Original Article

Assessment of the Toxicity of Polystyrene Microplastic in the Colon and Liver of Adult NMRI Mice

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ABSTRACT

Background: In recent years, microplastics (MPs), emerging environmental contaminants measuring less than 5 mm in diameter, have garnered significant attention.

Objectives: This study aims to evaluate the impact of MPs on colon samples, which are directly exposed to MPs that enter the digestive tract through food, and on the liver, which is responsible for processing chemicals from the digestive tract in mice.

Methods: During this experiment, 36 adult male mice were randomly divided into four groups of nine animals each. Three groups received polystyrene MPs (PS-MPs) at doses of 0.001, 0.01, and 1 (gavage) for 42 days; a control group was also considered. Tissue samples were collected for histomorphological, histomorphometric, inflammatory factor, and gene expression analyses 24 h after the last treatment.

Results: The results showed that receiving PS-MPs negatively affected on the histomorphology and histomorphometry of the colon and liver. Also, PS-MPs caused a significant increase ($P<0.05$) in inflammatory factors, such as tumor necrosis factor α (TNF-α) and prostaglandin E2 (PGE2), compared to the control group. In addition, a significant increase ($P<0.05$) in β-catenin and hypoxia-inducible factor 1-alpha (HIF-1α) messenger ribonucleic acid (mRNA) expression was observed in the groups treated with PS-MPs compared to the control group.

Conclusion: PS-MPs negatively affect histomorphology and histomorphometry and increase the concentration of TNF-α and PGE2 and the expression of *HIF-1α* and *β-catenin* genes in the colon.

Keywords: Colon, Liver, Microplastic, Inflammation, Polystyrene

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Introduction

Microplastics (MPs) are a global concern due to their widespread distribution and complex effects on living organisms. Recently, terrestrial ecosystems and biological health hazards, including human health hazards, have become the focus of parliamentarians' attention (Ghosh et al., 2023). MPs, a novel category of environmental contaminants composed of plastic particulates with a diameter of less than 5 µm, have emerged due to the extensive utilization and mass production of plastics globally (Barnes et al., 2009). Scientists have begun to devote considerable attention to MP pollutants in the 21st century, particularly in the last ten years (Chia et al., 2020). In 2015, MP pollution was ranked as the second most significant scientific challenge in environmental and ecological science, following global threats, such as ozone depletion, climate change, and ocean acidification, at the second United Nations Conference on the Environment (Jin et al., 2019).

Animals' intestinal mucosa is the first line of defense against intestinal infections (Kinnebrew & Pamer, 2012). Several prior investigations have demonstrated that the gut microbiota (Guvenc et al., 2024) stimulates the growth of intestinal epithelial cells, fortifies the intercellular adhesion of the intestinal mucosal epithelium, impedes pathogenic bacterial damage to the intestinal mucosa, and preserves the integrity of the intestinal barrier (Hemarajata & Versalovic, 2013). Therefore, the intestinal microbiota plays a critical role in regulating the host's metabolism and contributes to the pathogenesis of certain metabolic disorders. A growing body of evidence substantiated this notion (Guinane & Cotter, 2013).

It has been demonstrated that various types of environmental pollutants exhibit toxicological effects on the GI microbiota (Singh et al., 2022). Furthermore, several studies have demonstrated that MPs can interact with microorganisms and have even proposed that they may function as a unique habitat for microbes (Parsaeimehr et al., 2023). Previous studies have demonstrated that polystyrene microplastics (PS-MPs) can induce gut microbiota dysbiosis in rodents and zebrafish (Jin et al., 2018). Tumor necrosis factor α (TNF-α), a cytokine, impacts different cell types. TNF-α typically signals biological processes, including inflammation and cell death, by binding to TNFR1 and TNFR2 receptors (Jang et al., 2021, Zigam et al., 2023). Prostaglandin E2 (PGE2), which regulates numerous physiological and pathological processes, can be synthesized by an extensive variety of cell types within the body, including epithelia, fibroblasts, and infiltrating inflammatory cells in particular (Cheng et al., 2021). Significantly increased PGE2 production is observed in damaged tissue. PGE2 is produced from arachidonic acid, which is released from membrane phospholipids via phospholipase A2 catalyzed by stressors, including inflammation (St-Onge et al., 2007; Tithof et al., 2007). β-catenin is a significant diagnostic and prognostic indicator for colon cancer (Bhattacharya et al., 2019). This protein is involved in internal signaling and may play a significant role in colon cancer (Mesgari et al., 2023) and tumorigenesis (Zhao et al., 2022). Besides β-catenin, hypoxia-inducible factor 1-alpha (HIF-1α) is crucial for mammal tumor growth (Burslem et al., 2017). This protein product greatly improves oxygen availability. Increasing erythropoiesis and angiogenesis increase oxygen access. These events activate genes involved in glucose transport and metabolism (Watts et al., 2020).

This study subjected mature male NMRI mice to 2 µm PS-MPs. Previous studies showed that PS-MPs disrupt the structure of different body tissues. Therefore, the present study aims to investigate the PS-MPs' effect on histomorphology, histomorphometry, inflammation factors, and expression of *β-catenin* and *HIF-1α* genes in colon and liver tissue of mice treated with PS-MPs for 42 days.

Materials and Methods

Chemicals and materials

The two µm microplastic composed of PS- MPs solutions (78452-5ML-F) were acquired from Sigma Chemical (Germany). Before utilization, the PS-MPs were evenly distributed in deionized water and subjected to agitation by supersonic waves for 30 minutes (Jin et al., 2019).

Animals and experimental scheme

Five-week-old NMRI mice were purchased from the Razi Vaccine and Serum Research Institute (Tehran, Iran). All mice were housed in independent cages (standard size) in an animal room with 12 h of light and dark cycles. After a week of accommodation, the animals were weighed and randomly divided into four groups. The first group (nine in each group) was the control group exposed to distilled water (0.1 mL/kg body weight), and the other three groups received different doses of 2 µm PS-MPs (0.001, 0.01, and 1 mg/kg body weight) for the toxicological experiment (Wen et al., 2023). PS-MPs were diluted in distilled water, and the animals were con-

Table 1. Primer sequence

Primers	Forward	Reverse
HIF-1	CACAGGACAGTACAGGATGCTT	CGTGCTGAATAATACCACTTACAACAT
B-catenin	CTAAGCAGGAAGGGATGGAAGG	GATGGCAGGCTCAGTGATGTC
β-actin	GGCTGTATTCCCCTCCATCG	CCAGTTGGTAACAATGCCATGT

HIF-1: Hypoxia-inducible factor 1.

tinuously exposed for six weeks by gavage. During the whole experiment, a basic diet and water were always available. At the end of the experiment, all mice were fasted for 12 h, anesthetized with ketamine/xylazine (0.10 mL xylazine (1 mL ketamine and 8.90 mL distilled water with a dose of 0.1 mL/10 g body weight), and sacrificed. Tissues like the liver and colon were collected quickly and flash-frozen in liquid nitrogen; the samples were stored at −70 ˚C until further use. All experiments were performed following the Guiding Principles for the Use of Animals of the University of Tehran and every endeavor was made to reduce animal suffering (Anbara et al., 2021).

Histopathological analysis

Small sections of the colon and liver were promptly preserved in a 10% (v/v) formaldehyde solution after removal. After dehydration with ethanol, hyalinization with xylene, and subsequent embedding in paraffin wax at 56 ˚C, the fixed tissues were prepared. Five-micrometer-thick sections were cut from three colon and three liver samples from each group. Hematoxylin-eosin solution was subsequently used to stain liver and colon tissues. Imaging (DinoCapture 2.0) was then performed. In a histological study using hematoxylin-eosin staining, stained sections were graded based on the degree of tissue abnormality (Anbara et al., 2022). This abnormality was assessed using five parameters: The features and characteristics of colonic dysplasia and neoplasia (Sarikoç et al., 2013; Ilić et al., 2019; Vajed et al., 2024):

1. Nuclear pleomorphism (0, absence of pleomorphism; 1, mild-to-moderate pleomorphism; and 2, severe pleomorphism).

2. Mucosal stratification (0, monolayer covering and lack of stratification; 1, moderate stratification; and 2, severe stratification).

3. Nuclear polarity (0, proper nuclear polarity; 1, mild lack of nuclear polarity; and 2, severe lack of nuclear polarity).

4. Goblet cell content (0, normal goblet content; 1, moderate absence of goblet cells; and 2, severe absence of goblet cells).

5. Crypt abnormality (0, normal crypts; 1, moderate disorganization of the crypt; and 2, severe disorganization).

Normal colon crypts score 0, while colon cancer has a maximum score of 10.

Measurement of inflammatory factors

The pro-inflammatory factor TNF-α and anti-inflammatory factor PGE were quantified using the manufacturer's method and an ELISA kit (eBioscience).

DNA extraction, quantitative polymerase chain reaction (qPCR) amplification

The liquid nitrogen was pulverized in a sterile porcelain mortar. Total ribonucleic acid (RNA) was extracted from 50 mg of powdered colon tissue. In summary, RNA extraction was involved in these stages. Tissue samples (50 mg) were sampled to one milliliter of TRIzol (Invitrogen, USA). Add 250 microliters of chloroform and centrifuge for 15 minutes at 4 ˚C and 12000 rpm, then transfer the supernatant containing Total RNA to a microtube, add isopropanol, and precipitate RNA at 4 ˚C and 1400 rpm. After washing with 70% alcohol and drying, 50 µL of DEPC-treated water was added to the microtubes and stored at -80 ˚C (Table 1).

Statistical analysis

Data were analyzed using SPSS software, version 22. Values of the measured parameters are shown as Mean±SD. Differences between groups were evaluated using one-way analysis of variance followed by Tukey's post hoc test.

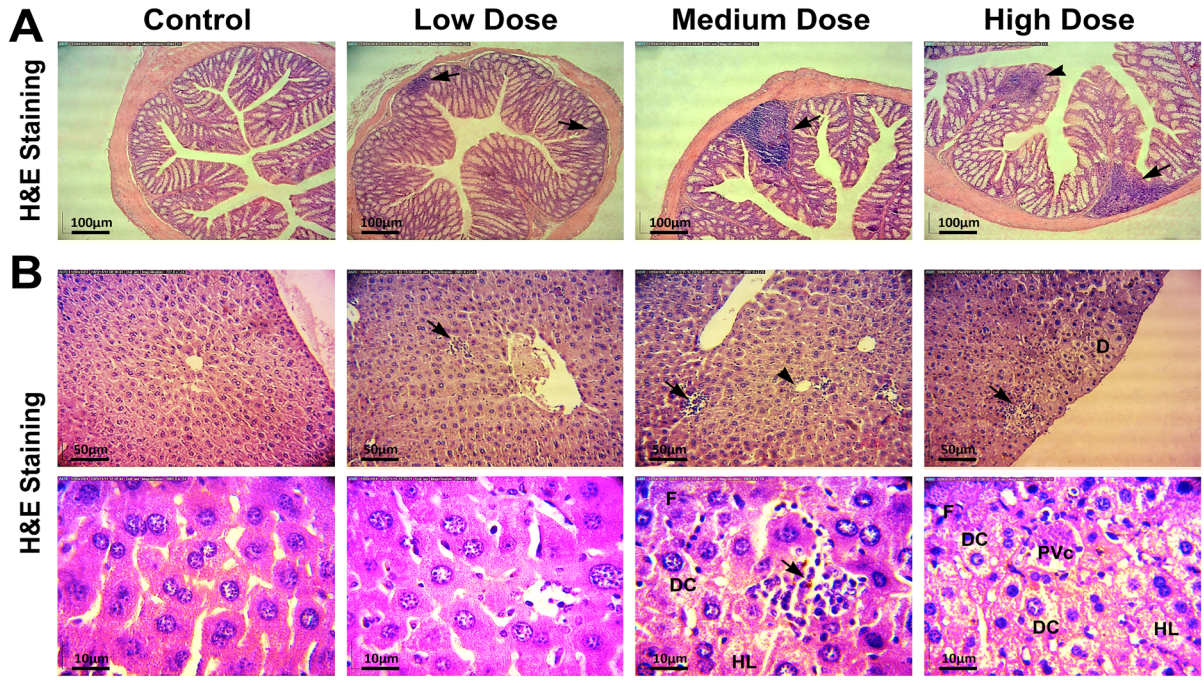

Figure 1. Histological study of the intestine with H&E stain

A) Cross section of the colon, scattered lymphoid accumulations (arrow), scattered ectopic lymphoid accumulation (head arrow), and decrease of muscle layer thickness in groups with PS-MPs, B) Hepatocytes with clear nucleus, cytoplasmic area, and central venule of healthy liver in the control group, PVc, lysed, fragmented cell nuclei (F), disruption of the cytoplasmic area of cells (DC), infiltration of lymphoid cells in the portal space (head arrow), and the presence of inflammatory mononuclear cells (arrow), and deformed cells (D) in groups with PS-MPs.

Results

Microplastic polystyrene causes histomorphometric changes in colon and liver tissue

The mucosa and muscular layers of the colon tissue structure of mice in the control group were devoid of abnormalities. Furthermore, the colons of mice in the medium- and high-dose PS-MP treatment groups contained substantial lymphocyte masses. A multitude of inflammatory cells was identified within the colon of PS-MP-treated mice. Masses containing immune cells were measured in all experimental groups. In contrast, in mice treated with PS-MPs, we observed portal vein hyperemia (PVc) and hepatocyte lysis by histological analysis (Figure 1).

Effect of PS-MPs on the deforma cells

An assessment was conducted to determine the mean quantity of deformed cells (characterized by a pyknose nucleus and furrowed cytoplasm) in both the control and PS-MPs-treated groups. A significant dose-dependent increase was observed in the groups exposed to PS-MPs (Table 2).

Effect of PS-MPs on the Kupffer cells

The number of Kupffer cells in the high-dose group was substantially greater than that in the control group, as determined by comparing the PS-MPs treated dermatological groups to the control group ($P<0.05$) (Figure 2).

The messenger ribonucleic acid (mRNA) expression level of *HIF-1a* and *β-catenin*

HIF-1 and *β-catenin* are significant genes implicated in colon cancer. Consequently, their expression in colon tissue serves as an indicator of their cancerous nature. The results revealed elevated expression of *HIF-1* and *β-catenin* genes in groups exposed to polystyrene compared to the control group ($P<0.05$). *HIF-1* and *β-catenin* are known cancer genes whose expression is increased by microplastic treatment (Figure 3).

Effect of PS-MPs on TNF-α and PGE2 factors

Variations in the concentrations of TNF-α and PGE2 indicated that the medium- and high-dose groups exhibited a significant increase ($P<0.05$) in this factor relative to the control group (Figure 4).

Table 2. Changes in histopathology index in colon tissue with hematoxylin-eosin staining after PS-MPs consumption (n=9)

Dysplastic Cells	Mean±SD			
	Control	Low Dose	Medium Dose	High Dose
Nuclear pleomorphism	0.4±0.27	0.97±0.28	1.66±0.31*	1.78±0.39*
Mucous stratification	1.3±0.35	1.62±0.31	1.71±0.31*	1.85±0.08*
Lack of nuclear polarity	0.38±0.08	0.68±0.21*	1.39±0.33**	1.52±0.27**
Reduction of goblet cells	1.44±0.19	1.27±0.37	0.82±0.27	0.64±0.13***
Crypt anomaly	0.26±0.21	0.86±0.38	1.63±0.16**	1.73±0.19**

*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001 Significant differences compared to the control group.

Note: Degree of tissue abnormalities: Semi-qualitative.

Discussion

A satisfactory body of research has been conducted concerning the impacts of MP on the physiological processes of aquatic organisms within the worldwide ecological system (Jalaudin Basha et al., 2023). However, little is known regarding the effects of MPs on sophisticated terrestrial animals, particularly mammals (Liu et al., 2023). MPs have become pervasive in terrestrial ecosystems due to human activities. For instance, plastic particulates generated during the manufacturing process of widely utilized products, such as toothpaste, facial cleansers, detergents, and scrubs, constitute a significant environmental contributor to MP (Kannan & Vimalkumar, 2021). Sajjad et al. identified the substantial quantity of plastic film utilized in agriculture as a significant source of MPs in the land environment (Sajjad et al., 2022). Furthermore, the sludge application has resulted in MPs in certain agricultural soils across Europe, with concentrations ranging from 1000 to 4000 particles per kilogram of soil. MPs in these terrestrial ecosystems harm terrestrial fauna and potentially impact human health through contact (Ren et al., 2020; Hussain et al., 2024).

MPs have the potential to ascend the food chain and reach higher levels in living organisms, or they may penetrate the human food chain via salt (Saeedi, 2023). Furthermore, MPs can accumulate in the intestines of animals and enter the bloodstream via the intestinal barrier (Huang et al., 2021). To substantiate this notion, a prior investigation documented that MPs can traverse the intestinal barrier and accumulate within the hepatic tissue

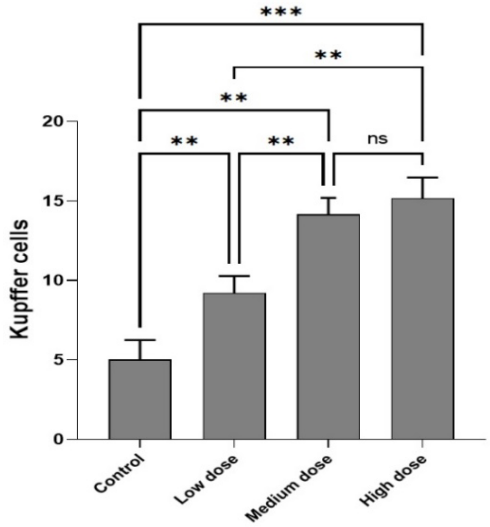

Figure 2. Average number of Kupffer cells

Note: Asterisks indicate significant differences between groups: *P<0.05, **P<0.01, ***P<0.001, and ****P<0.0001. Values are presented as Mean±SD (n=9).

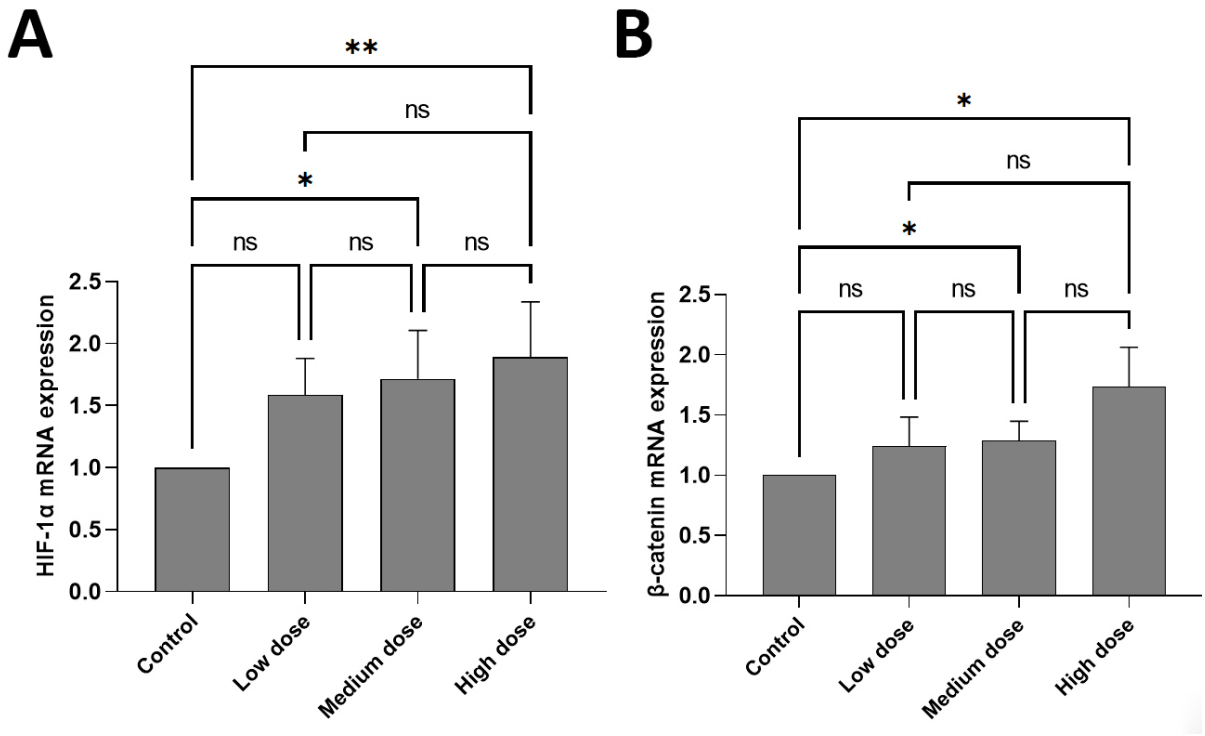

Figure 3. The relative mRNA levels of (A) HIF-1), (B) β-catenin in mouse colon detected with q-PCR by normalizing to β-actin

Note: Asterisks indicate significant differences between groups: *P<0.05, **P<0.01, ***P<0.001, and ****P<0.0001. Values presented are Mean±SD (n=9).

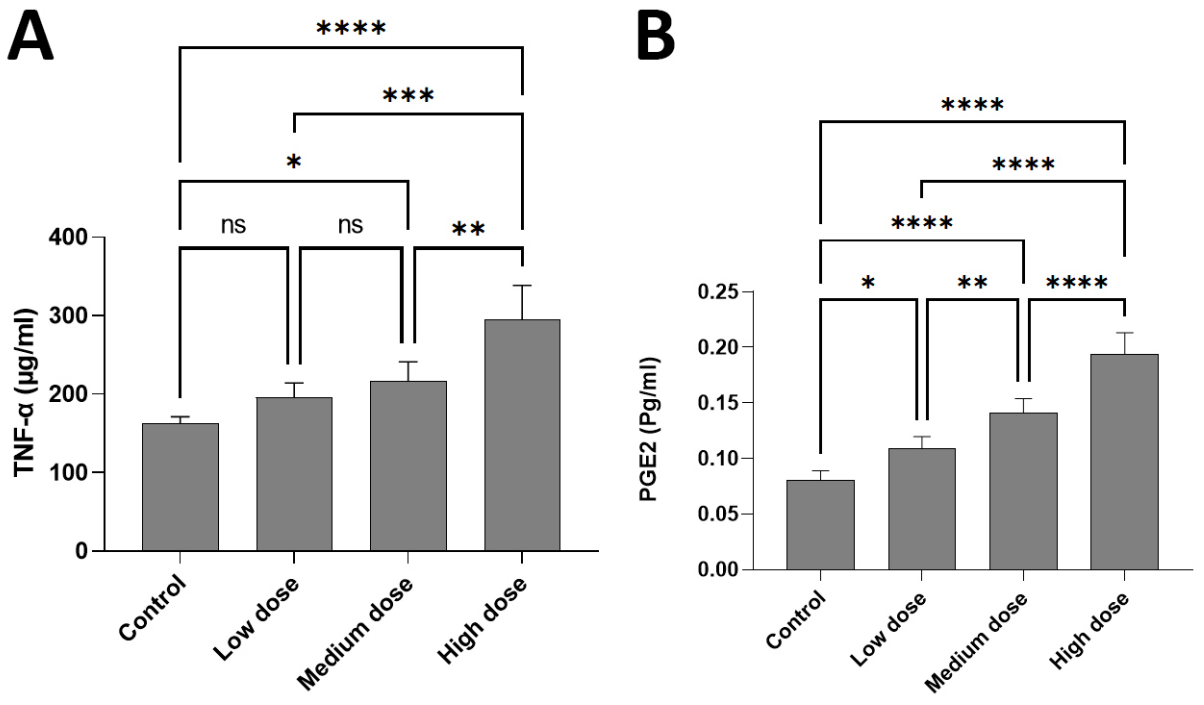

Figure 4. The relative levels of (A) TNF-α, (B) PGE2 in mouse colon

Note: Asterisks indicate significant differences between groups; *P<0.05, **P<0.01, ***P<0.001 and ****P<0.0001. Values presented are Mean±SD (n=9).

of commercial European anchovies. In patients afflicted with intestinal diseases, alterations in tissue permeability due to inflammatory conditions substantially enhance the transport efficacy of MPs (Vagner et al., 2022). MPs affect the intestinal barrier and microbiota and disrupt the intestinal barrier (Takiishi et al., 2017).

Treatment with MPs induces a wide range of physiological responses, including increased inflammatory cytokines in the gut and reduced mucus secretion and composition of GI microbiota (Choi et al., 2021a). In particular, chronic constipation has been reported in rats following oral administration of PS-MPs. This condition is characterized by impaired mucin secretion, chloride ion and water transport across the colon, and impaired GI motility (Choi et al., 2021b). This study investigated inflammatory responses induced by MPs in the colon. The results showed that the expression of TNF-α inflammatory cytokines increased significantly in the colon and liver.

β-catenin and *HIF-1* are two crucial genes implicated in the progression and metastasis of colon cancer; therefore, they are regarded as viable therapeutic targets for the diagnosis of colon cancer (Chen et al., 2023). Although MPs have been observed to influence the expression of these genes, no investigation into their impact on gene expression has been conducted to date. Colonic cancer examination is not feasible; therefore, current research is inaccessible. This pertains to the expression levels of these genes and the impact of MPs on their expression levels.

An additional discovery made in our research was that polystyrene MP substantially elevated Cirrhosis in the liver. Liver tissue cirrhosis can directly or indirectly impact the generation of bile acids. The liver plays a significant role in the synthesis of bile acids (Sauerbruch et al., 2021; Poudineh et al., 2022). Any impairment or abnormality in liver function, such as Cirrhosis of the hepatic tissue, can result in a reduction or elevation in bile acid production (Johnson & Sherding, 2006). The hepatic diseases can lead to obstruction of the bile ducts due to liver inflammation, resulting in this consequence. Bile acid circulation from the intestine to the liver can be utilized to facilitate the digestion and absorption of lipids and recycle scarce bile acids (Chiang, 2013). The digestion and assimilation of lipids would be disrupted if this circulation ceased, rendering bile acids unusable (Ticho et al., 2020). All these results conclusively demonstrated that polystyrene MP poses a risk to host health due to their ability to induce metabolic disorders. In contrast to previous research, the in-vivo consequences of MP ingestion in aquatic organisms are considerably more pronounced. Illustratively, MPs can perturb the organism's dietary behavior, growth rates, and reproduction (Amran et al., 2022). Additionally, they can stimulate inflammatory reactions, including vacuolation, infiltration, and necrosis (Chen et al., 2023).

Conclusion

In our investigation, the histological composition of the mouse's colon and liver was modified after a 6-week exposure to PS-MPs. Our study showed that mice exposed to PS-MPs displayed increased nuclear pleomorphism, mucosal stratification, loss of nuclear polarity, decreased goblet cells, and aberrant crypts. These results indicated that PS-MPs may play a role in the progression of colon cancer in mice. Liver tissue showed signs of Cirrhosis, hyperemia, lysed and fragmented cell nuclei, wrinkling, disruption of the cytoplasmic area of cells, infiltration of lymphoid cells in the portal space, and the presence of inflammatory mononuclear cells and malformed cells. It directly impacts liver function and can lead to issues in bile acid synthesis.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of University of Tehran, Tehran, Iran (Code: IR.UT.VETMED.REC.1400.002).

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Authors' contributions

Conceptualization and supervision: Somaye Zangane, Hojjat Anbar; Review and editing:Nicola Bernabo; Project management: Hassan Morovvati.

Conflict of interest

The authors declared no conflict of interest.

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مقاله پژوهشی

ارزیابی سمیت میکروپلاستیک پلی استایرن در کولون و کبد موش های بالغ NMRI

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چکیده

زمینه مطالعه: میکروپلاستیک‌ها (MPs)، آلاینده‌های محیطی نوظهور با قطری تقریباً کمتر از ۵ میلی متر هستند، که در سال‌های اخیر توجه قابل توجهی را به خود جلب کرده اند.

هدف: این مطالعه به منظور بررسی تأثیر میکروپلاستیک‌ها بر روی نمونه‌های بافتی کولون که مستقیماً در معرض میکروپلاستیک‌هایی هستند که از طریق غذا وارد دستگاه گوارش می‌شوند و کبد که مسئول پردازش مواد شیمیایی از دستگاه گوارش در موش است، انجام شد.

روش کار: در این آزمایش ۳۶ موش نر بالغ به طور تصادفی به چهار گروه ۹ تایی تقسیم شدند. سه گروه در دوزهای ۰/۰۰۱، ۰/۰۱ و ۱ میلی گرم بر کیلوگرم وزن بدن PS-MPs را (از طریق گاواژ) به مدت ۴۲ روز دریافت کردند. یک گروه کنترل نیز در نظر گرفته شد. ۲۴ ساعت پس از آخرین درمان، نمونه‌های بافتی برای بررسی هیستومورفولوژیکی، هیستومورفومتری، عوامل التهابی و بیان ژن جمع‌آوری شد.

نتایج: یافته‌ها نشان داد که دریافت PS-MPs اثرات منفی بر هیستومورفولوژی و هیستومورفومتری کولون و کبد دارد. همچنین دریافت PS-MPs باعث افزایش معنی دار ($P>0/05$) در عوامل التهابی مانند TNF-α و PGE2 نسبت به گروه کنترل شد. علاوه بر این، افزایش معنی‌داری ($P>0/05$) در بیان mRNA ژن β-کاتنین و HIF-1α در گروه‌های تحت درمان با PS-MPs نسبت به گروه کنترل مشاهده شد.

نتیجه‌گیری نهایی: به نظر می‌رسد PS-MPs می‌تواند اثرات منفی بر هیستومورفولوژی و هیستومورفومتری داشته باشد و غلظت فاکتورهای TNF-α و PGE2 و بیان ژن‌های HIF-1α و β-کاتنین را در روده بزرگ افزایش دهد.

کلیدواژه‌ها: کولون، کبد، میکروپلاستیک، التهاب، پلی استایرن

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