd) in humans is about 1.16 L, suggesting moderate tissue distribution, and the drug is moderately bound in systemic circulation. It undergoes hepatic metabolism mainly via cytochrome P450 enzymes CYP2C9 and CYP2C19, producing a major metabolite M2 through phase I metabolism, which has a shorter half-life than the parent drug. Clearance data from animal studies show a low clearance rate of around 0.05 L/h/kg, with an elimination half-life in humans of approximately 10.25 hours, supporting once-daily dosing. Excretion primarily involves metabolite elimination after hepatic processing.[11]

PHARMACODYNAMICS

Iguratimod (IGU) is a novel disease-modifying anti-rheumatic drug (DMARD) with multiple immunomodulatory and anti-inflammatory effects. Its pharmacodynamic properties primarilyinvolve suppression of inflammatory cytokines, modulation of immune cell function, and inhibition of pathological processes in autoimmune conditions such as rheumatoid arthritis.[12]

REVIEW OF LITERATURE

Literature review of Iguratimod

Table 1: Reported methods for assessment of Iguratimod.

Sr. no	Title/ Method	Description	Ref.no
UV VISIBLE SPECTROSCOPY			
1	Development and Validation of UV Spectrophotometric Method for Estimation of Iguratimod in Tablet Dosage Form	**Solvent:** Methanol **Detection:** 257nm **Linearity:** 5-30µg/Ml	13
HIGH PERFORMANCE LIQUID CHROMATOGRAPHY			
2	Development and Validation of HPLC Method for Estimation of Iguratimod in Formulation	**Stationary phase:** C_{18} Column (250 × 4.6 mm, 5µm) **Mobile phase:** Acetonitrile: Water (80:20 %v/v) **Detection:** 256 nm **Flow rate:** 1.0 mL/min	14
3	A Study Of Method Development And Validation For Quantification Of Iguratimod In Pharmaceutical Dosage Form By RP-HPLC Method	**Stationary phase:** C_{18} Column(150 × 3.9mm, 5µm) **Mobile phase:** buffer pH 2.5 and Methanol (58:42 %v/v) **Detection:** 257nm **Flow rate:** 1.2 mL/min	15
4	HPLC Method Development and Validation of Iguratimod Tablet Dosage Form	**Stationary phase:** C_{18} Column(250 x 4.6mm, 5µm) **Mobile phase:** Methanol and Acetonitrile (50:50 %v/v) **Detection :** 260 nm **Flow rate:** 1.0 mL/min	16
5	Determination of Iguratimod in rat plasma by high performance liquid chromatography (HPLC) method and application	**Stationary phase:** C_{18} Column(150 × 4.6mm, 5µm) **Mobile phase** : Acetonitrile and Acetic acid aqueous solution, pH 4.5 (40:60 % v/v) **Detection :** 257 nm **Flow rate:** 1 mL/min	17
6	Preparation of a Major Metabolite of Iguratimod and Simultaneous Assay of Iguratimod and Its Metabolite by HPLC in Rat Plasma	**Stationary phase**: C_{18} Column(150 × 4.6mm, 5µm) **Mobile phase:** Methanol and water (55:45 %v/v) + 0.1% Trifluoroacetic acid **Detection**: 257 nm **Flow rate:** 1 mL/min	18
7	Stability Indicating HPLC Method Development and Validation for Estimation Of Iguratimod In Tablets	**Stationary phase:** C_{18} Column(150 × 4.6mm, 5µm) **Mobile phase:** Methanol: buffer (pH 3.0±5.0): Aecetonitrile(10:50:40 %v/v/v)	19

		Detection: 265nm **Flow rate:** 1.0 mL/min	
HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY			
8	Development and Validation of Stability Indicating HPTLC Method for Estimation of Iguratimod in pharmaceutical dosage form	**Stationary phase:** Silica gel $60F_{254}$ plates **Mobile phase:** Chloroform: Methanol: Formic acid ratio (8:2:0:2 %v/v/v) **Detection** : 257nm **Linearity:** 200-1200 ng/band	20
LC-MS/MS METHOD			
9	Simultaneous determination of Iguratimod and its metabolite in rat plasma using a UPLC-MS/MS method: Application for drug-drug interaction	**Stationary phase:** UPLC BEH C_{18} column(50 × 2.1mm, 1.7µm) **Mobile phase :** Acetonitrile and water with 0.1% formic acid (50:50 %v/v) **Detection** : 256 nm **Flow rate:** 0.4 mL/min	21
10	A rapid and sensitive LC–MS/MS method for analysis of Iguratimod in human plasma: Application to a pharmacokinetic study in Chinese healthy volunteers	**Stationary phase** Ultimate® XB-C_{18} column (50 × 2.1mm, 3.5µm) **Mobile phase:** Gradient of Acetonitrile and Water containing 2mm ammonium acetate + 0.1% formic acid (40:60 %v/v) **Detection** : 257 nm **Flow rate:** 0.40 mL/min	22

The literature review in the article provides an overview of current analytical methods for developing and validating Iguratimod, a synthetic drug used for rheumatoid arthritis, highlighting both official and novel laboratory techniques like HPLC, UV spectrophotometry, HPTLC, and LC-MS/MS that ensure drug quality and efficacy; it underscores the continual progress in analytical science, supporting reliable clinical use and further research in Iguratimod's safety and therapeutic potential.

CONCLUSION

In this review, the pharmacological profile, underlying mechanisms, and validated analytical methods for Iguratimod have been comprehensively summarized. Iguratimod displays distinctive benefits in suppressing inflammation, modulating immune responses, and protecting bone tissue, making it particularly advantageous for patients with rheumatoid arthritis who do not sufficiently respond to conventional therapies. The drug's favorable pharmacokinetics allows for convenient once-daily dosing and good tolerability in clinical use. A wide range of well-established analytical techniques, including UV spectrophotometry, RP-HPLC, HPTLC, and LC-MS/MS, ensures accurate determination, safety, and quality of Iguratimod formulations for clinical and research purposes. With ongoing research and increasing clinical experience, Iguratimod holds promise as an alternative or adjunct therapeutic in autoimmune and inflammatory conditions, underscoring its growing role in advancing rheumatoid arthritis management.

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