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RESEARCH PAPER

Toxicity of Silica Nanoparticles on Liver Function, Oxidative Stress, and Inflammatory Cytokines in Time Manner in vivo

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ABSTRACT

Silica dioxide nanoparticles (SiNPs) are common nanoparticles used in industry, particularly in cosmetics, food, and other applications. However, exposure to high doses can induce toxicity and pose a significant risk. This study was designed to assess potential toxicity caused by SiNPs in *vivo*. In this study, twenty-eight male rats were consumed and set into four groups (eight rats per group) as follows: first group (CON), which received no treatment, served as the control group, while the remaining groups were exposed to a single oral dose of silica nanoparticles (2000 mg/kg). Rats in group SiNPs-1were sacrificed after one day, rats in group SiNPs-7 after seven days, and rats in group SiNPs-14 after fourteen days of exposure. Blood serum was collected for serological biochemical tests, and liver extracts were collected to assess oxidative stress. A significant increase in peak toxicity, including liver function biomarkers, acute oxidative shock, and intense release of serological pro-inflammatory cytokines in SiNPs-1 rats, was observed compared to unexposed control rats. In SiNPs-7, the toxic response was less pronounced, while in SiNPs-14, the liver function, oxidative, and inflammatory indicators were significantly reduced, resembling those of the control group. A single exposure to high concentrations of silica nanoparticles disrupts liver function markers, oxidative stress, and pro-inflammatory cytokines. However, this damage improves gradually in a time-related manner.

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INTRODUCTION

In general, liver represents a vital organ and body's detoxification center, it processes foreign compounds (xenobiotics), converting them into less toxic substances that can be eliminated [1,2]. This physiological function also leaves the liver highly vulnerable to toxicity, with exposure to chemicals or toxins capable of causing cellular and functional damage [3]. Hepatotoxicity has risen significantly alongside rapid industrialization and

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technological development [4].

One contributing factor is the unprecedented influx of environmental and industrial pollutants, especially nanoparticles that enter and spread through the environment [5,6].

Currently nanotechnology integration into medical fields changing the medical sector by improved diagnostic accuracy, enhanced treatments, and increased drug efficacy [7,8]. Because they have several distinctive physical and chemical advantages as small size (1-100 nm) relative to their surface area [9] and this allows them to penetrate cell membranes more easily and rapidly, delivering doses that induce dysfunction and toxicity [10]. Silica nanoparticles (SiNPs) are among the generality widely manufacture and used nanoparticles; their stability and low cost have made them a regular part of consumer industries [11]. They are also used in medical applications such as drug delivery, cosmetics, printer inks, and food [12]. Humans and animals are potentially exposed to these nanoparticles in the environment, whether through high doses or continuous exposure [13].

Several previous in vivo studies have shown that nanoparticles, once they reach the bloodstream, tend to accumulate in the liver, inducing severe toxic damage [14,15]. Thus exceeds the liver's capacity to resist oxidation inducing lipid peroxidation, DNA damage, and protein destruction, ultimately leading to hepatocytes necrosis and impaired liver function [16]. In addition, hepatocellular damage activates the immune system and sets off an acute inflammatory response [17]. The effects extend throughout body and appear as serum abnormalities as pro-inflammatory cytokines rise, while anti-inflammatory cytokines are suppressed or impaired and this imbalance can sustain the inflammation, causing further damage to liver tissue [18].

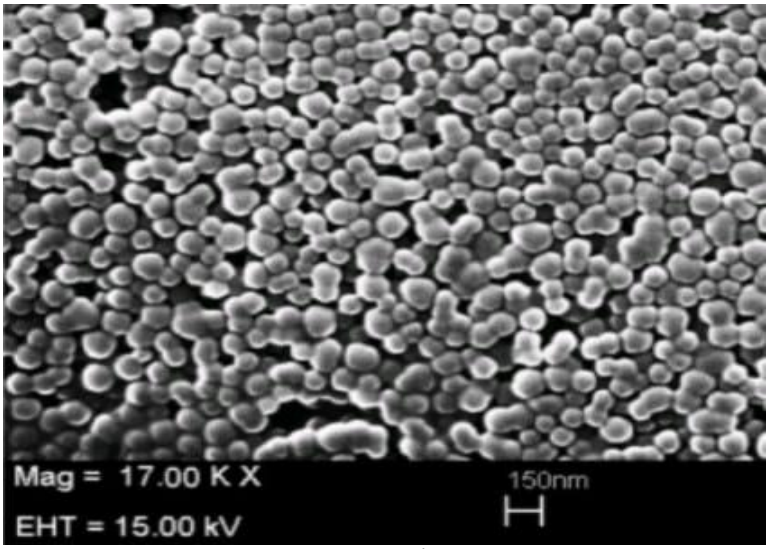


Fig. 1. SiO_2-NPs size according to SEM assay.

Table 1. Basic specifications of SiO_2-NPs dispersion.

Product	Silicon Oxide Dispersion
Mol. formula	SiO_2
Mol.-weight	60.09 g/mol
Form	Liquid
Solvent	DMF, IPA Ethanol, Water, ethyl
Concentration	d25 wt%
APS	5-35nm
Purity	99.99 %
PH	8-11
Color	Translucent

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Accurate risk assessment of silica nanoparticle use in the food and pharmaceutical industries remains a challenge due to the need for more conclusive evidence of its safety [19]. Despite increasing scientific research on nanomaterial toxicity, acute toxicity following oral exposure and its pathological progression are still not fully understood [20]. Therefore, this experiment was designed to estimate the time-dependent acute hepatotoxicity of silica nanoparticles in a rat model.

MATERIALS AND METHODS

Nanoparticles

Silicon oxide nanoparticles (SiO_2-NPs) aqueous dispersion amorphous with particle sizes ranging from 5 to 35 nm (Fig. 1) purchased from Nanoshel UK Limited Company, with specifications reported in Table 1.

Experimental rats

In this experiment, twenty-eight adult male albino rats, weighing between 195 and 205 grams, were consumed. They were taken from a privet laboratory animal center at an Iraqi university. The experimental protocols were consistent with the approach approved by the National Institutes of Health in 1978 for laboratory animal research. They were housed in suitable cages with appropriate ventilation, humidity, temperature, and lighting, and provided with standard food and water. After they had been acclimated to ideal environmental conditions for seven days, and to ensure accurate comparisons across time periods, the laboratory animals were set into 4 groups (8 rats per group) as illustrated in Table 2.

Following experimental period ended, all rats were dissected; blood was collected by cardiac puncture and samples were placed into tubes containing no anticoagulant for biochemistry analyses. The anesthetized rats were autopsied, livers separated, and kept until used to assess the level of hepatic oxidative stress biomarkers.

Statistical analysis

All data were processed by GraphPad Prism program (version 9.0), and were displayed as mean and standard deviation. The differences between groups were detected by applying ANOVA followed by Duncan's post hoc test. A p-value of less than five percent was adopted as significant. Different superscript letters (a-d) were used within different groups to indicate significant variations.

Biochemical Analysis

Blood drawn from each rat was carefully prepared by cardiac puncture, and the serum was separated by centrifugation at appropriate speed and time. This was done to perform assays for liver function biomarkers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) levels in the serum using a spectroscopic approach with kits from specific manufacturers, according to the manufacturer's protocol and with customized reagents.

Oxidative stress parameters

Liver homogenate extracts were prepared as previously described using commercial ELISA kits.

Malondaldehyde (MDA) levels were determined colorimetrically according to the thiobarbituric acid reactants substances protocol described by Draper and Hadley [22]. Reduced glutathione (GSH) levels were determined using a modified procedure by Ellman [23] based on a spectrophotometric absorption approach. The concentrations of catalase enzyme (CAT) were measured by hydrogen peroxide decomposition analysis according to Aebi method [24], superoxide dismutase (SOD) was assessed, as previously mentioned by Marklund and Marklund [25].

Table 2. Experiment design and treatments of study groups.

Groups	Treatments
CON	Rats were administration of vehicle only by gavage tube (g.t.) and dissected after 24 hours for control.
SiNPs -1	Rats were administration of SiNPs by g.t. at 2000 mg/kg once and dissected one day later [21].
SiNPs -7	Rats were dosed with SiNPs by g.t. at 2000 mg/kg once and dissected after seven days.
SiNPs -14	Rats were intoxicated with SiNPs by g.t. at 2000 mg/kg once and dissected after fourteen days.

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RESULTS AND DISCUSSION

The results showed a sharp excess in serum levels of hepatic biomarkers (ALT, AST, and ALP) in SiNPs-1 group (112.6 ± 10.5;245.8 ± 18.4; 310.4 ± 22.1) compared to CON group (35.4 ± 4.2; 92.1 ± 7.8; 130.5 ± 11.2). In SiNPs-7 group (85.3 ± 8.1; 180.4 ± 14.2; 235.6 ± 17.8), these markers gradually decreased compared to the SiNPs-1 group, while the SiNPs-14 group (48.7 ± 5.6; 115.3 ± 9.5;158.2±12.4) demonstrated a marked return to normal levels as explain in Fig. 2.

Regarding oxidative stress biomarker, lipid peroxide (MDA) levels were significantly elevated in rats exposed to SiNPs, peaking on SiNPs-1 rats (7.8 ± 0.9) compared to control rats (2.1 ± 0.3). By day 7 (5.4±0.6), the elevation stabilized, and by day

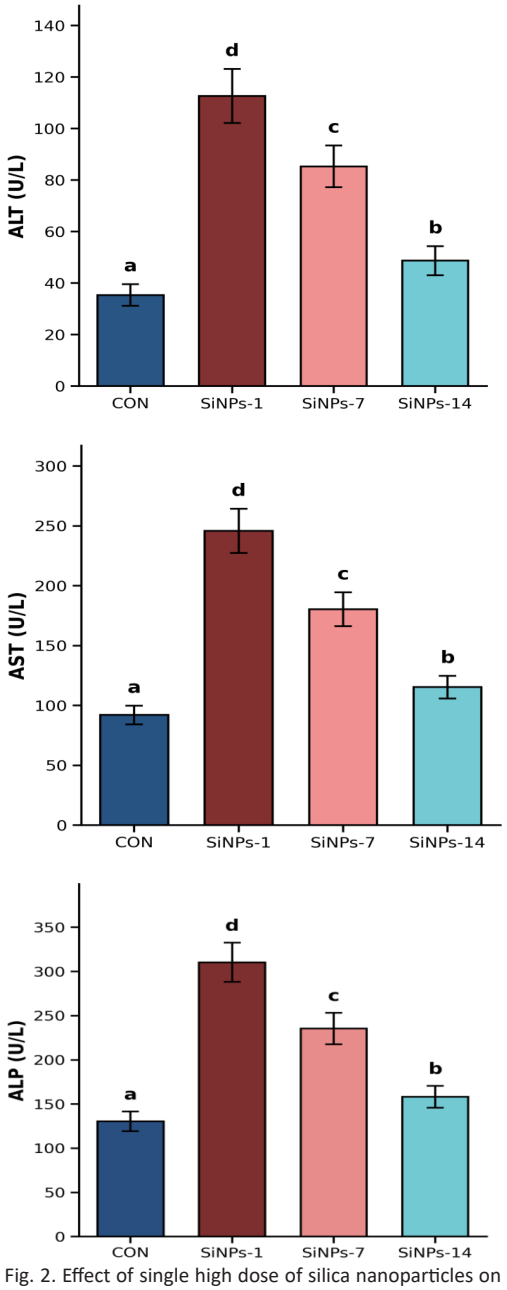


Fig. 2. Effect of single high dose of silica nanoparticles on liver function indicators (ALT, AST, and ALP) post 1, 7 and 14 days of exposure.

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14 (3.2 ± 0.4), a clear decline began, approaching normal levels.

On other hand, antioxidant levels (GSH, CAT, SOD) in SiNPs-1 rats were lowed (18.5 ±2.1; 15.6±1.8; 5.2 ± 0.8), indicating severe depletion compared to the control rats (45.3 ± 3.8; 42.5 ± 3.4; 16.8 ±1.5). However, recovery was observed in the SiNPs-7 group (27.4 ± 2.6; 24.1 ± 2.2; 8.7 ± 1.1), and in the SiNPs-14 group (38.2 ± 3.1; 35.8 ± 2.9; 13.4 ± 1.2), these antioxidants regained their activity and normal levels (Fig. 3).

Otherwise, serological inflammatory cytokines (TNF-α, IL-1β, and IL-6) exhibited a sharp and significant increase on day 1 (78.5 ± 6.4; 62.8 ±5.5; 85.4 ± 7.2) compared to the control group (14.2 ± 1.6; 12.1 ± 1.3; 18.5 ± 2.1).

On day 7 (45.3 ± 4.8; 38.6 ± 3.7; 52.1 ± 5.3), a relative decrease from the peak was observed, although inflammation persisted. However, by day 14(22.6 ± 2.3; 19.5 ± 2.1; 28.4 ± 2.9), serum cytokine levels had returned to near-normal levels as shown in Fig. 4.

Liver toxicity is extremely dangerous because it develops slowly and can accumulate without warning, and clinical symptoms may not appear until a considerable proportion of liver tissue has been damaged [26]. When a single, high, non-lethal dose of SiNPs is administered orally, it is absorbed via the intestine, trans-located via the hepatic portal vein to the liver and engulfed by Kupffer cells [27].

On the first day after exposure, the peak of acute toxicity and inflammation was observed, indicated by a very significant increase in serum liver function parameters compared to the control group. This demonstrates the immediate destruction and direct toxic effect of the nanoparticles on the cell membranes of hepatocytes (hepatocyte

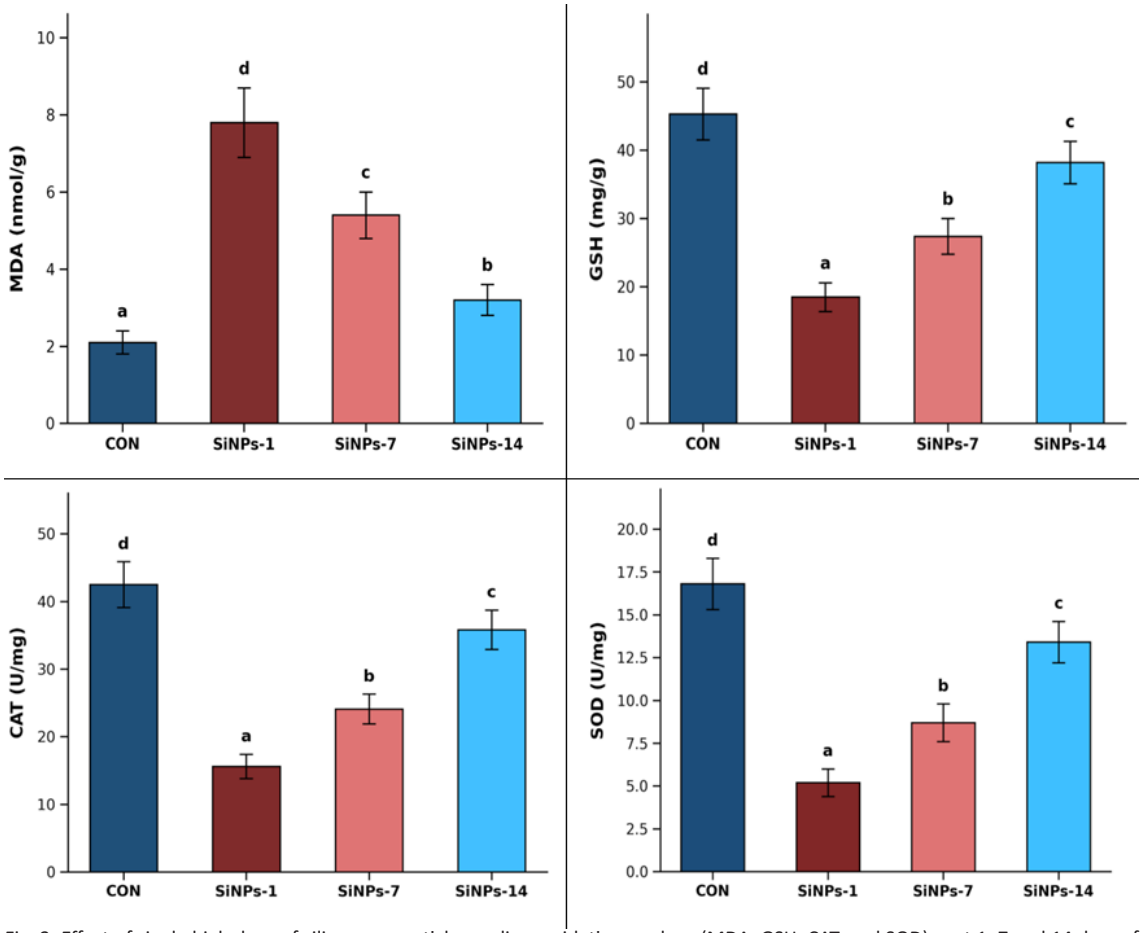


Fig. 3. Effect of single high dose of silica nanoparticles on liver oxidative markers (MDA, GSH, CAT, and SOD) post 1, 7 and 14 days of exposure.

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necrosis/lysis), leading to a massive leakage of these enzymes into the bloodstream [28,29]. These results are in same line with a similar study by Mehdi and Al-Husseini that demonstrated silica nanoparticle-induced liver toxicity in rats, manifested in elevated liver enzymes as well as inflammation and damage to liver cells [30]. Also, Zhou et al found that SiNPs penetrated liver tissue on the first and seventh days after mice were exposed to these nanoparticles, causing serious

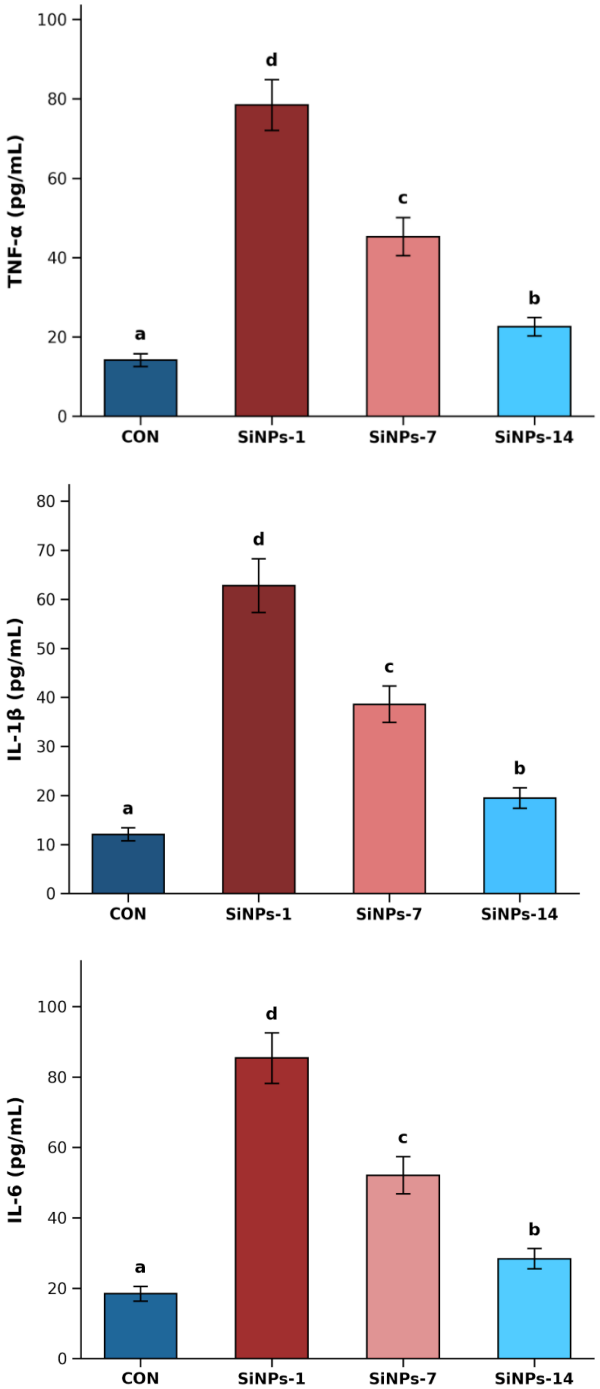


Fig. 4. Effect of single high dose of silica nanoparticles on serum cytokines (TNF-α, IL-1β, and IL-6) post 1, 7 and 14 days of exposure.

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damage [31].

As for the significant increase in malondialdehyde levels, it is a definitive indicator of lipid peroxidation in cell membranes resulting from the aggressive proliferation of free radicals and reactive oxygen species (ROS) due to acute oxidative shock induced by nanoparticle exposure [32,33]. These finding are agreement with previous in vivo studies that confirmed the major role of oxidative stress in silica NPs caused hepatotoxicity [34,35]. In a other study by Ali *et al* on white rats, both male and female, exposure to pure crystalline silica nanoparticles resulted in 95% alteration in hematological and serum liver function parameters, oxidative stress, and antioxidant levels in hepatic tissue, leading to hepatotoxicity [36]. In other experiment by Aouey *et al* they concluded that ROS-activated caspase signaling pathway plays a key role in SiNPs -stimulated apoptosis in hepatocytes in adult male rats [37].

Conversely, a marked decrease in reduced glutathione levels and the activity of antioxidant enzymes (superoxide dismutase and catalase) was observed, due to their rapid and intensive consumption by cells in a futile attempt to neutralize the oxidative storm [38].

In general, GSH represents a master endogenous antioxidant, has a vital role in preserving cells from oxidative stress by directly scavenging free radicals or by acting as a substrate for certain antioxidant enzymes through hydrogen atom acceptance or donation [39]. Hamdiken *et al* demonstrated cytotoxicity and oxidative stress caused by SiNPs in laboratory rats, with raise lipid peroxide concentrations and alterations in antioxidant shielding apparatus, along with a sharp decrease in antioxidant enzyme levels in liver tissues exposed to these particles at toxic doses [40]. A significant spike occurred in serum pro-inflammatory cytokines, with a dramatic raise in TNF-α, IL-1β, and IL-6 levels. This is attributed to the immediate activation of hepatocytes via the well-known inflammatory signaling pathway (NF-κB) upon phagocytosis of silica particles as foreign bodies [41]. Almanaa *et al.* demonstrated that silica nanoparticles cause acute toxicity in rats, both 24 and 96 hours post exposure. This manifested as impaired liver function with a sharp decrease in hematological and protein biomarkers, stress markers, and immuno-antioxidants, reflecting a deteriorating physiological state [42].

On the seventh day post-exposure, the stabilization phase and the shift towards tissue repair began, as evidenced by hepatic function biomarkers levels fell slightly and gradually from the first day, but they remained significantly above normal (control) levels. This suggested that intense tissue breakdown had stopped and that sub-acute inflammation had begun, while inflammatory cell infiltration and localized areas of damage persisted [43].

While MDA levels remain above normal and continue to raise, their rate of increase levels off rather than continuing upward. Similarly, antioxidant levels in liver tissue began to improve somewhat, showing a compensatory increase. This may be explained by the activation of genetic mechanisms within the Nrf2 pathway to produce additional antioxidants in response to residual stress [44]. Despite elevated levels of pro-inflammatory serum cytokines, these levels decreased compared to their peak on the first day after exposure, indicating continued localized hepatic inflammation. This phase represents the body's efforts to suppress the inflammation and initiate tissue repair and regeneration processes in liver cells, thus beginning the recovery process [45].

On the fourteenth day post-exposure, liver function enzyme levels obviously minimized, returning to near-normal levels, indicating remarkable repair and regeneration of damaged liver tissue. Also, oxidation markers improved significantly, approaching normal levels, demonstrating successful adaptation mechanisms and the gradual elimination of silica nanoparticles through gastrointestinal excretion or intracellular retention [46]. Similarly, serum inflammatory marker levels dropped to near-normal levels, indicating the resolution of acute systemic inflammation. At this stage, the liver demonstrated a remarkable capacity for cell regeneration, resulting in partial/near-complete recovery [47].

CONCLUSION

The results confirmed that a single, non-lethal ingestion dose of a high concentration of silica nanoparticles induced hepatotoxicity characterized by impaired in liver function, oxidative stress imbalance, and blood inflammatory cytokines. The peak of toxicity occurred particularly on the first day after exposure, but improvement and recovery began over time.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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