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Original Article

Nanoparaquat and Paraquat Effects on Oxidative Stress Biomarkers in Rat Brain

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Abstract

Background: The nervous system is particularly vulnerable to irreversible injury owing to its structural complexity and limited regenerative capacity. Paraquat (PQ), a widely used bipyridyl herbicide, is well-documented for its severe neurotoxic effects. Polysaccharide-based nanoparticles present a promising strategy to attenuate such toxicity by modulating bioavailability and providing sustained release. The present study was undertaken to develop PQ-loaded nanoparticles and evaluate their effects on neural tissue function.

Methods: In this study, 40 male rats were randomly divided into the following groups: control, N-acetylcysteine (NAC), PQ, nano-paraquat (NP) α or β, and combinations of NAC with PQ or NP α or β. Treatments were administered intraperitoneally for seven days. On the final day, animals were sacrificed under ketamine–xylazine anesthesia, and brain tissues were collected. Samples were either fixed in 10% formalin for histological evaluation or preserved in liquid nitrogen for biochemical assays. Oxidative stress and biochemical indicators, such as superoxide dismutase, catalase (CAT), total thiol groups (TTG), lipid peroxidation (LPO), and total antioxidant capacity (TAC), were measured. Histopathological changes were further examined using Congo red staining to assess the neuroprotective efficacy of paraquat nano-paraquat (PQNP) α or β ،formulations with or without NAC.

Results: This study showed that PQ significantly decreased TTG levels (P<0.01), CAT (P<0.001), and TAC (P<0.05) compared to the control group, while significantly increasing LPO (P<0.01). Additionally, PQNP β demonstrated a more effective modulation of oxidative stress markers in brain tissue than both PQNP α and PQ. The neuroprotective potential of PQNP β was further confirmed by histopathological findings, consistent with the biochemical results.

Conclusion: All things considered, our results show that the β form of PQNP causes less oxidative damage in the brain than both the α form and regular PQ. These findings imply that herbicides developed with nanotechnology might provide a safer and more efficient alternative to their traditional counterparts in the future.

Keywords
Brain, N-acetylcysteine (NAC), Nanoparaquat, Paraquat (PQ)

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Introduction

Paraquat (PQ; N, N′-dimethyl-4,4′-bipyridinium) is a widely used bipyridyl herbicide available in liquid, granular, or aerosol formulations, often combined with excipients such as dextran [1]. Its broad-spectrum efficacy, rapid action, and affordability have maintained its role in integrated weed management despite environmental concerns [2]. The principal mechanism underlying PQ toxicity involves the production of reactive oxygen species (ROS) via redox cycling within mitochondria, which precipitates oxidative stress, lipid peroxidation (LPO), and ensuing damage to cellular architecture [3]. This cascade results in multi-organ dysfunction, with the lungs being the most affected organ, often leading to fatal outcomes in severe cases [4]. Additionally, PQ exposure has been linked to neurotoxic effects, including the selective degeneration of dopaminergic neurons, which may contribute to the pathogenesis of Parkinson's disease [6]. Currently, there is no specific antidote for PQ poisoning. Treatment strategies primarily focus on supportive care and the use of antioxidants such as N-acetylcysteine (NAC), selenium, and vitamins C and E, which have shown varying degrees of efficacy in mitigating oxidative damage and improving patient outcomes [7, 8]. However, the effectiveness of these treatments remains limited, underscoring the need for the development of more effective therapeutic interventions [9,10].

In recent years, advances in nanotechnology have enabled the rational design and synthesis of materials with physicochemical properties tailored to those of their bulk counterparts. Despite considerable progress, comprehensive data on the differential toxicity and biological interactions of these materials remain limited [11]. Polymeric nanoparticles, in particular, have emerged as versatile platforms with wide-ranging applications in biomedicine, including targeted drug delivery, controlled release systems, medical imaging, and the development of advanced functional materials, as well as in fundamental studies in microfluidics and nanoscience [12, 13]. Particle morphology, surface charge, and size critically dictate cellular uptake, biodistribution, and functional performance; however, precise control over these parameters remains a major challenge for the rational optimization of nanoparticle-based systems [14]. Chitosan- and alginate-based nanoparticles have been successfully employed to encapsulate PQ, thereby enhancing soil adsorption, reducing environmental mobility, and attenuating nonspecific toxicity relative to the free herbicide [15]. In vitro studies using chitosan-TPP PQ nanoparticles in Chinese hamster ovary cells have reported decreased cytotoxicity, while environmental studies have highlighted the modulatory effects of AHS on nanoparticle stability, genotoxicity, and ecotoxicity, with particle sizes consistently ranging between 390 and 420 nm [16, 17]. More recent formulations integrating pectin, chitosan, and TPP further reduced cytotoxicity in alveolar and oral epithelial cells, limited soil penetration, and improved herbicidal efficacy in crop models, while maintaining particle diameters around 418 nm [18]. Although these results are promising, in vivo investigations remain limited, emphasizing the need for refined nanoparticle design and miniaturization to optimize safety and efficacy. Accordingly, the present study employs ionotropic gelation to fabricate chitosan-based PQ nanoparticles, exploiting electrostatic interactions for controlled loading, sustained release, and potential cellular and systemic protective effects in rat models [19, 20]. Such strategies inform the development of next-generation nanoherbicides that combine high efficacy with reduced ecological and toxicological impact.

This study aimed to determine the effects of paraquat nano-paraquat (PQNP) α or β on oxidative stress in the brain tissue of male Wistar rats.

Methods

Chemicals

Thiobarbituric acid (TBA), eosin dye, n-butanol, phosphate-buffered saline (PBS), 2,4,6-tripyridyl-s-triazine (TPTZ), PQ, and NAC were obtained from Merck (Germany). Chitosan and alginate were purchased from Sigma-Aldrich (USA). Formalin was supplied by Samchun Chemical (South Korea), while ketamine and xylazine were procured from Alfasan (Netherlands). Ethanol was obtained from Pars Shimi Teb (Iran).

Commercial ELISA kits from KiaZist Company (Ira n) were used to measure the levels of LPO, total anti oxidant capacity (TAC), and total thiol concentratio

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n. Additionally, all remaining reagents were of pharmaceutical grade and were used immediately after procurement.

Experimental Design

Ionotropic gelation was used to form PQNP α or β by exploiting the electrostatic interactions between polymers of opposite charges. The α-formulation produced nanoparticles with PQ encapsulated inside the polymeric matrix and adsorbed on the surface after a progressive addition of PQ solution to alginic acid under magnetic stirring for 60 minutes. To encourage pre-gelation, calcium chloride was first added dropwise to alginic acid in the β-formulation. A chitosan–PQ solution was then added over 60 minutes. This process produced core-shell nanoparticles with an alginate-based outer layer and a chitosan-rich core. Alginate was used for its buffering capacity and stabilizing impact, which reduced the chitosan hydrolysis. Both methods produced effective dual PQ loading and thermodynamically stable nanostructures [41].

Study Design

Animals

A total of 40 adult male Wistar rats, weighing 180-200 g, were obtained from the animal care facility at Hamadan University of Medical Sciences. Throughout the study, the animals were maintained under standardized laboratory conditions, including controlled temperature (20°C–25°C), relative humidity of approximately 50%, and a 12-hour light/dark cycle, with free access to standard chow and water. All procedures were conducted in accordance with the ethical criteria approved by the Hamadan University of Medical Sciences Ethics Committee (IR.UMSHA.REC.1403.004). Prior to the study, rats were acclimated for at least one week to ensure environmental adaptation and attainment of the desired body weight.

Study Method Design

Forty animals were kept in separate polycarbonate cages and randomly assigned to eight equal groups (n = 5). For seven consecutive days, treatments were administered once daily via intraperitoneal injection. The experimental groups were as follows: The negative control group received only normal saline (4 mg/kg). The positive control group was administered PQ (4 mg/kg). The PQNP α and PQNP β groups received PQNP type α and type β, respectively, each at a dose equivalent to 4 mg/kg of PQ. The sham group received NAC (300 mg/kg) to assess its baseline effects. The therapeutic groups included NAC + PQ, NAC + PQNP α, and NAC + PQNP β, in which NAC (300 mg/kg) was co-administered with PQ or its nanoparticle forms (α or β, equivalent to 4 mg/kg PQ) to evaluate the protective and therapeutic potential of NAC against PQ-induced toxicity [41].

Sampling

After treatment, brain tissues were collected for analysis. A ketamine–xylazine mixture (8:1) was injected intraperitoneally to deeply anesthetize the animals, and euthanized. To avoid any structural damage, brain tissues were meticulously removed using surgical scissors, a scalpel, and forceps. Samples were either snap-frozen in liquid nitrogen to assess oxidative stress indicators or promptly stored in 10% formalin for histopathological analysis [21].

Analysis of Oxidative and Antioxidative Stress Markers in the Brain

Approximately 1 g of brain tissue was homogenized in 2 mL of PBS (pH 7.4) under a nitrogen atmosphere [22]. The homogenate was centrifuged at 10,000 rpm for 15 minutes at 4°C, and the supernatant was collected and stored at –80°C for subsequent evaluation of oxidative stress and antioxidant markers, including LPO, TAC, total thiol groups (TTG), catalase (CAT), and superoxide dismutase (SOD). LPO was measured using the TBA method at 532 nm and expressed as nmol/mg protein [23]. TAC was assessed via Fe^{3+} reduction in the presence of TPTZ, forming a blue complex measured at 593 nm [24]. TTG was determined using Ellman's reagent (5,5-dithio-bis [2-nitrobenzoic acid]) with an absorbance at 412 nm [25].

Histological Studies

For histological analysis, brain samples were fixed in 10% formalin, paraffin-embedded, sectioned at 4 µm, and stained with hematoxylin and eosin (H&E). Slides were examined by a pathologist using a CX41 Olympus light microscope with a DP25 digital camera [26].

Statistical Analysis

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The mean ± standard deviation was used to represent all results. One-way analysis of variance and Tukey's post hoc test were used for statistical comparisons using GraphPad Prism software (version 8). Statistical significance was defined as a *P* value<0.05.

Results

Figure 1. Compared to the control group, the PQ-treated group had considerably higher LPO levels (*P*<0.01). In contrast, LPO was significantly lower in the groups that contained NAC (*P*<0.05), nano-PQ β (*P*<0.01), PQ + NAC (*P*<0.001), nano-PQ β + NAC (*P*<0.001), and nano-PQ α + NAC (*P*<0.01) than in the group that contained PQ.

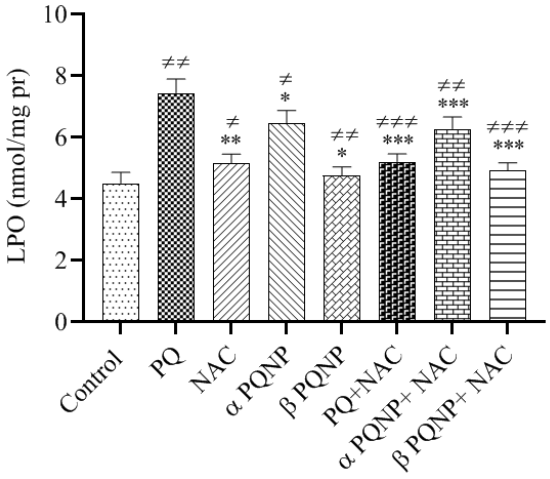

Figure 1: Effects of Nanoparaquat on the Lipid Peroxidation (LPO) Concentration in Brain Homogenate.

Data are expressed as mean ± SEM (n=5). Statistical significance: $^{\#\#}P$<0.001, $^{\#}P$<0.01 compared and $^{\neq}P$<0.05 compared to the paraquat group; ***P<0.001, **P<0.01, *P<0.05 compared to the control group.

Figure 2. Compared to the control group, the PQ group's TAC was considerably lower (*P*<0.05). In contrast to the PQ group, TAC was significantly higher in the nano-PQ β group (*P*<0.01), the PQ + NAC group (*P*<0.05), the nano-PQ β + NAC group (*P*<0.05), and the nano-PQ α + NAC group (*P*<0.05).

Figure 3. Compared to the control group, the PQ group's CAT activity was significantly lower (*P* < 0.001). Compared to the PQ group, the nano-PQ β group had significantly higher CAT levels (*P* < 0.01), followed by the PQ plus NAC group (*P* < 0.05), the nano-PQ β + NAC group (P < 0.01), and the nano-PQ α + NAC group (*P* < 0.01).

Figure 4. The PQ group's SOD activity was significantly lower than the control group's (*P* < 0.001). SOD levels, however, were significantly greater in the groups that received NAC (*P* < 0.05), nano-PQ β (*P* < 0.01), PQ + NAC (*P* < 0.01), nano-PQ β + NAC (*P* < 0.01), and nano-PQ α + NAC (*P* < 0.001) than in the group that received PQ.

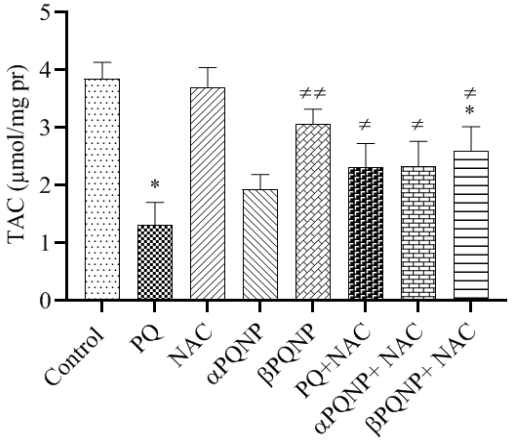

Figure 2: Effects of Nanoparaquat on the Total Antioxidant Capacity (TAC) Concentration in Brain Homogenate.

Data are expressed as mean ± SEM (n=5). Statistical significance: $^{\#}P$<0.01 compared and $^{\neq}P$<0.05 compared to the paraquat group; *P<0.05 compared to the control group.

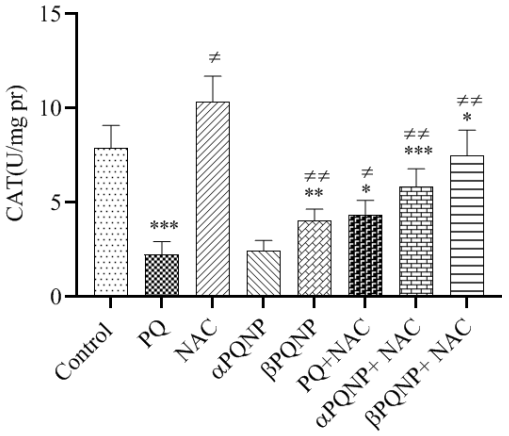

Figure 3: Effects of Nanoparaquat on the Catalase (CAT) Concentration in Brain Homogenate.

Data are expressed as mean ± SEM (n=5). Statistical significance: $^{\#}P$<0.01 compared and $^{\neq}P$<0.05 compared to the paraquat group; ***P<0.001, **P<0.01, *P<0.05 compared to the control group.

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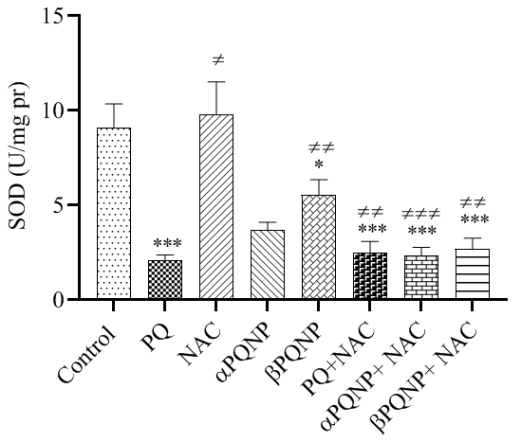

Figure 4: Effects of Nanoparaquat on the Superoxide Dismutase (SOD) Concentration in Brain Homogenate.
Data are expressed as mean ± SEM (n=5). Statistical significance: $^{\neq\neq}P<0.01$ compared and $^{\neq}P<0.05$ compared to the paraquat group; ***$P<0.001$, *$P<0.05$ compared to the control group.

Figure 5. Compared to the control, the PQ group showed a substantial decrease in TTG ($P<0.01$). In contrast, TTG levels were significantly higher in the groups that received NAC ($P<0.05$), nano-PQ β ($P<0.01$), PQ + NAC ($P<0.05$), nano-PQ β + NAC ($P<0.05$), and nano-PQ α + NAC ($P<0.01$) than in the PQ group.

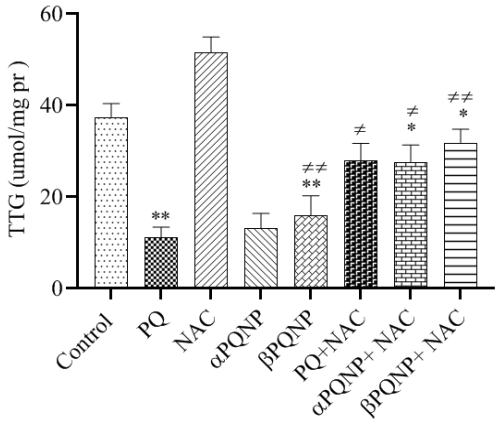

Figure 5: Effects of Nanoparaquat on the Total Thiol Groups (TTG) Concentration in Brain Homogenate
Data are expressed as mean ± SEM (n=5). Statistical significance: $^{\neq\neq}P<0.01$ compared and $^{\neq}P<0.05$ compared to the paraquat group; **$P<0.01$, *$P<0.05$ compared to the control group.

Histological Results

Figure 2. Representative H&E staining of hippocampal sections. In the PQ group, higher magnification of the CA4 region revealed shrunken pyramidal neuronal cell bodies with nuclear damage (arrowheads). In contrast, the negative control group displayed normal cellular morphology across all hippocampal subfields. In the PQNPα group, severe pyramidal cell injury (green square, panel B) and amyloid plaque deposition in the hippocampal region (blue circle, panel A) were observed. The PQNPβ group exhibited reduced cellular density in CA1 (panel B) and shrunken neurons, although intact cells remained in CA4 (panel C). In the NAC group, degenerated neurons in CA1 were identified (black arrows, panel B), while combined NAC + PQ treatment resulted in severe vacuolization (red circles, panel B), β-amyloid plaque necrosis (dark circle, panel A), and pericellular spaces surrounding necrotic and pyknotic neurons (orange arrows). In the PQNPα + NAC group, β-amyloid plaques (blue circles), shrunken cells, elongated degenerated nuclei, and acidophilic cytoplasm indicated hippocampal damage (red rectangles). In the PQNPβ + NAC group, regenerating and vacuolated cells were detected, with severe vacuolization (orange arrows), neuronal necrosis, and pericellular spaces around necrotic and pyknotic neurons (blue circles).

Discussion

Environmental pollution is increasing worldwide, threatening ecosystem stability, human health, and the survival of living organisms. Among agrochemicals, PQ is one of the most widely used herbicides, with high oral and dermal absorption potential. Its toxicity primarily stems from redox cycling and the generation of ROS, which trigger oxidative stress and apoptosis [28]. Under physiological conditions, a balance exists between ROS production and antioxidant defenses; however, disruption of this equilibrium, through enhanced ROS formation or reduced antioxidant capacity, leads to cellular injury, DNA fragmentation, protein oxidation, and LPO [29, 30]. PQ is a strong stimulator of superoxide anions, which initiate a cascade of secondary free radical formation, thereby amplifying oxidative damage to macromolecules [31].

Given these harmful effects, the development of nano-formulations has emerged as a potential alternative strategy in agriculture. Nanotechnology allows for the fabrication of nano-herbicides with enhanced physicochemical properties; however, their comparative toxicity to biological systems remains poorly understood [32]. In this study, we

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investigated the impact of PQNPα and PQNPβ formulations compared to PQ, focusing on oxidative stress biomarkers, antioxidant enzyme activity, and histopathological alterations in brain tissue. Previous research has largely focused on the agricultural efficacy and cytotoxicity of nanoparaquat [33], whereas our study provides in vivo insights into neurotoxic outcomes.

Our results revealed that PQ significantly increased LPO levels, depleted TTG, and inhibited critical antioxidant enzymes, including SOD and CAT, indicating severe oxidative stress in neural tissue. These findings are in line with earlier studies demonstrating PQ-induced oxidative imbalance in both neural and peripheral organs [34, 35]. Importantly, administration of NAC effectively ameliorated these alterations by enhancing antioxidant defenses and scavenging ROS, which is consistent with prior evidence of NAC-mediated protection against oxidative injury [36].

Histopathological examination supported the biochemical results, as PQ exposure produced neuronal shrinkage, nuclear pyknosis, vacuolization, and amyloid plaque deposition in hippocampal regions. NAC treatment, particularly in combination with PQNPβ, reduced neurodegenerative changes and improved neuronal morphology. Similar protective roles of antioxidant strategies, including NAC and SOD mimetics, have been reported in PQ-induced dopaminergic neurodegeneration [37]. Notably, the PQNPβ formulation displayed reduced toxicity compared to α-nano and native PQ, which may be attributed to differences in particle size, distribution, and ROS-generating potential [38].

Protein oxidation, reflected by depletion of TTG groups, was substantially attenuated by NAC, highlighting its role in preserving redox-sensitive protein function. This finding corresponds with studies showing NAC's ability to replenish intracellular glutathione and prevent irreversible oxidative protein modifications [39]. Furthermore, NAC restored SOD and CAT activity, facilitating the detoxification of superoxide anions and hydrogen peroxide, thus improving redox homeostasis. Tardiolo et al. also demonstrated that NAC restored antioxidant enzyme activity in ischemic brain injury models, further supporting our observations [40].

Overall, our biochemical and histological findings provide compelling evidence that NAC significantly mitigates PQ-induced neurotoxicity via antioxidative mechanisms. Moreover, PQNPβ demonstrated a relatively favorable toxicity profile compared to native PQ, though its long-term ecotoxicological consequences remain uncertain and warrant further investigation [41].

Future studies should also examine molecular signaling pathways, such as Nrf2 activation and regulation of pro-inflammatory cytokines, to better elucidate the protective role of NAC and the toxicological characteristics of PQNP [42].

Conclusion

This study demonstrated that NAC treatment significantly mitigated the severe oxidative and neurotoxic effects of PQ by strengthening antioxidant defenses and lowering lipid and protein oxidation. Particularly when paired with NAC, the PQNPβ formulation showed decreased neurotoxic potential, indicating that nano-herbicide formulations might offer a safer alternative with less toxicity to mammals. However, the need for thorough ecotoxicological evaluations before widespread agricultural use is underscored by the persistence of nano-formulations in soil and their possible ecological risks. Therefore, future research must incorporate molecular, systemic, and environmental evaluations to ensure both therapeutic efficacy and ecological safety, even though antioxidant therapies, such as NAC, show promise in reducing PQ-induced neurotoxicity.

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