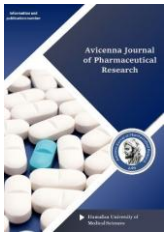
AJPR
Avicenna Journal of Pharmaceutical Research
Avicenna J Pharma Res. 2025 ;6(2): 81-87
DOI: 10.53208/ajpr.6.2.81
http://ajpr.umsha.ac.ir



Original Article

Polyrhodanine Nanoencapsulation Potentiates N-Acetylcysteine Against Paraquat-Induced Cytotoxicity in HepG2 Cells

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Article history:
Received: July 07, 2025
Revised: September 13, 2025
Accepted: September 23, 2025
Published: December 10, 2025

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Abstract

Background: Paraquat (PQ) poisoning causes severe oxidative stress–mediated hepatotoxicity. Although N-acetylcysteine (NAC) is a promising therapeutic agent, its low bioavailability remains a challenge for clinical application. This study evaluated whether N-acetylcysteine-loaded polyrhodanine nanoparticles (PR-NAC) enhance cytoprotection against PQ-induced injury in HepG2 cells compared with free NAC.

Methods: Cell viability was assessed using the MTT assay across increasing PQ concentrations, either alone or in combination with NAC or PR-NAC. Following determination of the PQ IC_{50} and evaluation of its interaction with safe doses NAC and PR-NAC, mitochondrial membrane potential ($\Delta\Psi m$), lactate dehydrogenase (LDH), superoxide dismutase (SOD) and catalase (CAT) activity were assessed.

Results: PQ exposure (IC_{50} = 17.47 µg/mL) significantly compromised cell membrane integrity, collapsed the $\Delta\Psi m$, and SOD and CAT activities. PR-NAC provided greater protection than free NAC, shifting the PQ IC_{50} to 26.41 µg/mL and restoring $\Delta\Psi m$ to levels close to those of the control group. PR-NAC also increased SOD and CAT activities to a degree comparable to that of NAC.

Conclusion: These findings demonstrate that PR encapsulation potentiates the efficacy of NAC, likely through enhanced cellular uptake and mitochondrial delivery, thereby preserving antioxidant defenses and mitochondrial function. Overall, PR-NAC shows promise as a broad-spectrum nanotherapeutic for oxidative stress-induced liver injury, although further *in vivo* investigation is required.

Keywords: Paraquat; Polyrhodanine; N-acetylcysteine; Oxidative stress; HepG2

Introduction

Globally, Paraquat (PQ; 1,1′-dimethyl-4,4′-bipyridinium dichloride) remains a widely used herbicide in many countries, yet its ingestion constitutes a serious medical emergency characterized by progressive multiorgan failure, with the hepatic and pulmonary systems bearing the greatest burden [9, 3]. The molecular basis of its

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[DOI: 10.53208/ajpr.6.2.81]

cytotoxicity lies in continuous intracellular redox cycling [4]. Following cellular entry, PQ accepts electrons from NADPH-dependent reductases to form a monocation radical, which subsequently reduces molecular oxygen to superoxide [13, 14]. This initiates a self-perpetuating cascade of oxidative injury, driving the excessive production of reactive oxygen species (ROS), rapid exhaustion of endogenous thiol-based antioxidant reserves such as glutathione, extensive lipid peroxidation of cellular membranes, and profound mitochondrial dysfunction [3]. This energetic collapse and oxidative assault ultimately culminate in hepatocyte necrosis and a pronounced local inflammatory response [1].

Currently, no specific antidote is available, and clinical management remains largely supportive, encompassing gastrointestinal decontamination and hemodialysis [7]. Within this therapeutic framework, N-acetylcysteine (NAC) stands as the adjunctive agent, valued for its capacity to replenish glutathione stores, directly scavenge ROS, and modulate inflammatory pathways [1, 2]. Nevertheless, despite its established clinical role, the full therapeutic potential of NAC is hampered by several pharmacokinetic hurdles, including suboptimal oral bioavailability, inefficient cellular penetration, rapid systemic metabolism, and adherence issues associated with its odor and gastrointestinal side effects [2, 12]. These constraints strongly motivate the development of advanced delivery strategies to maximize its efficacy.

Polymer-based nanocarriers, particularly polyrhodanine (PR), present a compelling avenue. PR nanoparticles are especially attractive owing to their inherent biocompatibility and favorable physicochemical traits [5]. Their partially protonated surface imparts a positive charge at physiological pH, which promotes robust electrostatic interactions with negatively charged cellular membranes [17], a feature that not only facilitates rapid internalization but also enhances the intracellular retention of loaded NAC. Furthermore, PR can be precisely synthesized with a uniform diameter, offering a high surface area for drug loading, while its accessible functional groups allow for efficient covalent conjugation of therapeutic agents [5]. In our previous investigation, we developed a PR-NAC nanoformulation and demonstrated its superior hepatoprotective efficacy over free NAC in a rat model of acetaminophen (APAP)-induced liver injury, evidenced by significant reductions in serum transaminases, effective attenuation of lipid peroxidation, robust restoration of thiol reserves, and marked histopathological improvement [12].

Given the mechanistic convergence of oxidative stress in APAP and PQ hepatotoxicity, it is hypothesized that PR-NAC would exert comparable cytoprotection against PQ-induced damage. Therefore, the present study was designed to systematically evaluate the protective effects of PR-NAC against PQ cytotoxicity in HepG2 cells, a well-validated human hepatoma line preserving essential metabolic and detoxification functions.

Materials and Methods

Chemicals and reagents

All chemical reagents were obtained from Merck (Darmstadt, Germany), unless stated otherwise. Paraquat, N-acetylcysteine (NAC), rhodamine 123, Triton X-100, dimethyl sulfoxide (DMSO), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), and phosphate-buffered saline (PBS) were supplied by Sigma-Aldrich (St. Louis, MO, USA). DMEM, fetal bovine serum (FBS), penicillin-streptomycin, and trypsin–EDTA were acquired from Gibco (UK).

This study employed the same polyrhodanine (PR) and N-acetylcysteine-loaded polyrhodanine nanoparticles (PR–NAC) that were previously synthesized and characterized in our earlier work. Briefly, the preparation involved the aqueous polymerization of rhodanine to yield PR, followed by the covalent immobilization of NAC via carbodiimide chemistry. The key physicochemical parameters, namely an average size of 82.1 nm, a zeta potential of −27.4 mV, and a loading efficiency of 3.4%, were consistent with those reported in our earlier work (Nili-Ahmadabadi, Abdpour et al. 2024) [12].

Cell culture

The HepG2 cell line was obtained from the Pasteur Institute of Iran (Tehran, Iran). Cells were cultured in 25 cm² flasks containing high-glucose DMEM supplemented with 10% fetal bovine serum and 1%

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penicillin-streptomycin, and were maintained at 37 °C in a humidified atmosphere of 5% CO_2.

Determination of safe and toxic doses of PQ and pharmaceutical formulations

To evaluate the half-maximal inhibitory concentration (IC_{50}) of PQ and to identify the safe dosage range of pharmaceutical formulations, cells were exposed to increasing concentrations of PQ (2.5–160 µg/mL), NAC (0.005–20 mM) and PR-NAC formulation (NAC dose equivalent) for a period of 24 h. Cell viability was assessed using the MTT assay. In brief, a 5 mg/mL solution of MTT reagent was added to each well, followed by a 4-h incubation at 37°C. Subsequently, 100 µL of DMSO was added to dissolve the resulting formazan crystals, and optical density was measured at 570 nm using a microplate reader (Synergy HTX, Biotek, USA). Finally, cytotoxicity was expressed as the concentration required to inhibit cell growth by 50% (IC_{50}).

Assessment of the cytoprotective potential of PR-NAC on PQ cytotoxicity

To assess the cytoprotective potential of the test formulations against PQ-induced cytotoxicity, HepG2 cells were treated according to the following experimental design. Five distinct groups were established: an untreated control group; a PQ group, which received PQ alone at its previously determined IC_{50} concentration (17.47 µg/mL); a free NAC group, co-treated with 5 mM NAC and PQ; a PR-NAC group, co-treated with PQ and PR-NAC (NAC equivalent dose); and an empty PR group, treated with PQ and unloaded PR nanoparticles. All treatments were applied concurrently and maintained for 24 h.

Cell membrane integrity

The extent of cell membrane disruption was determined by spectrophotometrically quantifying lactate dehydrogenase (LDH) activity released into the extracellular medium, with absorbance measured at 340 nm. All procedures were performed according to the reagent manufacturer's recommended protocol (Pars Azmoon Company, Iran; catalog no. HITACHI917).

Mitochondrial membrane potential

Alterations in mitochondrial membrane potential ($\Delta\Psi m$) were evaluated using rhodamine 123 (Rh-123) as a fluorescent probe. Following a 24-h treatment period, cells were incubated with 2 µM Rh-123 at 37 °C for 30 min. Fluorescence intensity was then recorded at excitation and emission wavelengths of 507 nm and 529 nm, respectively. The resulting values were normalized to those of the untreated control group and expressed as a percentage.

Evaluation of cellular antioxidant status

Cryopreserved cell lysates maintained at -80°C were brought to room temperature and subsequently centrifuged at 10000 rpm for 2 min at 4°C to pellet insoluble material. The clear supernatants were then collected, and commercial colorimetric reagent kits (Navand Salamat Co., Tehran, Iran) were employed to measure superoxide dismutase (SOD) and catalase (CAT) enzymatic activities within the HepG2 cell homogenates. Optical density readings were taken with a microplate reader (Synergy HTX, Biotek, USA), and enzyme activity levels were ultimately expressed as percentages with respect to the untreated control group.

Statistical analyses

All acquired data, drawn from five independent experimental replicates, were reported as mean values together with their corresponding standard error of the mean (SEM). Statistical processing was carried out using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Intergroup differences were examined by employing a one-way analysis of variance (ANOVA), followed by Tukey's multiple-comparison test. Differences were judged as statistically significant when the p-value fell below 0.05.

Results

Cytoprotective effects of PR-NAC against PQ-induced cytotoxicity in HepG2 cells

As depicted in Figure 1A, PQ alone exhibited an IC_{50} of 17.47 µg/mL (95% CI: 10.96-27.83 µg/mL). Co-treatment with the empty PR nanocarrier did not appreciably alter this value, yielding an IC_{50} of 19.78 µg/mL (95% CI: 13.77-28.42 µg/mL; Figure 1B).

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The addition of free NAC moderately increased the IC_{50} to 22.19 µg/mL (95% CI: 17.40-28.30 µg/mL; Figure 1C). In contrast, the PR–NAC formulation produced the most pronounced shift, elevating the IC_{50} to 26.41 µg/mL (95% CI: 16.67-41.85 µg/mL; Figure 1D), indicating a substantially enhanced protective effect compared with the free drug.

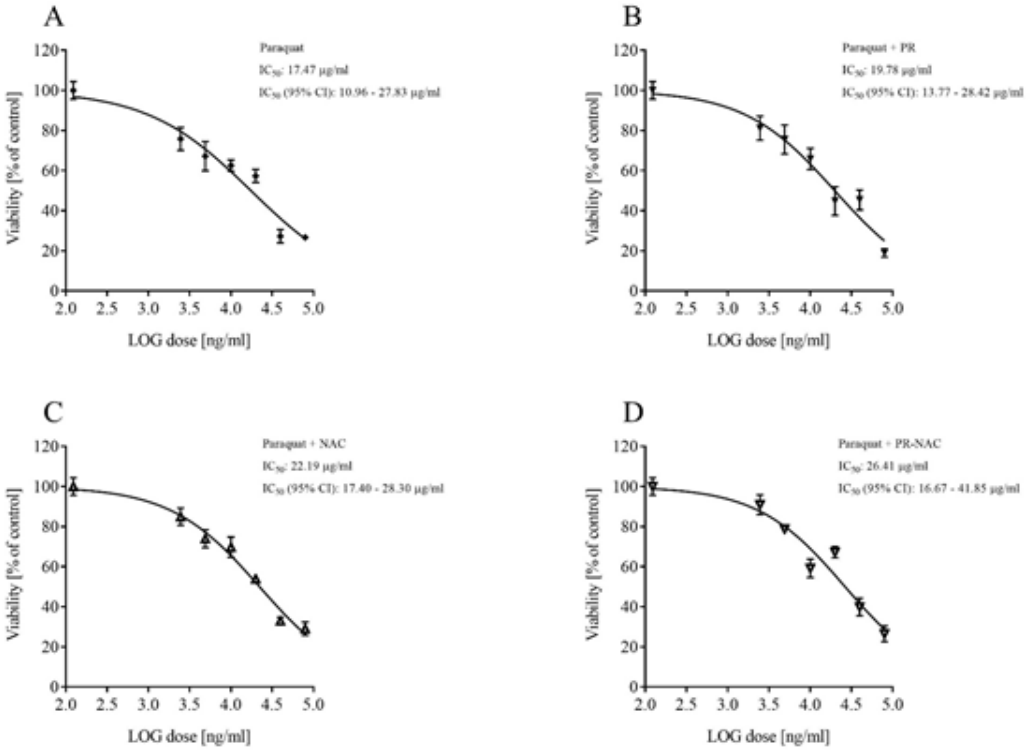


Figure 1. Cytoprotective effects of N-acetylcysteine-loaded polyrhodanine nanoparticles on paraquat-induced cytotoxicity in HepG2 cells. Cells were exposed to increasing concentrations of PQ (2.5-160 µg/mL) for 24 h (A), co-treated with PQ and polyrhodanine (B), co-treated with PQ and N-acetylcysteine (C), and co-treated with PQ and N-acetylcysteine-loaded polyrhodanine nanoparticles (D). Cell viability was evaluated by the MTT assay, and the results are expressed as a percentage of the control (untreated) group. Data are shown as the mean ± SEM from at least five independent experiments. PQ, paraquat; PR, polyrhodanine; NAC, N-acetylcysteine; PR-NAC, N-acetylcysteine-loaded polyrhodanine nanoparticles.

Cell membrane integrity

As shown in Figure 2A, exposure to PQ alone caused a significant increase in LDH release into the culture medium, reflecting substantial damage to cell membrane integrity ($P < 0.001$). Concurrent treatment with free NAC significantly mitigated this rise ($P < 0.001$). Similarly, application of the PR-NAC formulation diminished LDH leakage to a comparable extent as free NAC ($P < 0.001$), suggesting that both interventions were similarly effective in maintaining cell membrane integrity under the tested conditions. Of note, the empty PR nanocarrier had no appreciable effect on LDH release, suggesting that it did not appreciably affect LDH release under these conditions.

Mitochondrial membrane potential

Mitochondrial membrane potential (ΔΨm) was measured using rhodamine 123 fluorescence, as shown in Figure 2B. Exposure to PQ caused a marked decrease in ΔΨm, indicated by a significant decrease in fluorescence compared to the control group ($P < 0.001$). Treatment with free NAC partly restored the membrane potential ($P < 0.01$), while the PR-NAC formulation led to a greater recovery ($P < 0.001$), bringing ΔΨm close to the level seen in untreated cells. As expected, the empty PR carrier alone had no noticeable effect on ΔΨm.

Antioxidant enzyme activities (CAT and SOD)

The activities of the endogenous antioxidant enzymes CAT and SOD were assessed in HepG2

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cell homogenates, as illustrated in Figures 2C and 2D, respectively. PQ exposure significantly suppressed both CAT ($P < 0.001$) and SOD ($P < 0.001$) activities compared with the untreated control group. Co-treatment with free NAC partially restored CAT ($P < 0.05$) and SOD ($P < 0.001$) activities. Of note, administration of the PR-NAC formulation conferred a comparable recovery to that of NAC, elevating CAT and SOD activities ($P < 0.001$ for both). The empty PR nanocarrier alone did not produce any notable effect on enzyme activities.

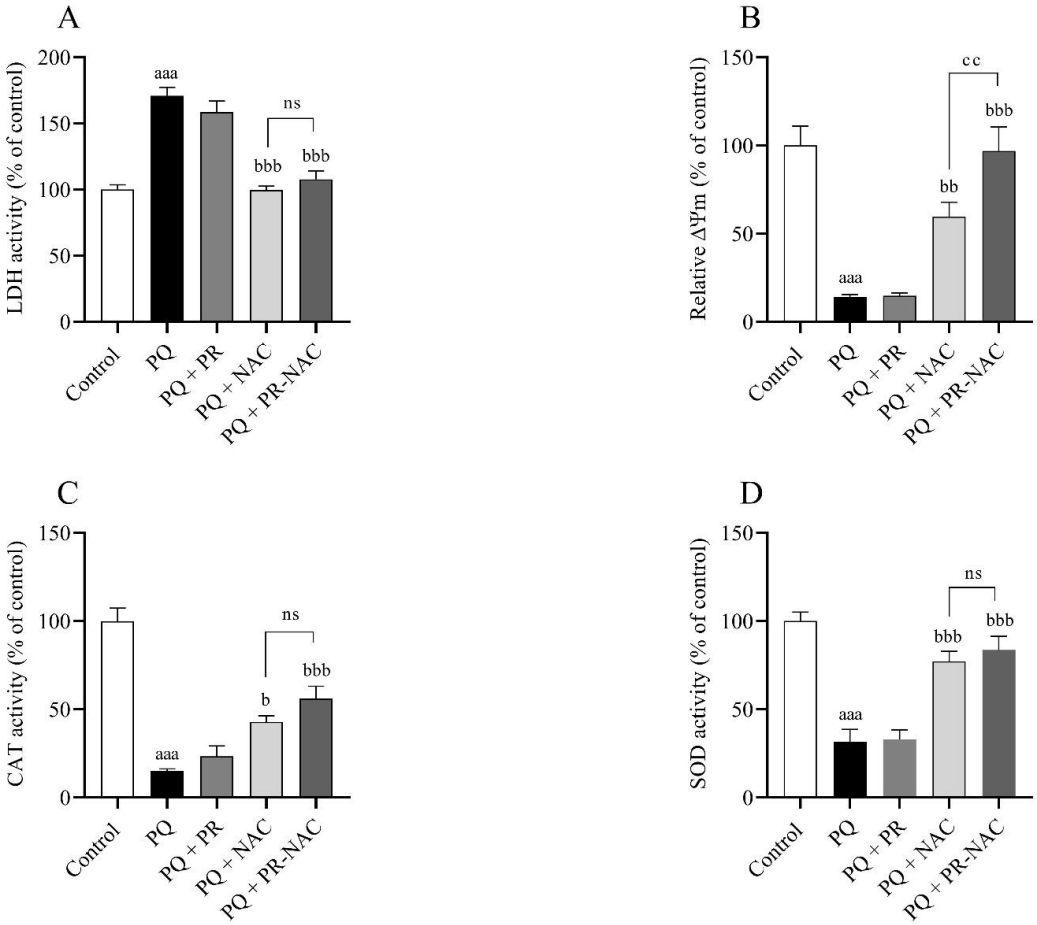


Figure 2. Comparative cytoprotective and antioxidant effects of free N-acetylcysteine (NAC) and N-acetylcysteine-loaded polyrhodanine nanoparticles (PR-NAC) against paraquat (PQ)-induced injury in HepG2 cells. Cells were treated with PQ (IC_{50}, 17.47 µg/mL) alone or co-treated with free NAC (5 mM), PR-NAC (NAC dose equivalent), or empty PR nanoparticles for 24 h. (A) Lactate dehydrogenase (LDH), (B) Mitochondrial membrane potential (ΔΨm), (C) Intracellular catalase (CAT) enzymatic activity, (D) Intracellular superoxide dismutase (SOD) enzymatic activity. Data are presented as mean ± SEM from five independent replicates. ^{aaa} $P < 0.001$ vs. the untreated control group; ^{b} $P < 0.05$, ^{bb} $P < 0.01$ and ^{bbb} $P < 0.001$ vs. the PQ-treated group; ^{cc} $P < 0.01$ for the PQ + NAC and PQ + PR-NAC group.

Discussion

The present study was designed to evaluate whether encapsulating NAC within PR nanoparticles could enhance its cytoprotective efficacy against PQ-induced hepatotoxicity in HepG2 cells. The results indicate that PR-NAC preserved both cell viability and ΔΨm more effectively than free NAC. The enhanced efficacy of PR-NAC can be attributed to several favorable properties of the PR nanocarrier system. With a mean hydrodynamic diameter of approximately 82 nm, PR nanoparticles are well suited for cellular internalization via endocytic pathways [11]. Additionally, the positive surface charge of PR, derived from protonatable tertiary amide groups, facilitates electrostatic interactions with the negatively charged cell membrane, thereby enhancing cellular uptake [17].

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The superior mitochondrial protection conferred by PR-NAC warrants particular attention. PQ-induced mitochondrial dysfunction is a hallmark of its hepatotoxicity [10], characterized by the collapse of mitochondrial membrane potential, opening of the permeability transition pore, and release of pro-apoptotic factors [6, 10]. The mitochondria serve as both a primary source and a major target of PQ-generated ROS; complex I of the electron transport chain can reduce PQ, perpetuating redox cycling and generating substantial oxidative damage within these organelles [16]. While free NAC partially restored ΔΨm, the substantially greater recovery achieved with PR-NAC likely reflects more efficient delivery of NAC to the mitochondrial compartment. Within mitochondria, NAC can directly scavenge ROS, replenish mitochondrial glutathione pools, and preserve electron transport chain integrity [8].

The restoration of endogenous antioxidant enzyme activities represents another key finding. SOD and CAT constitute the primary enzymatic defense against oxidative stress, with SOD converting superoxide anions to hydrogen peroxide and CAT subsequently detoxifying hydrogen peroxide to water and molecular oxygen [2]. PQ exposure significantly suppressed both enzyme activities, reflecting overwhelming oxidative stress and impairment of these defense systems by excessive ROS production. The recovery of SOD and CAT activities by PR-NAC can be mechanistically explained by the enhanced intracellular delivery of NAC, which serves as a precursor for glutathione synthesis and supports the redox homeostasis necessary for optimal enzyme function [12]. Additionally, NAC may directly protect antioxidant enzymes from oxidative inactivation by scavenging ROS before they can damage these proteins [15]. These findings are in agreement with our previous *in vivo* study demonstrating the hepatoprotective potential of PR-NAC against acetaminophen-induced liver injury [12].

Conclusion

Collectively, the data establish PR-NAC as a versatile and effective nanoplatform for delivering NAC against chemically induced hepatotoxicity. Future studies should explore the *in vivo* efficacy of PR-NAC in animal models of PQ poisoning, evaluate its pharmacokinetic profile, and investigate potential long-term safety considerations. Given the favorable biocompatibility profile of PR and the established safety of NAC, PR-NAC represents a promising therapeutic strategy for the management of PQ poisoning and other oxidative stress-related hepatic injuries.

CRediT authorship contribution statement

Yekta Kheradmand contributed to compiling the bibliography, performing biochemical analyses, and drafting the manuscript. Seyyed Alireza Hashemi and Navid Omidifar provided guidance and acted as advisors throughout the project. Fatemeh Ghaffari assisted with cellular and biochemical analyses. Amir Nili-Ahmadabadi and Davoud Ahmadimoghaddam conceived the study, supervised its execution, revised the manuscript, and served as the project supervisor.

Funding

This study was financially supported by the Vice-Chancellor of Research and Technology, Hamadan University of Medical Sciences, Hamadan, Iran (Grant No. 140402091081).

Data availability

All relevant data are within the paper.

Conflict of interest

The authors declare no competing interests.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Ethics Committee of Hamadan University of Medical Sciences (approval number: IR.UMSHA.REC.1404.099).

Acknowledgments

The authors thank the staff of the Toxicology and Pharmacology Laboratory and the Laboratory Animal Care Center at HUMS for their cooperation and support during this project. During the preparation of this manuscript, the authors used DeepSeek-V3.2 and SidER software for language editing and grammar correction.

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[DOI: 10.53208/ajpr.6.2.81]

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