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Article

Curcumin as a Multi-Targeted Nutraceutical for Metabolic Disorders: Consolidating Clinical and Molecular Evidence

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Abstract

Curcumin, the principal curcuminoid of *Curcuma longa* (turmeric), has garnered significant scientific attention for its multifaceted therapeutic potential. This review examines clinical evidence that provides mechanistic insights into antioxidant, anti-inflammatory, antidiabetic, antihyperlipidemic, antihypertensive, and endothelial effects. Results across diverse investigations indicate that curcumin intake improves biomarkers including total antioxidant capacity, superoxide dismutase, malondialdehyde, high-sensitivity C-reactive protein, interleukin-6, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting blood glucose, HbA1c, QUICKI, HOMA-IR, and flow-mediated dilation. Curcumin may offer a low-toxicity complement to conventional therapy, although bioavailability and variable responses remain challenges.

Keywords: oxidation, inflammation, endothelial function, nutraceutical, bioavailability

Abbreviations: **TAC**, total antioxidant capacity. **MDA**, malondialdehyde. **Nrf-2**, nuclear factor erythroid 2–related factor 2. **SOD**, superoxide dismutase. **GSH**, glutathione. **hs-CRP**, high-sensitivity C-reactive protein. **IL-6**, interleukin 6. **CGRP**, calcitonin gene-related peptide. **TLR-4**, Toll-like receptor 4. **BCL-2**, B-cell lymphoma 2. **TG**, triglycerides. **TC**, total cholesterol. **LDL-C**, low-density lipoprotein cholesterol. **HDL-C**, high-density lipoprotein cholesterol. **VLDL**, very low-density lipoprotein. **FBG**, fasting blood glucose. **SBP**, systolic blood pressure. **DBP**, diastolic blood pressure. **HbA1c**, hemoglobin A1c. **HOMA-IR**, Homeostatic Model Assessment of Insulin Resistance. **QUICKI**, Quantitative Insulin Sensitivity Check Index. **FMD**, flow-mediated dilation. **PP**, pulse pressure. **ICAM-1**, intercellular adhesion molecule-1. **VCAM-1**, vascular cell adhesion molecule-1.

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1. Introduction

Noncommunicable diseases (NCDs), including type 2 diabetes, cardiovascular disease, and metabolic syndrome, have become major global health challenges [1]. Central to the pathophysiology of these conditions are interconnected mechanisms that involve oxidative stress, low-grade chronic inflammation, endothelial dysfunction, hyperlipidemia, and insulin resistance [2,3].

Oxidative stress results when an imbalance is observed between the body's antioxidant defenses and generation of reactive oxygen species, leading to DNA damage, cellular dysfunction, and lipid peroxidation [4,5]. Inflammation, facilitated by cytokines such as interleukin-6 (IL-6), interleukin-1beta (IL-1β), and tumor necrosis factor-alpha (TNF-α), further aggravates metabolic and vascular disorders [3]. Likewise, dyslipidemia and insulin

resistance contribute to arterial stiffness, atherosclerosis, and impairment of endothelial function, thus elevating the risk for hypertension and cardiovascular complications [6]. Therefore, integrative approaches targeting these overlapping molecular pathways are urgently needed for the prevention and management of metabolic and cardiovascular disorders.

Management of the aforementioned health complications involves the use of statins, non-steroidal anti-inflammatory drugs (NSAIDs), antidiabetics, and antihypertensives that are effective but often associated with negative impacts, such as liver impairment, kidney damage, stomach problems, and long-term dependency [7,8]. Moreover, synthetic medications typically target isolated pathways rather than addressing the multifactorial etiology of chronic diseases [8].

Among preventive and complementary strategies, curcumin—the primary curcuminoid in *Curcuma longa* (turmeric)—has garnered attention due to its broad-spectrum pharmacological effects and favorable safety profile. Curcumin has been utilized in various traditional medicine systems, including Islamic, Chinese, and Ayurvedic, primarily for digestive issues, organ protection, and inflammatory conditions like arthritis; it also supports immune function and offers benefits for the heart, liver, and nervous system [9]. Curcumin exerts pleiotropic (multi-target) effects by modulating inflammatory cytokines, oxidative stress markers, lipid metabolism, and endothelial function.

As illustrated in Figure 1, curcumin interacts with several intracellular signaling cascades, including nuclear factor erythroid 2–related factor 2 (Nrf2), nuclear factor-κB (NF-κB), Toll-like receptors (TLRs), and endothelial adhesion molecules, thereby influencing oxidative balance, inflammation, and vascular integrity [9,10]. The data compiled in this review strongly support curcumin's antioxidant effects (e.g., increased TAC, GSH, and SOD; decreased MDA), anti-inflammatory action (e.g., reduced hs-CRP, IL-6, TNF-α), lipid-lowering ability (e.g., reduced TG, TC, LDL-C), glycemic control, and improved endothelial function (e.g., increased FMD, reduced ICAM-1/VCAM-1). Despite these promising outcomes, no comprehensive synthesis has integrated findings from clinical trials spanning these diverse health domains. This review aims to fill that gap by critically appraising curcumin's therapeutic potential across oxidative stress–linked disorders, with implications for clinical and nutraceutical applications—an essential step toward advancing translational research and evidence-based integrative therapies in metabolic medicine.

2. Antioxidant Activity

Preclinical studies have shown that curcumin activates Nrf-2, thus upregulating SOD and catalase [11,12]. These mechanistic insights are strongly supported by clinical evidence in a range of populations. In overweight and obese girls, Saraf-Bank et al. [13] reported that curcumin intake significantly improved total antioxidant capacity (TAC) and reduced malondialdehyde (MDA), a marker of lipid peroxidation. Rodrigues et al. [12] recorded a notable increase in catalase activity after curcumin intake in hemodialysis patients, although a paradoxical decline in glutathione peroxidase was observed. Karimi et al. [11] observed an increase in Nrf-2 and SOD with a reduction in MDA levels among sepsis patients, confirming the activation of redox-sensitive signaling by curcumin. Likewise, Bateni et al. [14] reported a significant improvement in TAC and a reduction in MDA among patients with metabolic syndrome, again likely through Nrf-2-dependent mechanisms. Additional trials in HIV-infected individuals [15], patients with coronary heart disease and diabetes [16], and women with rheumatoid arthritis [17] reported improvements in systemic antioxidant status after curcumin supplementation.

3. Anti-inflammatory Effects

Curcumin intake may target multiple inflammatory pathways to impart its anti-inflammatory activities, including suppression of nuclear factor-kappa B (NF-κB) signaling, a key regulator of inflammation, as well as modulation of toll-like receptor 4 (TLR-4), and decreasing expression of anti-apoptotic proteins like B-cell lymphoma 2 (BCL-2). Additionally, curcumin has the ability to increase the levels of anti-inflammatory cytokines and reduce neuropeptides, such as calcitonin gene-related peptide (CGRP). In overweight girls, Saraf-Bank et al. [13] observed significant reductions in hs-CRP and IL-6, which represent down-regulation of systemic inflammation. In patients suffering from sulfur mustard-induced pruritic lesions, Panahi et al. [18] delineated alterations in hs-CRP, IL-8, and CGRP following curcumin intake. A robust anti-inflammatory effect was demonstrated by Karimi et al. [11], wherein intake led to a marked decline in IL-6, IL-18, IL-1β, TLR-4, and BCL-2, while simultaneously increasing IL-10, an anti-inflammatory cytokine among sepsis patients. These results reflect the dual role of curcumin in both suppressing pro-inflammatory mediators and enhancing anti-inflammatory signaling. In another clinical trial, curcumin intake resulted in a notable reduction in hs-CRP levels compared to a placebo group in patients with chronic inflammatory bowel conditions [19]. Pakfetrat et al. [20] and Bateni et al. [14] reported reductions in inflammatory biomarkers in patients with hemodialysis and metabolic syndrome, respectively, with a focus on decreased NF-κB p65 transcription.

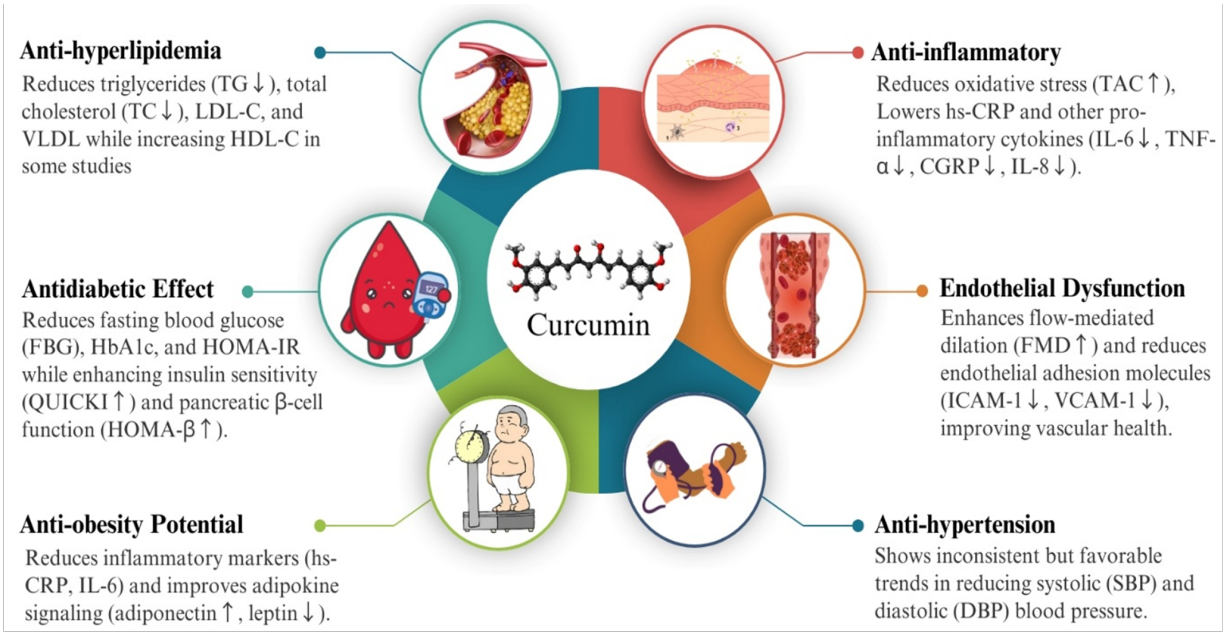

Figure 1. Curcumin molecular targets

Figure 1. Curcumin molecular targets and their associated signaling cascades.

4. Antihyperlipidemic Effects

Curcumin intake in clinical trials showed consistent and significant decline in TG, TC, LDL-C, and VLDL across patients with type 2 diabetes [21], metabolic syndrome [22], NAFLD [23], and PCOS [24], while HDL-C increases were statistically significant in 4/6 trials [22–25], though one study reported a neutral effect [21] and one stated decline [26]. These inconsistencies may reflect shorter durations or population-specific factors (e.g., baseline lipid profiles). Mechanistic insights reveal that curcumin activates AMP-activated protein kinase (AMPK), which in turn suppresses lipogenic transcription factors such as SREBP-1c; reduced activity of key enzymes such as HMG-CoA reductase further decreases hepatic lipogenesis and cholesterol biosynthesis [27–29]. The upregulation of ABCA1 following curcumin intake promotes reverse cholesterol transport, thereby encouraging cholesterol efflux and enhancing HDL function [30]. Taken together, the evidence suggests that curcumin may shift plasma triglyceride and fatty acid profiles toward catabolism rather than biosynthesis. Notably, the observed decline in MDA in NAFLD patients underscores curcumin's antioxidant capacity, which alleviates lipid peroxidation and protects lipoproteins from oxidative damage—a key factor in preventing atherogenesis [23]. The dose-dependent efficacy, with higher doses (≥1500 mg/day) yielding more consistent HDL increases, suggests bioavailability and exposure influence the extent of lipid modulation. Collectively, data from clinical trials position curcumin as a multi-target agent that positively influences lipid profile by integrating metabolic regulation with antioxidant and anti-inflammatory properties.

Table 1. Health impacts of curcumin intake in clinical trials.

Dose/duration	Subjects	Outcomes	References
Antioxidant			
500 mg/10 weeks	n=60, overweight and obese girls	TAC ↑, MDA ↓	[13]
1 g/day for 12 weeks	n=60, hemodialysis patients	Catalase ↑, glutathione peroxidase ↑	[12]
320 mg/day for 10 days	n=40, sepsis patients	MDA ↓, Nrf2 ↑, SOD ↑, TAC ↑	[11]
80 mg/day for 12 weeks	n=50, patients with metabolic syndrome	TAC ↑, MDA ↓	[14]

Dose/duration	Subjects	Outcomes	References
1 g/day for 30 days	n=120, HIV-infected individuals	MDA ↓	[15]
1 g/day for 12 weeks	n=60, type 2 diabetes + coronary heart disease	MDA ↓, TAC ↑, GSH ↑	[16]
500 mg/day for 8 weeks	n=48, women with rheumatoid arthritis	TAC ↑	[17]
Anti-inflammatory			
500 mg/day for 10 weeks	n=60, overweight and obese girls	hs-CRP ↓, IL-6 ↓	[13]
1 g/day for 4 weeks	n=60, sulphur mustard–induced pruritic skin lesions	hs-CRP ↓, IL-8 ↓, CGRP ↓	[18]
320 mg/day for 10 days	n=40, sepsis patients	IL-6 ↓, IL-18 ↓, IL-1β ↓, TLR-4 ↓, BCL-2 ↓, IL-10 ↑	[11]
1500 mg/day for 12 weeks	n=70, ulcerative colitis patients	hs-CRP ↓	[19]
1 g/day for 12 weeks	n=60, hemodialysis patients	hs-CRP ↓	[12]
80 mg/day for 12 weeks	n=50, metabolic syndrome	hs-CRP ↓, NF-κB transcription ↓	[14]
1500 mg/day for 12 months	n=227, type 2 diabetes	hs-CRP ↓, IL-6 ↓, IL-1β ↓, TNF-α ↓	[31]
Antihyperlipidemic			
1500 mg/day for 10 weeks	n=44, type 2 diabetes	TG ↓, TC ↓, LDL-C ↓; HDL-C (no change)	[21]
1890 mg/day for 12 weeks	n=32, metabolic syndrome	TG ↓, TC ↓, LDL-C ↓, non-HDL ↓, VLDL ↓; HDL-C ↑	[22]
500 mg/day for 12 weeks	n=60, polycystic ovary syndrome	TG ↓, TC ↓, LDL-C ↓, VLDL ↓; HDL-C ↑	[25]
2 g/day for 8 weeks	n=64, NAFLD	TG ↓, TC ↓, LDL-C ↓, LDL/HDL ratio ↓, VLDL ↓, MDA ↓; HDL-C ↑	[23]
500 mg/day for 12 weeks	n=72, type 2 diabetes	TG ↓, TC ↓, LDL-C ↓; HDL-C ↓	[26]
1500 mg/day for 12 weeks	n=200, PCOS	TG ↓, TC ↓, LDL-C ↓; HDL-C ↑	[25]
1500 mg/day for 12 months	n=227, type 2 diabetes	LDL-C ↓; TG/HDL-C ratio improved	[31]
Antidiabetic			
80 mg/day for 8 weeks	n=80, type 2 diabetes	FBG ↓, HbA1c ↓	[32]
1500 mg/day for 10 weeks	n=44, type 2 diabetes	Serum adiponectin ↑	[21]
300 mg/day for 3 months	n=44, obesity + type 2 diabetes	FBG ↓, HbA1c ↓, HOMA-IR ↓	[33]
80 mg/day for 12 weeks	n=60, diabetic foot ulcer	FBG ↓, HbA1c ↓, HOMA-IR ↓	[34]
500 mg/day for 12 weeks	n=60, PCOS	FBG ↓, HOMA-IR ↓, QUICKI ↑	[25]

Dose/duration	Subjects	Outcomes	References
1500 mg/day for 12 months	n=227, type 2 diabetes	FBG ↓, HbA1c ↓, HOMA-IR ↓	[31]
Endothelial function and blood pressure			
800 mg/day for 8 weeks	n=18, postmenopausal women	FMD ↑, DBP ↓, SBP ↓	[35]
5 g single dose	n=18, healthy adults	FMD ↑, SBP ↓, DBP ↑, PP ↑	[36]
2 g/day for 12 weeks	n=20, older adults	FMD ↑, DBP ↓, SBP (no change); NO bioavailability ↑	[37]
500 mg/day for 12 weeks	n=72, type 2 diabetes	DBP ↓, SBP ↓	[26]
200 mg/day for 8 weeks	n=59, healthy subjects	FMD ↑	[38]
320 mg/day for 10 days	n=40, sepsis patients	ICAM-1 ↓, VCAM-1 ↓	[11]
150 mg single dose	n=14, sedentary young men	FMD ↑	[39]

5. Antidiabetic Potential

Clinical evidence supports curcumin's antidiabetic properties across diverse patient populations (80–1500 mg/day for 2–12 months). In short-term trials, curcumin intake considerably reduced FBG and HbA1c levels in subjects with type 2 diabetes [32,33], obesity [33], and diabetic foot ulcer [34], as well as improved insulin sensitivity by reducing HOMA-IR and elevating QUICKI [25]. In long-term trials, curcumin intake sustained glycemic control with significant reductions in FBG, HbA1c, HOMA-IR, and leptin, along with elevated serum adiponectin and HOMA-β, indicating improved pancreatic β-cell function [31,40]. Aforementioned benefits are attributed to the ability of curcumin to activate AMPK (enhances glucose uptake) and downregulate PEPCK and G6Pase (suppresses hepatic gluconeogenesis) [41]. Notably, the protective effects of curcumin on pancreatic β-cells are due to the radical scavenging and anti-inflammatory potential of curcumin, thereby maintaining insulin secretion capacity. The repeated elevation of adiponectin across trials [21,31,40] highlights curcumin's positive modulation of adipokine signaling, which further enhances insulin sensitivity as well as metabolic homeostasis.

6. Hypertension and Endothelial Function

Curcumin intake consistently showed positive effects toward endothelial function, albeit its impacts on blood pressure (i.e., SBP and DBP) were inconsistent. Curcumin significantly enhances nitric oxide (NO) bioavailability by two main mechanisms: reducing oxidative stress and downregulating proinflammatory cytokines (TNF-α↓, IL-6↓, ICAM-1↓, VCAM-1↓). Clinically, this translates to improved endothelial function, evidenced by dose-dependent increases in flow-mediated dilation (FMD; 1.5–3.2% absolute improvement) across trials [42–44]. In contrast, impact on blood pressure was generally favorable (trend toward reduction) but outcomes were not consistent across clinical trials due to baseline hypertension severity, curcumin doses, or trial durations.

7. Premenstrual Syndrome and Dysmenorrhea

While curcumin's benefits in metabolic disorders are well-established, its systemic anti-inflammatory and antioxidant effects also demonstrate clinical efficacy in treating gynecological conditions. Emerging evidence shows particular promise for managing premenstrual syndrome (PMS) and dysmenorrhea, where oxidative stress and inflammation contribute significantly to pathophysiology [45–49]. In a randomized controlled trial, supplementation with 500 mg/day of curcumin for 10 days significantly reduced dysmenorrhea-related pain by 64% and improved overall PMS symptoms, as indicated by a decrease in the Premenstrual Syndrome Screening Tool (PSST) score from 32 to 21 [45]. Additionally, participants reported notable reductions in common menstrual discomforts, including breast tenderness (24%), back pain (17%), bloating (16%), and weight gain (23%) compared to baseline measurements. Beyond its analgesic effects, curcumin supplementation has been associated with enhanced cognitive function in women with PMS. The same dosage regimen (500 mg/day for 10 days) led to significant improvements in memory retention, inhibitory control, selective attention, and overall cognitive task performance, suggesting potential neuroprotective benefits [46]. These cognitive enhancements may be particularly valuable for women experiencing brain fog or concentration difficulties during the luteal phase of the menstrual

cycle. At a biochemical level, curcumin appears to modulate inflammatory and oxidative stress pathways implicated in dysmenorrhea. One study observed a significant decline in nitric oxide levels (from 93.3 to 85.9 μmol/L), indicating a possible reduction in oxidative stress [49]. Furthermore, when co-administered with piperine (a bioavailability enhancer), curcumin supplementation resulted in a marked decrease in serum Immunoglobulin E (IgE) levels (from 223.6 to 161.3 IU/mL), suggesting an anti-allergic effect [48]. Although changes in interleukin-10 (IL-10) and interleukin-12 (IL-12) were not statistically significant, a notable reduction in high-sensitivity C-reactive protein (hs-CRP) levels (from 0.30 to 0.20 mg/L) further supports curcumin's anti-inflammatory properties without altering iron metabolism [47]. However, small sample sizes and short trial durations were considerable limitations. Importantly, curcumin was well-tolerated with no reported adverse effects, reinforcing its safety profile as a complementary therapy.

8. Current Challenges and Future Directions

Despite the mounting clinical and molecular evidence supporting curcumin's role as a multi-targeted nutraceutical for the management of metabolic disorders, several key challenges continue to impede its clinical translation. Key issues involve low systemic bioavailability, lack of standardization, unclear dose–response relationship, limited mechanistic validation, and regulatory barriers. The problem concerning the bioavailability of native curcumin involves its rapid metabolism, limited solubility, and inadequate absorption, which restricts its clinical utility [50,51]. Although nano-formulations, phospholipid complexes, and conjugated derivatives have improved bioavailability in preclinical studies, there remains a lack of robust long-term clinical trials evaluating safety, efficacy, and optimal dosing regimens [52–55]. Moreover, the lack of standardization causes curcumin supplements to vary widely in purity and composition, posing challenges for clinical reproducibility and regulatory compliance. Establishing universally accepted standards for curcumin formulations with well-defined pharmacokinetics and pharmacodynamics profiles is essential to ensure consistency in research and therapeutic applications. Dose–response relationships remain unclear, as clinical studies have employed highly variable curcumin doses, often yielding inconsistent therapeutic outcomes [45,56]. Future research must establish evidence-based dosing guidelines, including the minimum effective dose, therapeutic range, and potential toxicity thresholds for chronic use in metabolic disorders. Mechanistic validation in humans remains limited; although in vitro and animal studies suggest that curcumin modulates key pathways (e.g., NF-κB, AMPK, and PPARγ), its mechanisms of action in humans are still poorly understood. Translational research incorporating systems biology and multi-omics approaches (e.g., genomics, proteomics) is needed to bridge this gap. Despite promising preclinical data, regulatory and clinical barriers have prevented curcumin from being widely adopted in clinical practice, largely due to the lack of sufficient large-scale trials and real-world efficacy data. Multicenter studies and cost-effectiveness analyses are critical for regulatory approval and integration into mainstream medicine. Future research priorities may consider advanced delivery systems (liposomes, micelles, solid lipid nanoparticles) to enhance curcumin stability, absorption, targets, and safety as well. Moreover, synergistic or combination therapies, personalized medicine, and biomarker-driven trials may play an important role.

9. Economic Significance

The rising global burden of metabolic disorders imposes substantial financial strain on healthcare systems, particularly in low- and middle-income countries. Curcumin's natural origin, low production costs, and minimal side effects position it as a cost-effective alternative or adjunct to expensive synthetic drugs (e.g., statins, NSAIDs, antidiabetics), which often require long-term use and incur high costs for managing adverse effects. The global curcumin market is growing, driven by increasing demand for natural therapeutics and preventive healthcare. By mitigating reliance on costly pharmaceuticals, curcumin aligns with sustainable healthcare goals, offering economic benefits for patients, industries, and public health systems worldwide.

10. Conclusions

Despite curcumin's therapeutic potential, clinical translation faces key challenges: poor bioavailability due to rapid metabolism and low solubility, inconsistent formulation standards, and variable dosing in trials. Curcumin in combination with piperine may help address some of these issues. While advanced delivery systems (e.g., phospholipid complexes, nanoparticles) show promise in preclinical studies, human trials lack robust long-term safety and efficacy data. Standardization of curcuminoid content and pharmacokinetic profiling are critical for reproducibility. Dose optimization requires correlation between plasma levels and clinical outcomes, particularly for metabolic endpoints. Mechanistic insights from animal models (e.g., NF-B/AMPK modulation) need validation in human studies using omics approaches. Regulatory approval hinges on large-scale trials and real-world evidence, especially in combination therapies. Future research should prioritize GMP-compliant curcumin–piperine combinations, biomarker validation, and global collaborative trials to establish curcumin as an evidence-based adjunct therapy.

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