# Effects of Subchronic Microplastic Exposure on Inflammatory Cytokines and Oxidative Stress Biomarkers in Experimental Rats

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**Abstract** -Background: Microplastics (MPs) are novel environmental pollutants that have been shown to be associated with inflammatory and redox alterations in living tissue. The aim of this study was to assess the inflammatory effect of subchronic MP exposure on circulating inflammatory cytokines, as well as the oxidative stress markers and liver and renal indices in adult male rats and the recovery after MP withdrawal. Forty adult male Wistar albino rats (200–250 g) were randomly divided into four groups of 10 rats each: control group, low dose polyethylene microplastic group (5 mg/kg/day), high dose polyethylene microplastic group (50 mg/kg/day), and recovery group (50 mg/kg/day for 45 days followed by 14 days without the microplastic). Microplastics were gavaged orally for 45 days. Levels of serum interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine were measured. One-way ANOVA with Tukey post-hoc tests were performed to analyse the data. Results: MP exposure produced a dose-dependent increase in IL-6 (control 18.86 ± 2.95 vs high-dose 44.85 ± 6.29 pg/mL) and TNF-α (control 22.46 vs high-dose 49.89 pg/mL; both $p < 0.001$). The antioxidant enzymes SOD and CAT levels decreased significantly in the MP-exposed groups ($p < 0.001$) while MDA increased significantly ($p < 0.001$). There was no significant difference in the mean values of IL-10, GSH, ALT, AST and creatinine ($p>0.05$). The inflammatory and oxidative parameters in the recovery group approached, but did not attain, control levels. Conclusions: Subchronic MP exposure results in an exposed dose-dependent systemic inflammatory and oxidative response in rats, which partially recovers from exposure but remains for some time after it ends, suggesting possible health effects associated with environmental accumulation of microplastics.

Objective: To assess the effects of microplastics on oxidative stress, inflammation, cytokines IL-6 and TNF-α, and antioxidant enzymes in rats. The aim of this study was to evaluate the effect of microplastics on oxidative stress, inflammation, cytokines IL-6 and TNF-α, and antioxidant enzymes in rats.

**Keywords:** *Microplastics; Oxidative stress; Inflammatory cytokines; IL-6; TNF-α; Subchronic exposure; Antioxidant enzymes; SOD; CAT; Wistar rats*

## 1. Introduction

The term microplastics (MPs) is used for plastic particles less than 5 mm in size and represents a plastic pollution that is on the rise and present in all parts of the environment, including water, soil, air and the food chain. Their bioaccumulation has introduced significant concern about their possible toxicity to human and animal health. Due to their high surface area to size ratio, MPs can permeate biological tissues, end up in various organs and provoke cellular responses which affect the tissue homeostasis [1,2].

MPs are formed from larger plastic fragments and primary sources like cosmetics and industrial abrasives, and are now ubiquitous both in the marine and terrestrial environments [21,22]. The main routes of human exposure are via ingestion of contaminated food and water and inhalation, with MPs found in human faces, suggesting they are systemically absorbed [23,24]. The estimated amount of internal burden due to MP has been estimated to increase with age, and this has raised concerns about chronic low-level exposure [25].

Experimental and in vitro studies have confirmed that ingested polystyrene and polyethylene particles are taken up by mammalian tissues and can perturb the gut barrier, microbiota, and metabolic homeostasis [26-28]. Agricultural soils represent an additional and growing reservoir of environmental MPs [29]. Collectively, these observations underscore the toxicological relevance of MPs to mammalian systems and motivate controlled animal studies of their biological effects [30,31].

A growing body of experimental evidence indicates that MP exposure activates inflammatory signalling pathways and promotes the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). These mediators play central roles in the initiation and amplification of systemic inflammation and have been linked to a range of chronic

pathological conditions [3,4]. Experimental rat models have been widely used to quantify such cytokine responses to xenobiotic and inflammatory challenges, including measurement of IL-6 and TNF-α by enzyme-linked immunosorbent assay [5,6]. In parallel, the anti-inflammatory cytokine interleukin-10 (IL-10) modulates the immune response and may counterbalance excessive inflammatory activity [7].

In addition to inflammation, MPs are believed to impair cellular redox balance and create excessive amounts of reactive oxygen species (ROS), which can overwhelm the endogenous antioxidant defense systems. Malondialdehyde (MDA) is a known lipid peroxidation end product and a sensitive indicator of oxidative damage, while superoxide dismutase (SOD) and catalase (CAT) are key antioxidant enzymes, and reduced glutathione (GSH) is the primary non-enzymatic antioxidant [8,9]. Protective and antioxidant agents have been shown to lower MDA and restore antioxidant capacity in rodent models of chemically induced injury [10], and MDA, together with hepatic transaminases (ALT, AST), is frequently employed to characterize tissue damage in such models [11]. An imbalance between ROS production and antioxidant capacity contributes to oxidative stress, which underlies the pathogenesis of numerous degenerative and metabolic disorders [12].

Although several studies have addressed the toxicological impact of MPs, data describing the dose-dependence of the inflammatory and oxidative response, and particularly the capacity for physiological recovery following the cessation of exposure, remain limited. Therefore, the present study was designed to evaluate the effects of subchronic MP exposure on inflammatory cytokines (IL-6, TNF-α, IL-10), oxidative stress biomarkers (MDA, SOD, CAT, GSH), and hepatic and renal biochemical indices (ALT, AST, creatinine) in adult male rats, and to assess the reversibility of these changes during a recovery period.

## 2. Materials and Methods

### *2.1. Study Site and Duration*

Experimental studies were done at the Pharmacology Laboratory, Samarra, Iraq. The overall study length consisted of the acclimatisation phase of 7 days, the exposure phase of 45 days and, for the recovery group, the recovery phase of 14 days without exposure.

### 2.2. Experimental Animals

Forty adult male Wistar albino rats aged 8-10 weeks and weighing 200-250g were used in this study. The animals were kept at the Pharmacology Laboratory, Samarra, Iraq, under standard laboratory conditions (temperature 22 ± 2 °C, RH 50 ± 10 %, and 12 L/D cycle) with free access to a standard pellet diet and water. Rats were acclimatised for a week before the experiment.

### *2.3. Ethical Approval*

All experimental procedures were approved by the Institutional Animal Ethics Committee, University of Samarra (Approval No. 127A, dated 20 March 2025), and were conducted in accordance with internationally recognized guidelines for the care and use of laboratory animals.

### *2.4. Experimental Design and Microplastic Administration*

After acclimatization, the animals were randomly allocated into four equal groups (n = 10 per group):

**Group I (Control):** received distilled water (vehicle) orally by gavage.

**Group II (Low-dose MP):** received polyethylene microplastics at 5 mg/kg body weight/day.

**Group III (High-dose MP):** received polyethylene microplastics at 50 mg/kg body weight/day.

**Group IV (Recovery):** received the high dose (50 mg/kg/day) for the 45-day exposure period, followed by a 14-day recovery phase without exposure before sampling.

The microplastics used were polyethylene particles with a particle size of 10–50 µm, administered by oral gavage once daily for a total exposure period of 45 consecutive days. Rats in the low-dose and high-dose MP groups received microplastics orally at doses of 5 and 50 mg/kg body weight/day, respectively, while the recovery group received the high dose (50 mg/kg/day) for the exposure period, followed by cessation of exposure during the 14-day recovery phase.

### *2.5. Sample Collection*

At the end of the experimental period, rats were fasted overnight and anaesthetized using ketamine/xylazine intraperitoneally. Blood samples were collected by cardiac puncture, allowed

to clot at room temperature, and centrifuged at 3000 rpm for 15 min to obtain serum. The separated serum was stored at −20 °C until biochemical and immunological analyses.

### *2.6. Biochemical and Immunological Assays*

Serum IL-6, TNF-α, and IL-10 were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits supplied by SunLong Biotech Co., Ltd. (Hangzhou, Zhejiang, China), following the manufacturer's instructions. The assays were performed using the Rat IL-6 ELISA kit (Cat. No. SL0411Ra), the Rat TNF-α ELISA kit (Cat. No. SL0722Ra), and the Rat IL-10 ELISA kit (Cat. No. SL0415Ra). In brief, samples and standards were added to antibody-precoated microplate wells, incubated with HRP-conjugated antibody, developed with TMB chromogen, and the absorbance was read at 450 nm; analyte concentrations were determined from a standard curve. Serum oxidative stress biomarkers, including malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH), were determined using commercially available rat assay kits (SunLong Biotech Co., Ltd., Hangzhou, Zhejiang, China) according to the manufacturers' instructions. MDA was measured as an index of lipid peroxidation, whereas SOD and CAT activities were assessed as enzymatic antioxidant markers. The antioxidant activity was measured as the GSH level, which was used as an indicator of the non-enzymatic antioxidant activity. Absorbance was measured at each of the wavelengths indicated in the respective kit protocol using a microplate reader, and concentrations/activities of enzymes were determined from the standard curves. Blood serum ALT, AST and creatinine were determined with commercially available diagnostic kits following the manufacturer's instructions and an automated biochemical analyzer was used to analyze them.

### 2.7. Statistical Analysis

Data is presented as mean ± standard deviation (SD). Prior to parametric analysis, normality of data distribution was checked by the Shapiro–Wilk test, while homogeneity of variance was checked by Levene's test. Statistics were performed on differences between the four groups using one-way analysis of variance (ANOVA) and Tukey's post-hoc test for multiple comparisons. A probability value of $p< 0.05$ was deemed to be statistically significant. The group size ($n = 10$) was selected to be similar to group sizes used in similar rodent toxicity studies, and is recognized as a limitation of the study. IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) was used to conduct all analyses.

## 3. Results

### *3.1. Inflammatory Cytokines*

Subchronic MP exposure induced a marked, dose-dependent elevation of pro-inflammatory cytokines. Serum IL-6 increased from 18.86 ± 2.95 pg/mL in the control group to 27.23 ± 3.85 pg/mL in the low-dose group and 44.85 ± 6.29 pg/mL in the high-dose group ($F = 65.34$, $p < 0.001$). A similar pattern was observed for TNF-α, which rose from 22.46 ± 3.91 pg/mL in controls to 49.89 ± 5.34 pg/mL in the high-dose group ($F = 48.59$, $p < 0.001$). Post-hoc analysis confirmed that both cytokines were significantly higher in every MP-exposed group relative to control, and that the high-dose group differed significantly from the low-dose group ($p < 0.001$) (Figures 1 and 2).

In contrast, the anti-inflammatory cytokine IL-10 showed no statistically significant difference among the groups (control 34.65 ± 8.68 pg/mL vs high-dose 32.70 ± 6.69 pg/mL; $F = 0.55$, $p = 0.651$), indicating that MP exposure did not elicit a compensatory anti-inflammatory response under the present experimental conditions.

### *3.2. Oxidative Stress Biomarkers*

Microplastic exposure produced significant oxidative stress. The lipid peroxidation marker MDA increased in a dose-dependent manner from 2.50 ± 0.34 nmol/mL in controls to 3.48 ± 0.54 and 5.59 ± 0.78 nmol/mL in the low- and high-dose groups, respectively ($F = 50.07$, $p < 0.001$).

Concurrently, the activities of the antioxidant enzymes declined significantly. SOD decreased from 74.35 ± 7.25 U/mL in controls to 45.33 ± 9.21 U/mL in the high-dose group ($F = 15.17$, $p < 0.001$), while CAT fell from 54.88 ± 5.53 to 31.20 ± 3.87 U/mL ($F = 40.08$, $p < 0.001$). Reduced glutathione (GSH) showed a downward trend in the exposed groups, but the overall difference did not reach statistical significance ($F = 1.40$, $p = 0.260$) (Figures 3–5).

### *3.3. Hepatic and Renal Biochemical Indices*

No statistically significant differences were detected among the groups for the hepatic enzymes ALT ($F = 0.86$, $p = 0.469$) and AST ($F = 1.10$, $p = 0.361$), or for serum creatinine ($F = 0.42$, $p = 0.742$). These findings suggest that, within the exposure period studied, MP administration did not produce overt hepatocellular or renal functional impairment as reflected by these conventional markers.

### *3.4. Recovery Following Exposure*

In the recovery group, inflammatory and oxidative parameters shifted back toward control values but did not fully normalize. IL-6 (28.05 ± 3.10 pg/mL), TNF-α (31.46 ± 6.36 pg/mL), and MDA (3.74 ± 0.56 nmol/mL) in the recovery group were significantly lower than in the high-dose group ($p < 0.001$) yet remained significantly elevated compared with controls ($p < 0.05$). Likewise, SOD and CAT activities in the recovery group recovered partially relative to the high-dose group. These results indicate that cessation of MP exposure permits partial, but incomplete, restoration of redox and inflammatory homeostasis [19,20].

**Table 1. Serum inflammatory, oxidative stress, and biochemical parameters (mean ± SD, n = 10) across the four experimental groups.**

| Parameter | Control | Low-dose MP | High-dose MP | Recovery |
|---|---|---|---|---|
| **IL-6 (pg/mL)** | 18.86 ± 2.95 | 27.23 ± 3.85 | 44.85 ± 6.29 | 28.05 ± 3.10 |
| **TNF-α (pg/mL)** | 22.46 ± 3.91 | 30.42 ± 5.16 | 49.89 ± 5.34 | 31.46 ± 6.36 |
| **IL-10 (pg/mL)** | 34.65 ± 8.68 | 36.14 ± 8.42 | 32.70 ± 6.69 | 37.19 ± 9.23 |
| **MDA (nmol/mL)** | 2.50 ± 0.34 | 3.48 ± 0.54 | 5.59 ± 0.78 | 3.74 ± 0.56 |
| **SOD (U/mL)** | 74.35 ± 7.25 | 62.47 ± 9.31 | 45.33 ± 9.21 | 60.72 ± 12.25 |
| **CAT (U/mL)** | 54.88 ± 5.53 | 48.89 ± 4.97 | 31.20 ± 3.87 | 44.64 ± 5.53 |
| **GSH (mg/dL)** | 7.46 ± 0.50 | 6.58 ± 1.32 | 6.94 ± 1.01 | 7.17 ± 0.95 |
| **ALT (U/L)** | 45.09 ± 6.85 | 42.58 ± 7.07 | 48.23 ± 10.99 | 46.51 ± 6.84 |
| **AST (U/L)** | 95.71 ± 14.57 | 91.51 ± 17.78 | 103.75 ± 15.29 | 94.73 ± 14.85 |
| **Creatinine (mg/dL)** | 0.66 ± 0.11 | 0.64 ± 0.10 | 0.70 ± 0.11 | 0.67 ± 0.16 |

*MP, microplastic. Values are mean ± standard deviation.*

**Table 2. One-way ANOVA results and significant pairwise comparisons (Tukey post-hoc test).**

| Parameter | F value | p value | Significant pairwise differences (Tukey) |
|---|---|---|---|
| **IL-6 (pg/mL)** | 65.34 | <0.001 | C–L, C–H, C–R, L–H, H–R |
| **TNF-α (pg/mL)** | 48.59 | <0.001 | C–L, C–H, C–R, L–H, H–R |
| **IL-10 (pg/mL)** | 0.55 | 0.651 | None (NS) |
| **MDA (nmol/mL)** | 50.07 | <0.001 | C–L, C–H, C–R, L–H, H–R |

| Parameter | F value | p value | Significant pairwise differences (Tukey) |
|---|---|---|---|
| **SOD (U/mL)** | 15.17 | <0.001 | C–L, C–H, C–R, L–H, H–R |
| **CAT (U/mL)** | 40.08 | <0.001 | C–H, C–R, L–H, H–R |
| **GSH (mg/dL)** | 1.40 | 0.260 | None (NS) |
| **ALT (U/L)** | 0.86 | 0.469 | None (NS) |
| **AST (U/L)** | 1.10 | 0.361 | None (NS) |
| **Creatinine (mg/dL)** | 0.42 | 0.742 | None (NS) |

*C, Control; L, Low-dose MP; H, High-dose MP; R, Recovery. NS, not significant ($p > 0.05$).*

*Pairwise codes denote group comparisons that were statistically significant at $p < 0.05$.*

*Figures*

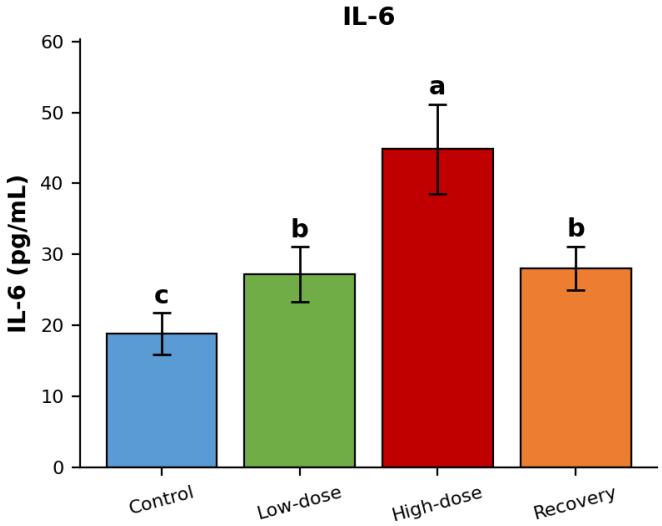


**Figure 1.** Serum IL-6 concentrations across the four experimental groups. Bars represent mean ± SD (n = 10). Groups not sharing a common letter differ significantly (Tukey, $p < 0.05$).

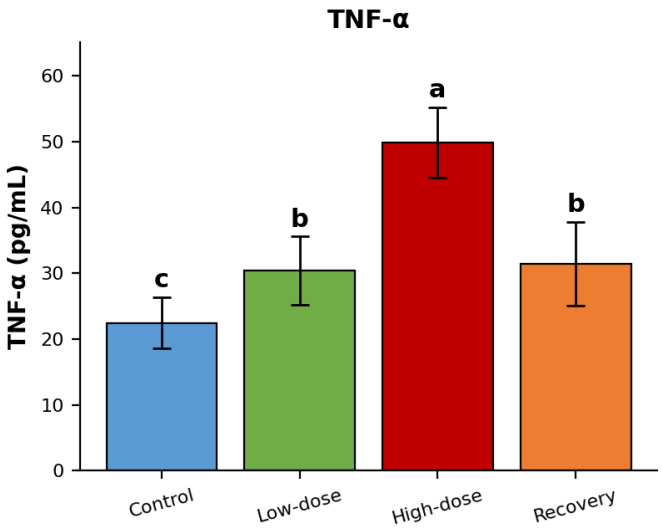


**Figure 2.** Serum TNF-α concentrations across the four experimental groups. Bars represent mean ± SD (n = 10). Groups not sharing a common letter differ significantly (Tukey, $p < 0.05$).

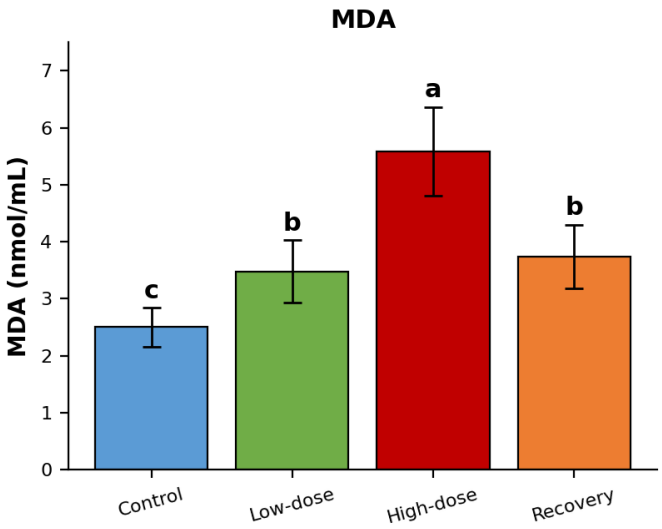


**Figure 3.** Serum MDA concentrations across the four experimental groups. Bars represent mean ± SD (n = 10). Groups not sharing a common letter differ significantly (Tukey, $p < 0.05$).

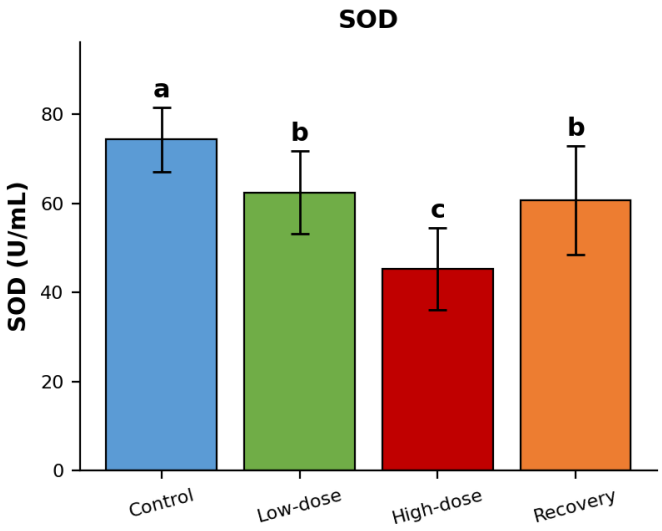


**Figure 4.** Serum SOD activity across the four experimental groups. Bars represent mean ± SD (n = 10). Groups not sharing a common letter differ significantly (Tukey, $p < 0.05$).

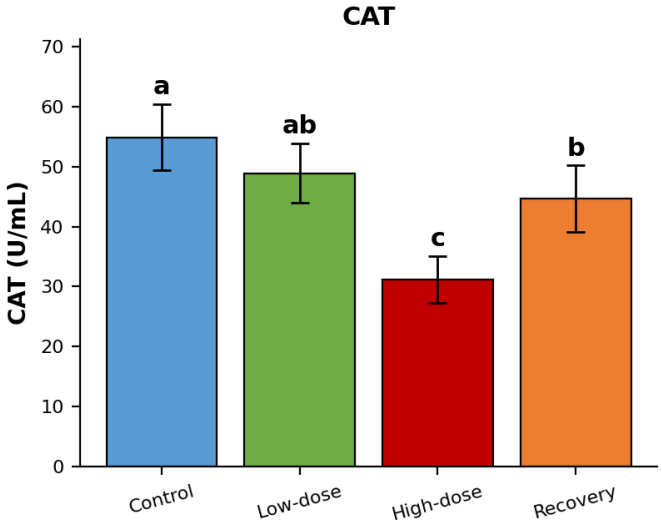


**Figure 5.** Serum CAT activity across the four experimental groups. Bars represent mean ± SD (n = 10). Groups not sharing a common letter differ significantly (Tukey, $p < 0.05$).

## 4. Discussion

The present study demonstrates that subchronic exposure to microplastics induces a dose-dependent systemic inflammatory and oxidative response in adult male rats. The pronounced elevation of IL-6 and TNF-α in the MP-exposed groups is consistent with the concept that MPs act as a persistent immunological stimulus, activating innate immune cells and promoting the

transcription of pro-inflammatory mediators [3,4,13]. Comparable serum elevations of IL-6 and TNF-α, and their attenuation by anti-inflammatory or antioxidant agents, have been reported in Iraqi experimental rat studies using similar cytokine assays [5,6].

Mechanistically, the internalisation of microplastic particles by phagocytic cells is thought to activate pattern-recognition pathways and the nuclear factor-kappa B (NF-κB) signalling cascade, leading to enhanced synthesis of IL-6 and TNF-α [13,14]. The dose-dependent nature of this response in our data, with the high-dose group exhibiting the greatest cytokine elevation, supports a direct relationship between the magnitude of MP burden and the intensity of inflammation. There was no significant change in IL-10, indicating that there was not enough activation of the compensatory anti-inflammatory arm of the immune response that might have been beneficial in maintaining a pro-inflammatory state [7].

This is confirmed by the oxidative stress results. The significant increase in MDA (lipid peroxidation marker) and the simultaneous decrease of SOD and CAT (enzymatic antioxidant defence) suggest increased lipid peroxidation, which is one of the features of ROS-mediated membrane damage, and a parallel decrease in SOD and CAT activity, indicating that the enzyme is being used for eliminating excess ROS [8,9,15]. This pattern (high MDA and low SOD and CAT) is a classical signature of oxidative stress found in models of micro and nanoplastic toxicity [16], and protective treatment with antioxidants has been shown to result in a decrease in MDA with a corresponding increase in SOD and CAT in Iraqi rat models of drug-induced oxidative stress [10,12]. This non-significant difference in GSH could be due to the relatively low concentrations of GSH or because of the dynamic turnover of this tripeptide and/or compensatory synthesis during the exposure period.

The inflammatory and oxidizing environment seen here at the molecular level is compatible with inflammatory and redox-sensitive transcription factors that are known to promote ROS production, and the reverse, ROS that promote inflammatory transcription factors: redox-ROS inflammatory [32,33,34]. In fact, recent reviews particularly point to MPs as a cause of inducing oxidative stress and inflammatory responses in various organ systems, thus confirming our findings in a biological sense [35,36]. The overall environmental impact of MPs and their ability to exert effects via these conserved redox–inflammatory pathways have led to a call for systematic toxicological assessment [37,38]. Given the close relationship between antioxidant defenses and

inflammatory tone and their role in other disease-related processes, chronic imbalance as a result of MP exposure could have long-term pathological consequences beyond those of the parameters measured here [39,40].

Importantly, liver and kidney markers (ALT, AST and creatinine) were not elevated by the study endpoints, suggesting that there was no evident liver or kidney dysfunction in the subjects during the period of exposure studied. This dissociation between early molecular disturbances (inflammation and oxidative stress) and later functional impairment is biologically plausible: Subcellular and biochemical disturbances, such as rises in transaminases like ALT and AST, are often observed before measurable organ damage is seen [11,17]. It also proposes that inflammatory and redox parameters can be better indicators of MP toxicity than the common clinical chemistry parameters in the early stage of toxicity [18].

An important observation is that there was some recovery after exposure cessation. This marked, high dose to low dose, significant decrease in IL-6, TNF alpha and MDA levels in the recovery group is important because they represent a level of biological reversibility when the stimulus is removed. Residual MP retention, however, or oxidative damage will persist after recovery, indicating that a single recovery phase is not enough to restore homeostasis or that some oxidative damage may remain, causing the inflammatory state to last longer [14].

There are a few caveats to note. The 45-day subchronic exposure period and the single 14-day recovery period were investigated, but longer exposure and recovery periods and more time points would provide better characterisation of the kinetics of injury and repair. Secondly, the animals in the recovery group were sampled slightly later, 14 days after the other groups (after the extra recovery period), though this time difference is small compared to the adult period, it should be taken into account when analysing the recovery data. Third, no histopathological studies were carried out in hepatic and renal tissues; hence, the deduction that normal ALT/AST, and creatinine levels indicate that there was no obvious tissue damage needs to be verified in future by tissue-level studies. Fourth, the amount of tissue burden of microplastics was not quantified, and the fact that particles might be retained throughout the recovery phase is an interpretation. Fifth, no formal power analysis was done to justify the size of the group. Lastly, the results from rats have to be carefully extrapolated to human exposure situations. Even with these constraints, the data show to

be consistent and internally coherent in demonstrating inflammation and oxidative stress in response to MP.

## 5. Conclusion

The effects of subchronic microplastic exposure are dose-dependent increases of pro-inflammatory cytokines (IL-6 and TNF-α) and a notable imbalance of the oxidative balance with an elevation of MDA and a reduction in SOD and CAT activity, without any apparent impairment of the hepatic and renal functions during the experimental period. These changes are reversible, but only to a certain extent, after the person stops using drugs. The findings indicate that inflammatory and oxidative markers are potentially good early indicators of microplastic toxicity, and show that the environment contains a deposit of microplastics with potential health implications. Additional research to include histopathological, molecular and extended recovery studies is recommended.

## Declarations

**Ethical approval:** Institutional Animal Ethics Committee, University of Samarra (Approval No. 127A dated 20 March 2025).

**Conflicts of interest:** The authors declare that they have no conflicts of interest.

Author's Statement of Conflict of Interest: There is no conflict of interest.

**Data availability:** Data generated and analysed in the present study are available from the corresponding author on reasonable request.

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