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Gut microbiota as an emerging target for the health implications of microplastics

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ABSTRACT: Microplastics (MPs) formed from fragmentation of plastic have been detected globally. Once enter the food chain, they can pose a significant threat to the public health. While MPs contamination in the food chain is well recognized the health implications of MPs consumption on human health remain poorly understood. In this review, we aimed to review the effects of MPs exposure on gut microbiota (GM), and to understand how the interactions between MPs and GM contributing to the detrimental effects of MPs on the intestinal barrier (disruption of mucus and tight-junction proteins), systemic immunity (inflammation and oxidative stress), and organs (neurotoxicity and reproductive toxicity). Emerging evidence supports a key role of GM in mediating the health implications of MPs. Meanwhile, an indirect effect of MPs as carriers of pollutants and the potential of bioactive substances in mitigating the toxicity of MPs are also discussed. Although touted as environmentally friendly, biodegradable microplastics (BMPs) may surprisingly pose a greater threat to public health, which deems further research.

Key words: microplastics, gut microbiota, intestinal barrier, toxicity, inflammation, oxidative stress

1. Introduction

Plastic pollution represents a critical environmental and public health challenge, with global plastic waste generation continuing to rise[1, 2]. Most plastic waste is not recycled but accumulates in natural environments, where it undergoes fragmentation into microplastics (MPs, < 5 mm) and nanoplastics (NPs, < 1 μm) through mechanical, UV, oxidative, and biological processes[3]. These particles have been detected worldwide, from the deepest oceans to the highest mountains, and can enter humans via the food chain, leading to bioaccumulation and potential health risks[4].

Studies across aquatic and terrestrial models have demonstrated that MPs induce oxidative stress, inflammatory responses, metabolic disorders, neurotoxicity, reproductive and developmental toxicity[5]. As the most commonly used investigative model, zebrafish exhibit inflammation and oxidative stress in the

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intestines after exposure to polyvinyl chloride (PVC) or polystyrene (PS) MPs, leading to metabolic disorders[6,7]. Additionally, neurotoxicity, liver damage, and immunotoxicity in other aquatic organisms such as discus fish (*Symphysodon aequifasciatus*), crucian carp (*Carassius carassius*), and bivalve species (*Tegillarca granosa*) have been reported following exposure to MPs[8-10]. Similar toxic effects of MPs have also been confirmed in mammalian models such as in mice/rats. PS MPs have been shown to induce oxidative stress through the Wnt/β-Catenin or Toll-like receptor 4/NADPH oxidase 2 (TLR4/NOX2) signaling pathways[11,12], leading to fibrosis in mouse ovaries or uteri. The apoptosis of mouse neurons caused by PS MPs occurs through the PI3K/AKT pathway[13].

The gut microbiota (GM), a complex microbial community essential for host nutrients, immunity, and development [14], has recently emerged as a key mediator of MPs toxicity. It has reported that MPs disrupt GM homeostasis, subsequently impairing intestinal barrier function and triggering systemic inflammation via axes such as the microbiota-gut-liver axis[15], gut-brain axis[16], and gut-liver-adipose tissue axis[17]. Therefore, GM is an emerging target for the detrimental effects of MPs consumption on various tissues and organs. Based on the digestive characteristics of MPs, whether non-biodegradable MPs (PS, polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), and PVC)[18,19] or biodegradable MPs (poly(ε-caprolactone) (PCL) and poly(lactic acid) (PLA))[20,21], the changes during in vitro simulated digestion are limited (monitored by changes in the size, shape, and molecular weight of MPs). Therefore, most MPs can accumulate and be absorbed in the gut after ingestion, disrupting the homeostasis of the GM, including a decrease in α-diversity[19,21,22], an increase in the abundance of potentially harmful pathogens (such as *Desulfovibrionaceae*, *Enterobacteriaceae*, and *Escherichia/Shigella*)[19,21-24], and a reduction in the abundance of beneficial bacteria (*Bifidobacterium*, *Lactobacillus*, and *Akkermansiaceae*)[21-23,25]. These disruptions compromise intestinal barrier integrity and initiate local-to-systemic immune activation[26].

While existing reviews have addressed MPs toxicity, sources, and distribution[27,28], few have systematically analyzed how MPs target the GM to drive barrier dysfunction and multi-organ toxicity. This review critically synthesizes evidence on MPs-induced GM dysbiosis, its consequences on intestinal barrier integrity, systemic immunity, and organ-specific pathologies, and discusses the role of GM in MPs biodegradation. We also evaluate the potential heightened risks of BMPs and highlight bioactive strategies for mitigating MPs toxicity. Understanding GM-mediated mechanisms may inform therapeutic interventions against MP-related health risks.

2. Search strategy

PubMed database was selected to carry out the bibliographic search. The advanced search builder was used by entering the following keywords included in the title/abstract: (“microplastic” OR “nanoplastic”) AND (“gut microbiota” OR “gut microorganisms” OR “intestinal microbiota” OR “intestinal microorganisms”) AND (“mice” OR “rat” OR “human”). All the articles published until the 1st of May 2024 were selected. A total of 146 publications were obtained and were evaluated for acceptability.

Firstly, the following inclusion and exclusion criteria were applied to select the articles after reading the abstracts:

Inclusion criteria:

–This article contains information on MPs/NPs-induced disturbances of GM in mammals, which effects may be relevant to MPs/NPs-induced diseases.

Exclusion criteria:

–The full text was not available in English

–The article was a review, a comment, or a meta-analysis

–The field of the article was out of the scope of this review

–The object of this article was not a model mammal animal

–This article is an experiment in vitro

In case of doubt, articles were in-depth analyzed, which implied reading the full article. After this process, 73 articles were finally selected. Research on PS was the most prevalent, with 48 studies, followed by PE (10 studies), PVC (3 studies), and 1 each on PES and PET. There were also 3 studies on mixed microplastics and 7 on human experiments. For convenience, MPs and NPs were collectively referred to as MPs thereafter.

3. The effect of MPs on gut microbiota

In the seven human cohort studies, MPs have been detected in fecal samples from individuals of all ages worldwide, ranging from infants to the elderly[29-35]. The most commonly detected MPs include PET, PE, PVC, PU, and PS, typically ranging from 20 to 500 μm in diameter[29,34]. Larger MPs tend to accumulate in the gut due to limited barrier penetration, making GM a primary target. The disruption of GM by MPs exhibited a dose-response relationship. For example, the Chao1 and Observed_species indices in the high-exposure group were significantly lower than those in the low-exposure group[30]. Additionally, the relative abundance of *Lactobacillales*, *Bifidobacterium*, *Rikenellaceae*, *Alistipes* and *Streptococcus* was lower in the high-exposure group compared to the low-exposure group[30,34].

Intervention with MPs for at least 4 weeks in animal experiments *in vivo* resulted in significant changes in the structure of GM (**Figure 1**). Although the results varied widely across different experiments due to the diversity of GM, some general trends were observed and analyzed. When GM was disturbed by MPs, the α-diversity changed, representing the stability of the gut microecological system. In general, the occurrence of related diseases will induce a decrease in the α-diversity of GM. However, within the scope of this review, a total of 13 studies confirmed an increase in the α-diversity of GM induced by MPs, while 21 studies reported a decrease (**Table 1**). Further analysis revealed that α-diversity of GM was more likely to increase when MPs were administered mixed in food or drinking water for voluntary intake, especially under conditions of low dosage and shorter intervention duration. Conversely, a decrease in α-diversity of GM was often observed under high-dose or prolonged exposure regimens. This pattern suggests that minimizing external stress and involuntary disturbance to the animals may help maintain microbial

community robustness in the gut. In addition, the increases in α-diversity could be due to low doses of MPs providing new ecological niches for the growth of microbial communities on the surface of MPs[36]. However, the decrease in α-diversity in most studies indicates that the structure of GM has been disrupted and dysbiosis has occurred.

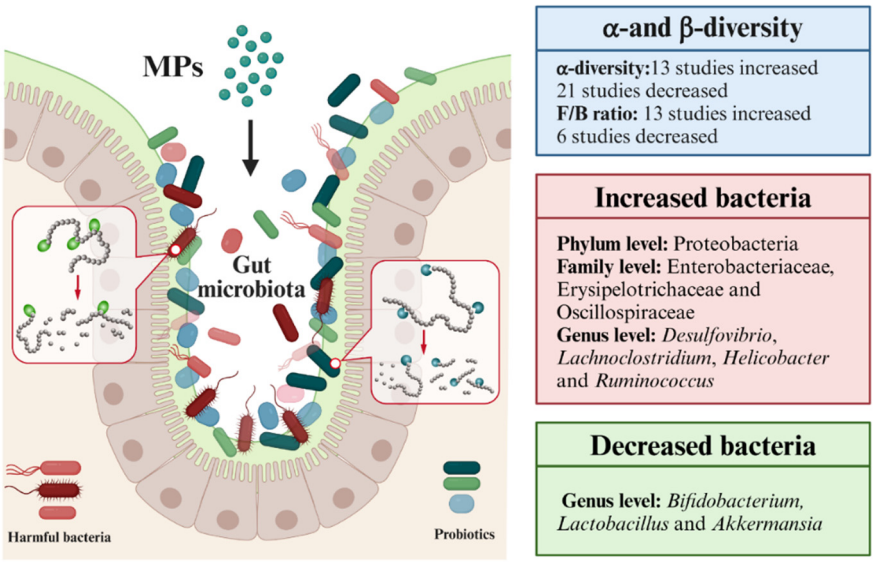

Figure 1. Perturbation on the diversity and community structure of GM by MPs. When MPs enter the intestine and interact with the GM, the α- and β- diversity of the GM both changed, mainly manifested in the promotion of some potentially harmful bacteria (Proteobacteria phylum, Enterobacteriaceae, Erysipelotrichaceae and Oscillospiraceae family, *Desulfovibrio*, *Lachnolostridium*, *Helicobacte*r and *Ruminococcus* genus) and the suppression of probiotics (*Bifidobacterium*, *Lactobacillus* and *Akkermansia* genus). At the same time, MPs can be degraded into oligomers or monomers under the action of enzymes expressed by the GM, further affecting the homeostasis of the GM.

The F/B ratio is a key indicator in β-diversity and is associated with various diseases. An increase in the F/B ratio is generally considered indicative of poor health, especially in metabolic syndrome[37]. In this review, we found that 13 studies indicated an increase in the F/B ratio, while 6 studies reported a decrease after MPs intervention (**Table 1**). The changes of the F/B ratio appear to be closely linked to alterations in beneficial bacteria. Specifically, a decrease in the relative abundance of *Akkermansia*, *Faecalibaculum*, and *Lactobacillus* is often associated with an increase in the F/B ratio. Additionally, these opposite results also may be related to different types and dose of MPs, as well as intervention conditions and animal model. For example, low-density PE (LDPE)-MPs decreased the α-diversity of GM, whereas oxidized LDPE (Ox-LDPE)-MPs showed a slight increase. This may due to the increase in oxygen-containing functional groups and zeta potential affected the interaction between MPs and cell membranes, reducing the accumulation of Ox-LDPE-MPs in the intestine[38]. PS MPs/NPs modified with carboxyl or amino groups led to a further reduction in α-diversity compared with unmodified MPs/NPs, which were relatively less toxic to humans[39]. A detailed study examining the relationship between the size and concentration of MPs/NPs with GM revealed that smaller-sized MPs/NPs have a more negative impact on diversity than larger sizes[40]. Additionally, at the same particle size, higher concentrations of MPs/NPs have a greater impact on GM than lower concentrations[40]. Therefore, the functional group modifications, particle size, and concentration of exposed MPs affect the extent of toxicity.

Table 1 Overview of in vivo studies of the effects of MPs exposure on the GM.

Category of MPs	Mice model	Intervention methods	Change of α-diversity	Change of F/B	Change of structure of GM	References
PE MPs (10-150 μm)	Male C57BL/6 mice	Foods 2, 20, and 200 μg/g 5 weeks	All groups: abundance and diversity↑		All groups: Staphylococcus↑ Parabacteroides↓ 60 and 600 μm: Bacterodides, Muribaculum, unidentified_Clostridiales and Akkermansia↓ 60 μm: Lactobacillus and Dubosiella↑ 600 μm: Blautia and Desulfovibrio↑	[62]
PE MPs (5 μm)	Male C57BL/6 mice	Drink water 1 mg/L, 10 mg/L 21 days	The overall number and abundance↑		Desulfovibrio, Clostridia, Enterorhabdus, Bacteroides, and Gemella↑, Dubosoella↓	[100]
PE MPs (10-20 μm)	Male C57BL/6 mice Prenatal, post-weaning, puberty, and adult models	Drink water, 100 ppm/100 μL Prenatal model: 2 weeks Post-weaning model: 2weeks Puberty model: 2 weeks Adult models: 12 weeks	Diversity↑		Lactobacillus reuteri↓ Alistipes putredinis and Barnesiella intestinih↑	[102]
LDPE MPs and Ox-LDPE (2.6 -13 μm)	Male C57BL/6 mice	Gavage 1 mg/per/day 28 days	LDPE-MPs: α-diversity↓, Ox-LDPE-MPs: α-diversity↑	F/B↑	All groups: Firmicutes↑ Bacteroides, Verrucomicrobiae and Lactobacillus↓	[38]
PE MPs (30 and 200 μm)	Male Balb/c mice MPs+As	Foods 12, 20 and 200 μg/g 35days	α-diversity↑		Coriobacteriia, Gammaproteobacteria and Verrucomicrobiae↑	[109]
PE MPs (0.5, 5 and 50 μm)	Male C57BL/6 N mice MPs+high-cholesterol diet	Drink water 10 mg/L 8 weeks	α-diversity↓		Firmicutes↓ 0.5 and 5um MPs: Chloroflexi and Gemmatimonadetes ↑ 50um MPs: Myxococcota, Fusobacteriota, and Chlamydiae↑	[115]
PVC-MPs (40-300 μm), PLA-MPs (16-350 μm)	Male C57BL/6 mice	Gavage 0.1 and 0.5 mg/per/day 6 weeks	α-diversity↓		PVCH: Actinobacteria, Erysipelotrichi, Erysipelotrichales, Erysipelotrichaceae and Allobaculum↑ PLAH: Actinobacteria, Erysipelotrichi, Erysipelotrichales, Erysipelotrichaceae, and Allobaculum↓	[116]
PES MPs/NPs (5 μm and 50 μm)	Male ICR mice	Gavage 5 mg/kg/day	α-diversity↑		Rikenellaceae↑ FL: Lachnospiraceae_NK4A136_group, Dubosiella and Helicobacter↑	[15]

		6 weeks			FM: Lachnospiraceae_NK4A136_group, Roseburia and Dubosiella↑ Lactobacillaceae↓	
PS NPs (80 nm)	Male Sprague-Dawley rats	Drink water 50 and 100 μg/L 24 weeks	Abundance↑ diversity↓		Bacteroides, Paraprevotella, Mucispirillum and Helicobacter↑ Oscillibacter and Ruminococcus↓	[60]
PS, PS-COOH and PS-NH_2 MPs/NPs (5 μm, 70 nm)	Male C57BL/6 mice	Gavage 0.2 and 2 mg/kg/day 28 days	Diversity↓		Proteobacteria, Verrucomicrobia↑ Lactobacillus↑ [Eubacterium]_xylanophilum_group and the Lachnospiraceae_NK4A136_group↓	[39]
PS MPs (5 μm)	Male C57BL/6 mice	Gavage 0.1 mg/per/day 6 weeks	The number of OTUs and diversity↑		Firmicutes and p_Campilobacterota, Clostridia, Lachnospiraceae, f_Muribaculaceae and g_Anaerotruncus↑ g_Dubosiella↓	[117]
PS MPs (5 μm)	Male C57BL/6 mice	Drink water 100 and 1000 μg/L/day 90 days	α-diversity↓	F/B↓	Bacteroidota↑, Firmicutes↓ Lactobacillaceae↓, Prevotellaceae and Bacteroidaceae↑	[103]
PS MPs/NPs (10 μm, 5 μm and 80 nm)	Male C57BL/6 mice	Gavage 60 μg/per/day 42 days			Shannon index↑ Bacteroidetes and Proteobacteria↑ Verrucomicrobia↓ Lachnospiraceae_NK4A136_group↑, Akkermansia, Bacteroides, Ruminococceae_UCG_014, mucispirillum and Helicobacter↓	[118]
PS MPs (5 μm)	Male C57BL/6 mice	Gavage 0.1 mg/per/day 6 weeks	Abundance and diversity↑		Bacteroidetes and Proteobacteria↓, Desulfobacterota and Campilobacterota↑ Desulfovibrio, Helicobacter, Oscillospiraceae and Lachnoclostridium↑, Alistipes and Dubosiella↓	[90]
PS MPs (5 μm)	Male ICR mice	Gavage 0.1 mg/per/day 35 days	Abundance and diversity↑	F/B↓	Lactobacillus↓ Prevotella↑	[104]
PS MPs (0.05 and 5 μm)	Male C57BL/6 mice	Gavage 0.5 mg/per/day 8 weeks	Diversity↓	F/B↑	Allobaculum, Alistipes, Candidatus Saccharimonas, Parabacteroides, and Bacteroides↓, Ruminococcus, Acetatifactor, and Alloprevotella↑	[76]
PS MPs (200 and 800 nm)	Male C57BL/6 mice	Drink water 10^9 4 weeks	200 nm MP: total number, Chao 1, Shannon entropy, and phylogenetic diversity↑	F/B↓	200 nm MP: Actinobacteria, Bacteroidetes, and Saccharibacteria↑ Firmicutes↓	[119]

PS MPs (20, 500 and 5000 nm)	Male Balb/c mice	Gavage 6, 60 and 600 μg/per/day 28 days	PS-MNPs 20 high and PS-MNPs 500 medium groups: α-diversity↓(with dose and concentration-dependent)		Escherichia-Shigella, Enterobacteriaceae and Erysipelotrichales↑ Lachnospiraceae and Clostridia↓	[40]
PS MPs (500 nm)	Male C57BL/6 mice	Gavage 5 mg/kg/day 30 days	α-diversity (ACE, Chao and Shannon index)↓		Proteobacteria and Actinobacteriota↑ Akkermansia and Lachnospiraceae_NK4A136_group↓ Pseudomona↑	[66]
PS MPs (~1 μm)	Male C57BL/6 mice MPs+Cd	Drink water 10 μg/mL 8 weeks	Abundance and diversity↓		Lactobacillus and Prevotellaceae, Alistipes and Parasuttrerlla↓	[59]
PS MPs (5 μm)	ICR male mice MPs+epoxiconazole	Gavage 0.012 and 0.120 mg/kg/day 7 weeks	α-diversity↓	F/B↓	Bacteroidetes↑ Firmicutes↓	[106]
PS MPs (5 μm)	Male C57BL/6 mice MPs+cyclophosphamide	Drink water 100 μg/L and 1000 μg/L 90 days	ACE, Shannon and Chao index↓	F/B↑	Proteobacteria at phylum level and Enterobacteriaceae at family↑ Desulfovibrio, Alistipes, Oscillospiraceae and Allobaculum↑	[70]
PS MPs (1 μm)	Male ICR mice MPs+tetracycline hydrochloride	Gavage 1 mg/kg/day 5 weeks	α-diversity↓	F/B↑	Dubosiella, Blautia and Butyricicoccaceae↓ Proteobacteria and Lactobacillus↓ Akkermansia muciniphila and Mucispirillum gute↑	[69]
PS MPs (5 μm)	Male C57BL/6 mice MPs+tributyltin	Gavage 0.1 mg/per/day 33 days	α-diversity↓		Firmicutes↓ Lactobacillus, Bacteroides, Butyrivibrio, GCA-900066575, Eubacterium]_nodatum_group, Anaerotruncus and Marvinbryantia and Lachnospiracea_UCG-001↓ Actinobacteria and Protebacteria↑	[112]
PS MPs (100 nm)	Male C57BL/6N mice MPs+*Lactobacillus rhamnosus* GG	Gavage 5 mg/kg/day 4 weeks	α-diversity↑	F/B↓	Escherichia-Shigella and Bifidobacterium↑ Verrucomicrobiota, Proteobacteria and Bacteroidota↑, Firmicutes↓ Prevotellaceae_NK3B31_group, Prevotellaceae_UCG_001 and unclassified_Lachnospiraceae↓ unclassified_Clostridia_UCG_014↑	[83]
PS NPs (80 nm)	Male ICR mice MPs+maltol	Gavage 100 mg/kg/day 28 days	Diversity↓	F/B↑	Bacteroidetes and Actinobacteria↓ Firmicutes, Proteobacteria↑ Lactobacillus, Eubacterium_xylanophilum_group, Lachnospiraceae_NK4A136_group, Roseburia,	[61]

PS MPs (5 μm)	Male C57BL/6 mice MPs+ epigallocatechin gallate	Gavage 1 mg/per/day 28 days		F/B↑	Blautia and Ruminococcu↓ Parasutterella↑ Phylum level: Firmicutes↑, Bacteroidota, Campilobacterota, and Proteobacteria↓ Family level: Lachnospiraceae, Oscillspiraceae, Ruminococcaceae, and Anaerovoracaceae↑, Peptostreptococcaceae↓ Genus level: Akkermansia, Faecalibaculum, and Mucispirillum↓, butyrate-producing Butyricicoccus, Ruminococcus, and pathogenic microbiota Tuzzerella↑	[74]
PS MPs (5 μm)	Male C57BL/6 mice Dietary restriction	Drink water 200 μg/L 5 weeks	Abundance and diversity↑	F/B↑	Verrucomicrobiota and Akkermansia↓ Ileibacteria valens and Proteobacteria↑	[64]
PS MPs (0.45-0.53 μm)	Male C57BL/6 mice Obesity model	Drink water 1000 μg/L 4 weeks	HFD+MP: α-diversity↓		HFD+MP: Bacteroidetes↓, Proteobactria and Desulfovibrio↑	[65]
PS MPs (5, 50, 100 and 200 μm)	Male ICR mice Obesity model	Gavage 80 mg/kg/day 10 weeks	Diversity↓	F/B↓	Bacteroidetes↑, Firmicutes↓ Muribaculaceae and Helicobacteraceae↓, Prevotellaceae, Enterobacteriaceae, Desulfovibrionaceae, and Rikenellaceae↑	[105]
PS MPs (5 μm)	Male C57BL/6 mice Obesity model	Drink water 10 mg/L 10 weeks	α-diversity↑		Family level: Lachnospiraceae, Oscillospiraceae, Marinifilaceae, Akkermansiaceae and Deferribacterales↑ Bifidobacteriaceae and Atopobiaceae↓ Genus level: Desulfovibrio, Bifidobacterium and Parabacteroides↑	[87]
PS MPs (100 and 5000 nm)	C57BKS/Leprdb (db/db) mice Diabetes model	Drink water 200 μg/L 28 days	Health mice: abundance and diversity↑ Diabetes mice: diversity↓	Health mice: F/B↓, Diabetes mice: F/B↑	Health mice: Alloprevotella, Bacteroides, Dubosiella, Lachnospiraceae_NK4A136_group and Lactobacillus and Weissella↓, Helicobacter, Parabacteroides, Candidatus_Saccharimonas and Lachnoclostridium↑	[120]
PS MPs (5 μm)	Sprague-Dawley rat Vascular calcification model	Drink water 0.5 mg/L 120 days	Shannon index↓		Proteobacteria and Escherichia_Shigella↑	[72]
PE, PET, PP, PS and PVC MPs (150~300 μm)	Male KM mice	Gavage 4 mg/per/day 7 days	PET MPs: α-diversity↓ PE MPs: α-diversity↑	PE, PET and PP MPs: F/B↑ PS and PVC MPs: F/B↓	PP MPs: Firmicutes↑, Bacteroidetes↓ PE and PS MPs: Ruminococcaceae↑ PE, PP and PS MPs: Lachnospiraceae↑ PS, PE and PVC MPs: Alistipes↓	[71]

LDPE: low-density PE, Ox-LDPE: oxidized LDPE, PS-COOH: negatively charged carboxylated polystyrene, PS-NH_2: positively charged aminated polystyrene.

Further analysis revealed that MPs intervention primarily led to an increase in the relative abundance of certain harmful bacteria, such as Proteobacteria (phylum level), Enterobacteriaceae, Erysipelotrichaceae and Oscillospiraceae (family level), *Desulfovibrio*, *Lachnoclostridium*, *Helicobacter* and *Ruminococcus* (genus level). An increase in Proteobacteria, similar to the ratio of F/B, indicated the dysregulation of GM, which was caused by diet, and leading to low-level, chronic inflammation[41]. The enhancement of inflammatory responses in inflammatory bowel disease (IBD) by Enterobacteriaceae[42], the exacerbation of obesity by Erysipelotrichaceae[43] and high relative abundance of Oscillospiraceae in hyperlipidemic mice[44] demonstrated the risks on human health by these microbiotas. *Desulfovibrio*, *Helicobacter* and *Lachnoclostridium* are pathogenic bacteria in the intestine. The underlying pathogenic mechanism of *Desulfovibrio* was mainly attributed to the metabolites (such as H_2S)[45], while *Helicobacter* caused inflammatory cell infiltration by causing gastric damage[46]. The combination of *Helicobacter* with PE-MPs can induce the release of more inflammatory factors[46]. *Lachnoclostridium* increased trimethylamine-N-oxide (TMAO) levels in serum and accelerated plaque formation in the body, promoting the formation of atherosclerotic lesions[47]. The harmful effect of *Ruminococcus* on human health was controversial. Metagenomic studies have found that an increase in the abundance of *Ruminococcus gnavus* was associated with the severity of inflammatory and autoimmune diseases[48,49]. While *R. gnavus* promoted the development of neurons and regulated spatial memory ability through the metabolites (tryptophan and indole)[50]. Conversely, beneficial genera like *Bifidobacterium* and *Lactobacillus*, and the probiotic *Parabacteroides* were consistently depleted[51]. However, the relative abundance of *Akkermansia muciniphila*, a promising next-generation probiotic, in some diseases was inconsistent, it was increased in IBD but decreased in liver steatosis[52]. The same trend also appeared under different MP intervention models.

MPs can alter GM structure. For instance, bacteria (*Klebsiella oxytoca*, *K. pneumoniae*, *Enterobacter ludwigii* and *E. sichuanensis*) isolated from the human gut physically disrupted the surfaces of low-density PE (LDPE) or PP films[53], initiating the biodegradation phase of plastic biodeterioration. GM depolymerizes plastics through enzymatic reactions, including hydrolysis, oxidation, reduction, and esterification[54]. Genes encoding plastic-degrading enzymes in the human GM have been excavated through metagenomics: *feaB* (encoding benzaldehyde dehydrogenase), *pbsA* (encoding polyester degrading enzyme), and *alkA* (encoding alkane hydroxylase)[55]. Additionally, five PET hydrolases, HG1-5, were identified by using the hidden Markov model (HMM) from 4984 cultivated genomic datasets[56].The vast and complex microbial community of GM represents a highly promising source for the degradation of MPs. It dismantles the complex polymer structure of MPs and utilizes them as carbon source for growth and metabolism. The rich enzymatic resources of GM are particularly worth further exploration.

The majority of plastic-degrading enzymes belong to the class of hydrolases, such as cutinase (EC 3.1.1.74), lipase (EC 3.1.1.3), and carboxylesterase (EC 3.1.1.1). Bacterial hydrolases share common features, most notably the catalytic triad (Ser-His-Asp), which is characteristic of the α/β-hydrolase fold

family[57]. The associated hydrolysis mechanism is often described as a ping-pong reaction or an acylation/deacylation process[57]. Hydrolysis of the ester bond in plastics begins with a nucleophilic attack by the oxygen of the catalytic serine on the carbonyl carbon of the ester bond. A negatively charged aspartate residue stabilizes the positively charged histidine, forming a charge-transfer network that enables proton shuttling necessary for serine activation and subsequent nucleophilic attacks. In the first step (acylation), the nucleophilic serine attacks the ester bond, leading to the formation of a tetrahedral intermediate stabilized by the oxyanion hole, and ultimately resulting in a covalent acyl-enzyme complex. In the subsequent deacylation step, a water molecule performs a nucleophilic attack on the acyl-enzyme intermediate, generating a second tetrahedral intermediate and culminating in cleavage of the ester bond. The reaction products are then released.

Current researches primarily use 16S rRNA gene sequencing to detect changes in GM, which can only measure relative rather than absolute abundance of bacteria. As a result, individual differences can lead to variable outcomes. Additionally, the identification depth of the 16S rRNA gene sequencing was usually limited to the genus level, with limited resolution at the species level. Further investigation, such as using metagenomic sequencing or culturomics, could identify specific bacterial species interacting with MPs and elucidate the underlying mechanisms, shifting current correlational to causal research. These results can serve as important targets for MPs toxicity assessment and can become useful tools for monitoring human health.

4. The effects of MPs on intestinal barrier

Disruption and imbalance of GM will further affect cellular connection and the secretion of the mucous layer. As the physical-chemical barrier of defense in the gut, indicators such as intestinal permeability, mucous layer thickness, and tight junction proteins (TJPs) expression are key markers. Unlike the personalized differences observed in the GM, the intestinal barrier is uniformly disrupted when exposed to MPs (**Table 2**).

Table 2 Overview of in vivo studies of the effects of MPs exposure on the intestinal barriers.

Category of MPs	Mice model	Intervention methods	Change of intestinal barriers	References
PE MPs (36 m and 116 m)	Male C57BL/6 mice	Foods 100 g/g 6 weeks	Small intestine: villus/crypt ratio↓ The mRNA expression of Muc2 and Vill, Chga and Lgr5↓ Colon: mucosal surface area↑ The mRNA expression of Muc2, Vill, Chga, Lgr5, Ocln and F11r↑	[82]
PE MPs (10-150 m)	Male C57BL/6 mice	Foods 2, 20, and 200 g/g 5 weeks	High-dose group: the colon and duodenum tissue glands were loose, edema, lymphocyte and plasma cell infiltration in the lamina propria	[62]
PE MPs (1-10 m)	Male ICR mice	Drink water 0.002 and 0.2 g/g/day 30 days	Mucin density↓	[98]
PE MPs (45-53 m)	Male CD-1 mice	Gavage 100 mg/kg/day 30 days	Intestinal permeability: DAO activity↓ D-Lac level↑	[85]
LDPE MPs and Ox-LDPE (2.6 -12.61 m)	Male C57BL/6 mice	Gavage 1 mg/per/day 28 days	Duodenum and colon: the mRNA expression of Occludin, ZO-1 and Claudin-1↓, crypt depth↑ Duodenum: villi rupture, villi length↓	[68]
LDPE MPs and Ox-LDPE (2.6 -13 m)	Male C57BL/6 mice	Gavage 1 mg/per/day 28 days	Duodenum: villus rupture, goblet cell structure disorder villus lengths↓, crypt depths↑ Ox-LDPE-MPs accumulated in Caco-2 cells via endocytosis	[38]
PVC MPs (2 m)	Male C57BL/6 mice	Gavage 100 mg/kg 60 days	Serum: FITC-dextran↑ Colon: mucus secretion↓ the mRNA expression of Muc1, Muc2, Muc3, Klf4 and Retnlb↓	[77]
PS MPs (5 m)	Male C57BL/6 mice	Gavage 1 mg/day 28 days	Colon: crypt atrophy, widened crypt space the number of glands and PAS^+ goblet cells↓ the protein and mRNA expression of ZO-1, Occludin and Claudin5↓	[73]
PS NPs (80 nm)	Male Sprague-Dawley rats	Drink water 50 and 100 g/L 24 weeks	Intestinal fluff was sparse, shorter, and disappeared, inflammatory cell infiltration, capillary proliferation intestinal injury score↑ the protein expression of ZO-1 and Claudin-1↓ Serum: LPS↑	[60]
PS, PS-COOH and $PS-NH_2$ MPs/NPs (5 m, 70 nm)	Male C57BL/6 mice	Gavage 0.2 and 2 mg/kg/day 28 days	$PS-NH_2$: damaged crypts, disappeared wrinkles and villi, thinner intestinal and mucosa walls, and obvious inflammatory exudation layers The mRNA and protein expression of ZO-1, Claudin-1 and Claudin-3↓	[39]

Pristine PS (40 nm), PS-NH_2 (51 nm) and PS-COOH (50 nm) NPs	Male ICR mice	Drink water 80 g/L 9 weeks	inflammatory cell infiltration, intestinal histological score↑ PS-NPs: the mRNA expression of ZO-1and MUC2↑ PS-NH_2: the mRNA expression of ZO-1↓MUC2↑ PS-COOH: the mRNA expression of ZO-1↓	[67]
PS MPs (0.5 and 50 m)	Male ICR mice	Drink water 100 and 1000 g/L 5 weeks	the secretion of mucin↓ the mRNA expression of Muc1 and Klf4↓	[81]
PS MPs (5um)	Male ICR mice	Drink water 100 and 1000 g/L 6 weeks	Colon: the mucus secretion↓ the mRNA expression of Muc1, Muc2, Muc3, Klf4, Meprin- , Retnlb, Cftr, nkcc1 and Nhe3↓ ileum: the mRNA expression of Ano1, Cftr, SLC26A6, nkcc1 and Nhe3↓	[80]
PS MPs (40-60 m and 40-100 m)	Male C57BL/6 mice	Foods 50 and 500 mg/kg 21 weeks	The thickness of the mucus layer↓ IHC score of F4/80 and epithelial injury scores↑ (with dose-dependent)	[78]
PS M/NPs (1 m and 100 nm)	Male C57BL/6 mice	Gavage 0.5 mg/day 60 days	the mucus secretion↓ Serum: FITC-dextran↑	[84]
PS MPs (0.05 and 5 m)	Male C57BL/6 mice	Gavage 0.5 mg/per/day 8 weeks	Inflammatory cell infiltration, epithelial cell hyperplasia, goblet cell loss, crypt distortion and loss and diffuse submucosa	[76]
PS MPs (20, 500 and 5000 nm)	Male Balb/c mice	Gavage 6, 60 and 600 g/per/day 28 days	MPs accumulated in colon 14 days: disruption of the intestinal epithelium, shorter and disorganized intestinal villi, and intestinal crypt dysplasia 28 days: vacuolation in the intestine, a thinner basal lamina, and lymphocyte aggregation the mRNA expression of Claudin-1, Muc2 and Muc3↓ Serum: FITC-dextran↑	[40]
PS MPs (500 nm)	Male C57BL/6 mice	Gavage 5 mg/kg/day 30 days	inflammatory cell infiltration, crypt atrophy histologic score↑ mucus secretion↓ the mRNA expression of ZO-1, Claudin-1 and Occludin↓ Serum: FITC-dextran↑	[66]
PS M/NPs (5um and 50 nm)	Male Wistar rat	Gavage 0.1 mg/kg and 1mg/kg 28 days	Translocated bacteria in mesenteric lymph nodes, liver, and spleen Mucus secretion and the protein expression of MUC2↓ the mRNA expression of Muc1, Muc2, Klf4 and Meprin- ↓ the mRNA expression of Zo-1 and Occludin↓	[79]
PS NPs (80, 200 and 1000 nm)	Male C57BL/6 mice	Gavage 0.5 mg/kg 28 days	TEM: villous lodging, mitochondrial membrane rupture, endoplasmic reticulum injury and dysfunction in intestinal epithelial cells	[75]

PS MPs (500 nm)	Male C57BL/6 mice	Gavage: 0.01 and 0.1 mg/100 L 5 weeks Intravenous injection: 0.1 g/100 L 4 weeks	TEM: the length of microvilli↓ the gap between the microvilli↑ Serum: FITC-dextran↑	[121]
PS MPs (5 m)	ICR mice	Drink water 100 and 1000 g/L 6 weeks	the secretion of mucus↓ the mRNA expression of Muc1, Muc2, Muc3, Klf4, Meprin- , retnlb, Zo-1 and Claudin-1↓	[86]
PS MPs (~1 m)	Male C57BL/6 mice MPs+Cd	Drink water 10 g/mL 8 weeks	Chaotic crypt structure mucus↓	[59]
PS MPs (5 m)	ICR male mice MPs+epoxiconazole	Gavage 0.012 and 0.120 mg/kg/day 7 weeks	villus length↓	[106]
PS MPs (5 m)	Male C57BL/6 mice MPs+CTX	Drink water 100 and 1000 g/L 90 days	Colon length, muscular layer, goblet cells and mucin↓ inflammatory cells infiltration, crypt atrophy histology score↑ Serum: FITC-dextran↑ the mRNA expression of Claudin-1, ZO-1, Occludin and Muc-2↓	[70]
PS MPs (1 m)	Male ICR mice MPs+TCH	Gavage 1 mg/kg/day 5 weeks	Small intestine: breakage and atrophy of villi, crypt deepening and inflammatory cell infiltration Colon: inflammatory cell infiltration the concentration of Claudin-1↓	[69]
PS MPs (5 m)	Male C57BL/6J MP+ Cyanidin-3-O-glucoside	Gavage 0.1 mg/day 6 weeks	Disruption of goblet cells and morphological structures	[58]
PS MPs (100 nm)	Male C57BL/6N mice MPs+*Lactobacillus rhamnosus* GG	Gavage 5 mg/kg/day 4 weeks	Ciliary defect The mucus secretion↑	[83]
PS NPs (80 nm)	Male C57BL/6 mice MP+Melatonin/Bifico	Gavage 60 g/day 42 days	Incomplete colonic mucosal structure, loose and irregularly arranged lamina propria glands and inflammatory cell infiltration infiltrated the number of columnar cells and goblet cells↓ the mRNA and protein expression of Occludin, Claudin-1 and ZO-1↓	[16]
PS NPs (80 nm)	Male ICR mice MPs+maltol	Gavage 100 mg/kg/day 28 days	H&E: Ruptured intestinal epithelium, dysplastic crypts and aggregated lymphocytes AB-PAS: The mucus secretion↓ TEM: Edematous mucosal epithelium, disordered and absent microvilli, less tight junctions, swollen mitochondria, numerous fragmented and reduced cristae the protein expression of Occludin and ZO-1↓	[61]

PS MPs (5 m)	Male C57BL/6 mice MPs+EGCG	Gavage 1 mg/per/day 28 days	H&E: crypt atrophies, widened crypt space PAS: glands and goblet cells↓ Colon length↓ The protein expression of ZO-1, Occludin and Claudin5↓	[74]
PS MPs (5 m)	Male C57BL/6 mice Dietary restriction	Drink water 200 g/L 5 weeks	AB-PAS: the goblet cells and mucus secretion↓ Serum: DAO, D-Lactate, D-LDH and IFABP↑	[64]
PS MPs (5 μm, 1.064 g/cm^3)	Male C57BL/6 mice Colitis model	Drink water 500 ug/L 28 days	Vacuolated colonic mucosa, loose intestinal goblet cell The mRNA expression of Claudin-1 and Occludin-1↓	[63]
PS MPs (0.45-0.53 m)	Male C57BL/6 mice Obesity model	Drink water 1000 g/L 4 weeks	ND: Total goblet cells and mucus thickness↓ HFD: Intestinal permeability and crypt depth↑ villus height and width↓	[65]
PS MPs (5 m)	Male C57BL/6 mice Obesity model	Drink water 10 mg/L 10 weeks	The intestinal goblet cell contents and mucin secretion, the protein expression of MUC2 and the mRNA expression of Muc2, ZO-1, Occludin and Claudin3↓	[87]
PS MPs (5 m)	Sprague-Dawley rat Vascular calcification model	Drink water 0.5 mg/L 120 days	Damaged colonic lamina propria, shallower colonic crypts, less goblet cells, and inflammatory cell infiltration Serum: D-lactate and DAO↑	[72]
PE, PET, PP, PS and PVC MPs (150~300 m)	Male KM mice	Gavage 4 mg/per/day 7 days	Less goblet cells and inflammatory infiltration The order of inflammatory cells ratio was: PS > PVC > PET > PE > PP > CK	[71]
Mixed PVC (2 m) and PS MPs (1 m)	Male C57BL/6 mice	Gavage Each MPs 0.5mg/day (total 1 mg/day) 60 days	AB-PAS: mucus secretion↓ Serum: FITC-dextran↑ the mRNA expression of mucus secretion-related genes (Muc2, Muc3, Klf4, Retnlb and Mep1) and TJ related genes (Claudin-4, Claudin-5 and Zo-1)↓	[88]

LDPE: low-density PE, Ox-LDPE: oxidized LDPE, PS-COOH: negatively charged carboxylated polystyrene, PS-NH_2: positively charged aminated polystyrene.

Histological damage caused by MPs included colon shortening, sparse and broken intestinal villi, crypt atrophy, decreased numbers of columnar and goblet cells, loosely arranged lamina propria glands, and infiltration of immune cells[16,39,40,58-76]. After MPs intervention, the thickness of the mucus layer significantly reduced, and the relative expression of genes related to mucin secretion, *Muc1*, *Muc2*, *Muc3*, *Klf4*, *Meprin-β*, and *retnlb* all decreased at the mRNA level[77-81]. However, three studies indicated an increase in mucin secretion in the colon after MPs intervention[67,82,83]. This may result from initial stimulation of goblet cells by MPs, resulting in an abnormal increase in mucin secretion. With continued exposure to MPs, goblet cells were damaged, leading to reduced mucin secretion. Both endogenous D-lactate and exogenous FITC-dextran served as indicators of intestinal permeability. Elevated levels of D-lactate and FITC-dextran indicated increased intestinal permeability[40,64,66,70,72,77,84,85], while TJPs, including Zona Occludens 1 (ZO-1), Occludin, Claudin-1, Claudin-3, Claudin-4, and Claudin-5 were decreased in mRNA and protein levels[16,39,40,60,63,66-70,73,74,79,86-88].

MPs-triggered intestinal barrier disruption is accompanied by the induction of excessive intracellular reactive oxygen species (ROS) production. After MPs enter the cell via endocytosis, they are recognized as foreign substances and trigger innate immune defense mechanisms[89]. Exposure to PS MPs significantly increased ROS levels in colon tissue or Caco-2 cells[59,61,90]. As mitochondria are the primary cellular organelles for ROS production, MPs-induced mitochondrial damage, such as moderate swelling of the mitochondria, extensive fragmentation and reduction of the cristae[61], and membrane potential collapse[91] release more ROS through the “ROS-induced ROS-release” (RIRR) mechanism[92]. ROS are generated mostly in the form of superoxide and hydrogen peroxide. Both O^{2-} and H_2O_2 participate in signal transduction and act as key mediators driving oxidative stress cascades, activating downstream related pathways[93]. ROS was considered a crucial second messenger in both the canonical and non-canonical activation pathways of the nod-like receptor protein 3 (NLRP3) inflammasome. In the canonical pathway, ROS activated the NLRP3 inflammasome via nuclear factor kappa B (NF-κB), while in the non-canonical pathway, ROS activated NLRP3 inflammasome through caspase-11[94]. Activated NLRP3 inflammasome, in turn, activates Caspase-1, which converted pro-interleukin (IL)-1β and pro-IL-18 into mature IL-1β and IL-18, thereby affecting TJPs. Additionally, IL-1β can further upregulate the expression of intestinal myosin light-chain kinase (MLCK), inducing intestinal barrier dysfunction[95]. The ROS-mediated mitochondrial signaling pathway inducing cell apoptosis also represents an important mechanism for TJPs disruption[96] (**Figure 2**).

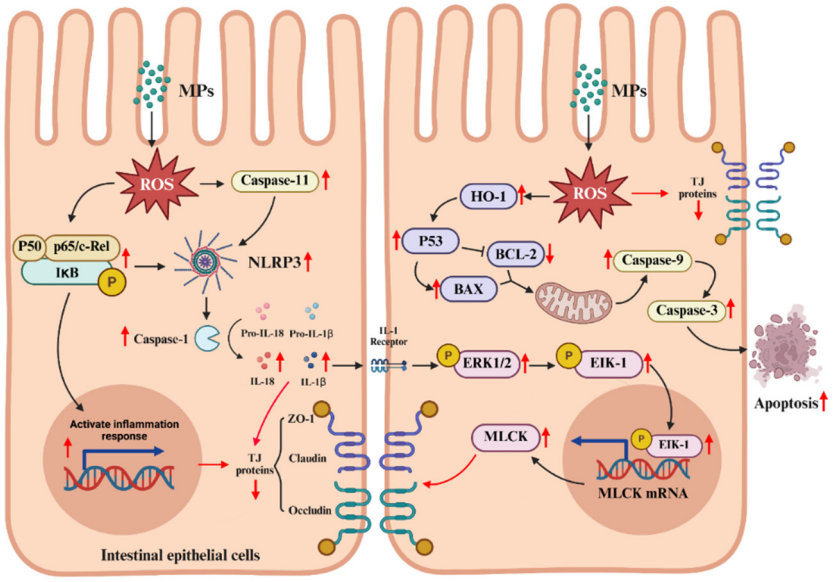

Figure 2. ROS mediated signaling pathways of tight junction protein damage caused by MPs. MPs promote the massive generation of ROS in colonic tissue, inducing TJ damage through oxidative stress, inflammatory responses (NF-κB/NLRP3 pathway), and affecting the cytoskeleton (NF-κB/NLRP3/MLCK pathway), while also causing cell apoptosis through the BCLl-2/BAX/Caspase-3 pathway, leading to intestinal epithelial cell damage.

5. The effects of MPs on immune response

Disruption of intestinal epithelial barrier function and increased intestinal permeability can lead to luminal content exposure and bacterial translocation, triggering intestinal immune responses, and may transform from local inflammation to systemic inflammation, further causing inflammation in various organs (**Figure 3**).

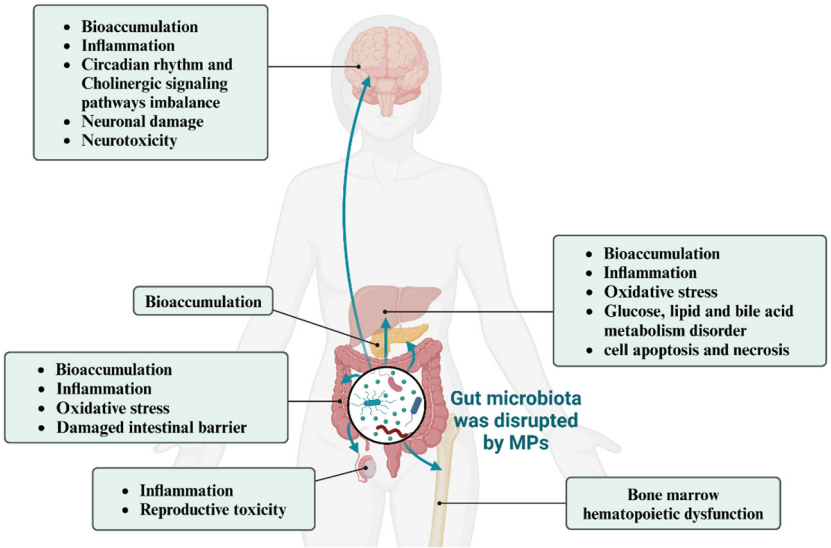

Figure 3. Toxicity in various organs induced by microplastics via disruption of gut microbiota. After MPs disrupt the structure of the GM and damage the intestinal barrier, triggering oxidative stress and inflammatory responses in the intestinal tissue, they enter the circulation and accumulate in various organs, causing physiological toxicity to brain tissue (inflammation, circadian rhythm and cholinergic signaling pathways imbalance, neuronal damage, and neurotoxicity), liver tissue (inflammation, oxidative stress, glucose, lipid metabolism and bile acid metabolism disorder and cell apoptosis and necrosis), testes (inflammation and reproductive toxicity), and bones (bone marrow hematopoietic dysfunction).

As the primary target organ of MPs intervention, the intestinal tissue exhibited reduced T lymphocytes, increased neutrophils, the upregulated expression of inflammatory cytokines, and the elevated levels of oxidative stress, following disruption of the GM and intestinal epithelial barrier (**Table 3**).

Table 3 Overview of in vivo studies of the effects of MPs exposure on the Inflammatory immune response and oxidative stress in different target

Category of MPs	Mice model	Intervention methods	Intestine	Serum	Other organs	References
PE MPs (36 μm and 116 μm)	Male C57BL/6 mice	Foods 100 μg/g 6 weeks	The mRNA expression of TNF, IFNγ, IL6 and IL1β↑ Polymorphonuclear neutrophils LY-6G^{+} cell↑ Anti-inflammatory macrophages CX3CR1^{+} CD11b^{h} cell↓			[82]
Pristine PS (40 nm), PS-NH_2 (51 nm) and PS-COOH (50 nm) NPs	Male ICR mice	Drink water 80 μg/L 9 weeks	The mRNA expression of IFNγ, IL-6, IL-10 and Tff-3↓, TLR3↑ PS-NH_2: the mRNA expression of TNF-α↑, IL-1β↓			[67]
PS MPs (20, 500 and 5000 nm)	Male Balb/c mice	Gavage 6, 60 and 600 μg/per/day 28 days	The number of CD45 cell (with size-dependent)↑ The level of sIgA, CD4^{+} and CD8^{+} T-lymphocytes↓			[40]
PS MPs (5 μm)	Male C57BL/6J MP+Cyanidin-3-O-glucoside	Gavage 0.1 mg/day 6 weeks	The levels of IL-6, IL-1β and TNF-α↑, IL-22 and IL-4↓ The mRNA expression of IL-6, IL-1β and Tnf-α↑ The protein expression of p-NF-κB, iNOS and COX-2↑			[58]
PE MPs (1-10 μm)	Male ICR mice	Drink water 0.002 and 0.2 μg/g/day 30 days	The mRNA expression of IL-8 and IL-10↑, IL-1β, ERK1 and NF-κB↓			[98]
LDPE MPs and Ox-LDPE (2.6-13 μm)	Male C57BL/6 mice	Gavage 1 mg/per/day 28 days	The level of SOD and GSH↓, MDA↑ The mRNA expression of TNF-α, IL-1β and IL-6↑			[38]
PS MPs (~1 μm)	Male C57BL/6 mice MPs+Cd	Drink water 10 μg/mL 8 weeks	The level of SOD↓, MDA↑			[59]
PS MPs (5 μm, 1.064 g/cm^3)	Male C57BL/6 mice Colitis model	Drink water 500 ug/L 28 days	The level of TNF-α, IL-1β and IFN-γ↑ The mRNA expression of GPx↑			[63]
PE MPs (10-150 μm)	Male C57BL/6 mice	Foods 2, 20, and 200 μg/g 5 weeks	20, 200: the percentage of Th17 and Treg cells among CD4^{+} cell↓ 200: the protein expression of	2: the level of IL-1α and IL-6↑ 20: the level of IL-1α and RANTES↑		[62]

			TLR4, AP-1 and IRF5↑	200: the level of IL-1α and IL-9↑		
PS MPs (5 μm)	Male C57BL/6 mice Obesity model	Drink water 10 mg/L 10 weeks	The mRNA expression of IL-17A and TNF-α↑	The level of LPS, IL-1β, IL-6, TNF- α, IL-17A↑, IL-10↓		[87]
PS MPs (5 μm)	ICR mice (male and female)	Gavage 10 μg/20 kg/day 1 month	The mRNA expression of IL-10, MyD88, TLR4 and CCR5↓	The level of IL-4 Th2 and Th17 cell↑, IL-12p70, RORγt, Treg and Th1 cell↓		[97]
PE, PET, PP, PS and PVC MPs (150~300 μm)	Male KM mice	Gavage 4 mg/per/day 7 days	The level of SOD, GSH, MDA and POD↑	PET and PVC MPs group: the level of TG↑		[71]
PS MPs (0.45-0.53 μm)	Male C57BL/6 mice Obesity model	Drink water 1000 μg/L 4 weeks	The mRNA expression of Tnfα, Il6, Il1β and Il22↑	The level of ALT, TG, NEFA, LDL-Chol and palmitic acid↑	Liver tissue: the mRNA expression of Tnfα, Il6 and Il1β↑	[65]
PS MPs (0.05 and 5 μm)	Male C57BL/6 mice	Gavage 0.5 mg/per/day 8 weeks	The level of IL-1β, TNF-α and IL-6↑		Brain tissue: the level of IL-1β, TNF-α and IL-6 in brain↑ The microglia number in the cortex and hippocampus↑	[76]
LDPE MPs and Ox-LDPE (2.6-12.61 μm)	Male C57BL/6 mice	Gavage 1 mg/per/day 28 days	The mRNA expression of TNF-α, IL-1β and IL-6↑	The level of LPS, white blood cell, lymphocyte and platelets↑	Brain tissue: the level of LPS and MDA, and the mRNA expression of TNF-α, IL-1β and IL-6 in cortex and hippocampus↑	[68]
Mixed PVC (2 μm) and PS MPs (1 μm)	Male C57BL/6 mice	Gavage Each MPs 0.5mg/day (total 1 mg/day) 60 days	The mRNA expression of IL-6, TNF-α and IL-1β↑	The level of ALT, AST, TG, TCH and TBA↑	Liver tissue: the level of TG, TCH, TBA and MDA↑, T-AOC, GSH and SOD↓ the mRNA expression of TNF-α and IL-1β↑	[88]
PS MPs (5 μm)	Male C57BL/6 mice MPs+EGCG	Gavage 1 mg/per/day 28 days	The protein of TLR4, MyD88, NF-κB and p-NF-κB↑ the mRNA expression of TNF-α, IL-6 and IL-1β↑	The level of LPS, TNF-α, IL-6, IL-1β, ALT, AST, ALP and LDH↑	Liver tissue: the protein of TLR4, MyD88, NF-κB and p-NF-κB↑ the mRNA expression of TNF-α, IL-6 and IL-1β↑	[74]
PS MPs (5 μm)	Male C57BL/6 mice	Gavage 0.1 mg/per/day 6 weeks	The level of ROS, TNF-α, IL-1β and CD45↑, SOD and CAT↓		Liver tissue: the protein of TNF-α、IL-1β和CD45↑	[90]
PS MPs (5 μm)	Male C57BL/6 mice MPs+CTX	Drink water 100 and 1000 μg/L 90 days	The level of TNF-α, IL-6 and MDA↑, IL-10, GSH and SOD↓			[70]
PS MPs (5 μm)	Male ICR mice	Gavage 0.1 mg/per/day	The protein expression of IL-17A and MCP1↑		Testes tissue: the protein expression of p-NF-κB p65,	[104]

		35 days			TNF-α, IL-1β, IL-6, IL-17A and MCP1↑	
PS MPs (500 nm)	Male C57BL/6 mice	Gavage 5 mg/kg/day 30 days	The mRNA expression of TNF-α and IL-1β↑		Brain tissue: the mRNA expression of IL-6 and IL-1β, and the protein expression of IBA-1 in hippocampus↑	[66]
PVC MPs (2 μm)	Male C57BL/6 mice	Gavage 0.5 mg/per/day 60 days		The level of ALT and AST↑ TG, TCH and TBA↓	Liver tissue: the level of TG, TBA and SOD↓, MDA↑ The protein expression of PTEN, p53, PI3K, p-Akt, cleaved caspase 3 and Bax↑, Nrf2 and Ho-1↓ The mRNA expression of Nrf2, Ho-1, SOD and NQo1↓	[122]
PES MPs/NPs (5 μm and 50 μm)	Male ICR mice	Gavage/intranasal administration 5/0.75 mg/kg/day 6 weeks		The level of AST and ALT↑, SOD↓		[15]
PS MPs/NPs (10 μm, 5 μm and 80 nm)	Male C57BL/6 mice	Gavage 60 μg/per/day 42 days		The percentage of lymphocyte cells↑, granulocytes↓ The level of IL-12p40, IL-10, IL-17A, MIP-1β and IL-12p70↓, Eotaxin↑		[118]
PS MPs (5um)	Male ICR mice	Drink water 100 and 1000 μg/L 6 weeks		The level of PYR↑, TG and TCH↓		[80]
PS MPs (5 μm)	Male C57BL/6 mice Dietary restriction	Drink water 200 μg/L 5 weeks		The level of TNF-α↑, sIgA↓		[64]
PS MPs (5, 50, 100 and 200 μm)	Male ICR mice Obesity model	Gavage 80 mg/kg/day 10 weeks		The level of TNF-α, IL-1β, LPS, TG, T-CH, BUN, AST and AChE↑, HFDL-C↓		[105]
PS MPs (5 μm)	Sprague-Dawley rat Vascular calcification model	Drink water 0.5 mg/L 120 days		The level of LPS, IL-1β, IL-6 and TNF-α↑		[72]
PS MPs (5um)	Male C57BL/6 mice	Gavage 1 mg/day 28 days		The level of LPS, IL-1β, IL-6 and TNF-α↑	Brain tissue: the protein expression of TLR4, MyD88 and P-NF-κB↑ in hippocampus The mRNA expression of TNF-α,	[73]

				IL-1β and IL-6↑in hippocampus	
PS NPs (80 nm)	Male Sprague-Dawley rats	Drink water 50 and 100 μg/L 24 weeks	The level of TNF-α, IL-1β, IL-6, Caspase3, BAX↑, Bcl2↓	Brain tissue: the level of TNF-α, IL-1β, IL-6, Caspase3, BAX↑, Bcl2↓ in amygdaloid nucleus	[60]
PS MPs (5 μm)	ICR mice	Drink water 100 and 1000 μg/L 6 weeks	F0: GLU, PYR, TG and NEFA↓, TCH, HDL-C and LDL-C↑ Female F1: GLU, PYR, TCH, TG and NEFA↓ Male F1: TG, HDL-C and NEFA↓, TCH and LDL-C↑	Liver tissue: F0: TCH and TG↑ F1: TCH↓	[86]
PS MPs (5 μm)	Male C57BL/6 mice MPs+tributyltin	Gavage 0.1 mg/per/day 33 days	The level of TG↓, AST↑	Liver tissue: the mRNA expression of IFN-γ and Mpeg1↑	[112]
PS MPs (100 nm)	Male C57BL/6N mice MPs+*Lactobacillus rhamnosus* GG	Gavage 5 mg/kg/day 4 weeks	The level of AST↑	Liver tissue: the mRNA expression of IL-6 and TNF-α↑	[83]
PS MPs (100 and 5000 nm)	C57BKS/Leprdb (db/db) mice Diabetes model	Drink water 200 μg/L 28 days	The level of TNF-α and IL-1β↑	Liver tissue: the level of TNF-α and IL-1β↑ The level of SOD↓, MDA↑	[120]
PS NPs (80 nm)	Male ICR mice MPs+maltol	Gavage 100 mg/kg/day 28 days		Colon tissue: the protein expression of Bcl-2↓, Bax and Cleaved caspase-3/Caspase-3↑ Liver tissue: the level of ALT, AST, LDH, ALP and γ-GGT↑	[61]
PE MPs (5 μm)	Male C57BL/6 mice	Drink water 1 mg/L, 10 mg/L 21 days		The mRNA and protein expression of TNF-α, IL-1β and IL-6↑, IL-10↓ Apoptosis-related regulators: the mRNA expression of BAX, BAK, Caspase6 and Caspase7↑, BCL-2↓ Necrosis-related regulators: RIPK1, RIPK3 and MLKL↑ The expression of TLR2/NF-κB/NLRP3 pathway↑	[100]
PVC-MPs (40-300 μm), PLA-MPs (16-350 μm)	Male C57BL/6 mice	Gavage 0.1 and 0.5 mg/per/day 6 weeks		Liver tissue: the level of SOD and MDA↑	[116]

PS MPs (0.5 and 50 μm)	Male ICR mice	Drink water 100 and 1000 μg/L 5 weeks	Liver tissue: TG and TCH↓, PYR↑	[81]
PS MPs (40-60 μm and 40-100 μm)	Male C57BL/6 mice	Foods 50 and 500 mg/kg 21 weeks	Liver tissue: HDL↓, LDL and TBA↑	[78]
PS MPs (5 μm)	Male C57BL/6 mice	Drink water: 0.001, 0.1, 1 and 10 μg/mL Gavage: 100 μg/ per/day 10 weeks	Liver tissue: AST/ALT↑ 0.1μg/mL MPs trigger more fat deposition and accumulation	[101]
PE MPs (10-20 μm)	Male C57BL/6 mice Prenatal, post-weaning, puberty, and adult models	Drink water, 100 ppm/100 μL Prenatal model: 2 weeks Post-weaning model: 2weeks Puberty model: 2 weeks Adult models: 12 weeks	Brain tissue: the level of IL-6 and IL-1β↑	[102]
PS MPs (5 μm)	Male C57BL/6 mice	Drink water 100 and 1000 μg/L/day 90 days	Testes tissue: the level of TNF-a and IL-6, the protein expression of IL-17 A, the mRNA expression of IL-17 RA, Act1, TRAF6, TAK1 and NF-κB↑	[103]

LDPE: low-density PE, Ox-LDPE: oxidized LDPE, PS-COOH: negatively charged carboxylated polystyrene, PS-NH_2: positively charged aminated polystyrene.

PS MPs activated intestinal inflammation through the TLR4/MyD88/NF-κB[74] or NF-κB/iNOS/COX-2 pathways[58]. Conversely, another study showed that PS MPs exhibited inhibitory effects on the expression of MyD88, TLR4, and CCR5 in intestinal tissue[97]. The immunotoxicity of PS MPs may involve type 2 immune responses, leading to Th2 cell hyperactivity, significant reduction in Th1 cells, and abnormal secretion of related cytokines[97]. In addition, although disturbances of inflammatory factors in colon tissue was observed under the exposure to PE MPs, the expression of TLR4 and MyD88 remained unchanged[98], suggesting that the immune response induced by MPs may involve alternative pathways. Beyond classical signaling pathways related to inflammation, the imbalance in the antioxidant defense system induced by MPs, such as the increase or decrease in the activity of superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), and the elevation in malondialdehyde (MDA) activity[59,70,71,83,90], was due to the disruption of cellular homeostasis caused by excessive ROS. Under exposure of MPs, there is significant crosstalk between inflammatory and oxidative stress signaling pathways, which accounts for their frequent co-occurrence (**Figure S1**).

Systemic inflammation was manifested by an increase in inflammatory cytokines (lipopolysaccharide (LPS), IL-1β, IL-6 and tumour necrosis factor (TNF)-α), lymphocytes, and oxidative stress levels (glutamic pyruvic transaminase (AST) and glutamic oxaloacetic transaminase (ALT)) in the serum, while the levels of IL-10, SOD, and granulocytes were decrease. Elevated serum inflammatory factors indicated an inflammatory response, while increased AST and AST levels were commonly used as biomarkers of liver injury[99]. Therefore, it suggested that MPs can translocate from the intestines to affect other organs. As the most important metabolic organ, the liver was particularly susceptible. In addition to inflammation and oxidative stress, the glucose and lipid metabolism[85], bile acid metabolism[78,88], and cell apoptosis and necrosis[100] in liver were also affected by MPs.

The results of hepatic transcriptome revealed that the processes of fatty acid metabolism, steroid metabolism, and lipid metabolism were all significantly altered after MPs intervention[86]. However, the expression of genes related to glucose metabolism (*Glut2*, *Gk*, *Pk*, and *Chrebp*) and lipid metabolism (*Fas*, *Scd1*, *PPar-γ*, *Srebp1c*, *Acl*, and *Acc*) in the liver were decreased at the mRNA level in MPs-treated group[86]. These results confirmed that MPs affected hepatic energy metabolism, including the processes of glycolysis and glucose transport, as well as fatty acid synthesis and fatty acid oxidation. Although showing different trends, MPs clearly disrupt hepatic metabolism, leading to visceral fat accumulation[101]. The increase in total bile acids (TBA) in the liver by MPs was also a classic physiological indicator of lipid metabolism abnormalities. The enterohepatic circulation of bile acids (BAs) recycles limited BAs, promoting lipid digestion and absorption. However, the accumulation of TBA in the liver disrupted this cycle, thereby affecting the digestion and absorption of lipids[88]. Additionally, MPs caused liver function damage by significantly increasing apoptosis-related regulatory factors (B-cell lymphoma associated X

(BAX), BCL-antagonist/killer (BAK), Caspase6, and Caspase7) and necrosis-related regulatory factors (RIPK1, RIPK3 and MLKL)[100].

Apart from the liver, the brain and testes also appear to be target organs affected by MPs. MPs exerted neurotoxic effects in mice by inducing oxidative stress, inflammatory responses, dysregulation of cholinergic signaling pathways, and decreased glucose metabolism in the mouse brain[66,68,73,102]. While PS-MPs have been reported to induce reproductive toxicity in mice by activating the gut-derived IL-17A signaling pathway[103,104]. The toxic reactions in these organs may originate from local immune responses in the colon or direct accumulation of MPs in various organs. Effective methods for detecting MPs in the body are lacking, so fluorescently labeled MPs were usually used to track their distribution and accumulation after ingestion. The accumulation of MPs in the colon is easily understood[66,80]. Additionally, PS MPs have been detected in blood vessels, liver, kidneys, spleen, heart, and lungs, but only those smaller than 5 μm[76,105,106]. The size of PE MPs detected in the brain was (3.9 ± 0.3) μm[102], indicating that smaller-sized PE fragments were capable of translocating and accumulating in the brain. Exposure to larger-sized MPs (40-100 μm) did not lead to tissue accumulation in mouse[78]. It was further confirmed by fecal microbiota transplantation (FMT) that MPs drive testicular inflammation, neuronal damage, hepatotoxicity and colitis through GM[66,70,74,87,103,104].

Due to the organic toxicity of MPs is closely linked to their particle size, biodegradable microplastics (BMPs) may pose a heightened toxicological risk compared to their conventional counterparts. Due to the biodegradability, BMPs are more prone to incomplete degradation within the gastrointestinal tract. This process can generate smaller particles and oligomers that exhibit enhanced bioavailability and mobility, potentially exacerbating their ability to induce intestinal barrier dysfunction, inflammatory responses, lipid metabolism and systemic toxicity[107,108]. Therefore, while concerns regarding the health effects of conventional non-biodegradable MPs remain, it is imperative to strengthen research on the potential toxicity of BMPs.

6. MPs as the carriers of pollutants

Besides direct effects, MPs can also act as carriers for various pollutants, including metals, organic pollutants, pharmaceuticals, and pathogens. Due to the large surface area, MPs can adsorb and transport other pollutants, leading to their accumulation in organisms. As shown in **Table 4**, co-intervention of MPs with arsenic (As)[109], cadmium (Cd)[59], epoxiconazole (EPO)[106], cyclophosphamide (CTX)[70], di-(2-ethylhexyl) phthalate (DEHP)[110] and sulfamethoxazole (SMX)[111] resulted in synergistic toxicity.

Table 4. Overview of in vivo studies of the effects co-exposure of MPs and pollutants

Category of MPs	Mice model	Intervention methods	Collective effect	Reference
PE MPs (30 and 200 μm)	Male Balb/c mice MPs+As	Feeds MPs: 12, 20 and 200 μg/g As: 6 μg/g 35 days	The exposure of PE MPs specifically upregulated intestinal metabolites, significantly improving the oral bioavailability of As	[109]
PS MPs (~1 μm)	Male C57BL/6 mice MPs+Cd	Drink water MPs: 10 μg/mL Cd: 30 μg/mL 8 weeks	Combined exposure (Cd+PS MPs) induced more severe intestinal epithelial damage, mucus barrier impairment, ROS generation, oxidative stress, and inflammatory response than single exposure	[59]
PS MPs (5 μm)	ICR male mice MPs+EPO	Gavage MPs: 0.012 and 0.120 mg/kg/day EPO: 0.080 mg/kg 7 weeks	Co-exposure to styrene and epoxiconazole produced a combined toxicity in mice through the synergistic effect of bioaccumulation in vivo, aggravating tissue damage in the liver and kidneys, oxidative stress, and metabolic disorders in mice.	[106]
PS MPs (5 μm)	Male C57BL/6 mice MPs+CTX	Drink water MPs: 100 and 1000 μg/L 90 days CTX：80 mg/kg 3 days	PS MPs aggravated CTX-induced hepatotoxicity by causing changes in GM	[70]
PS NPs (50 nm)	Male C57BL/6 mice MPs+DEHP	Gavage MPs: 1.8×10^{-4} μg/kg/day DEHP: 0.25 and 2.5 μg/kg/day 30 days	Enhanced toxic effects were observed when exposed to both PS NPs and DEHP, with the most pronounced damage in the colon.	[110]
PET MPs (2-631 μm)	Female KM mice MPs+SMX	Feeds MPs: 500 mg/kg SMX: 100 mg/kg 28 days	The effects of SMX + MPs on gut microbiota and ARGs were stronger than those of MPs or SMX alone, which may be attributed to the longer retention time of SMX and the synergistic effects of SMX and MPs.	[111]
PS MPs (1 μm)	Male ICR mice MPs+TCH	Gavage 1 mg/kg/day 5 weeks TCH: 0.3mg/kg/day 3 times/week, 5 weeks, 15 times in total	The combined effects of PS-MPs and TCH on intestinal physical and functional damage were less than those of MPs or TCH alone	[69]
PS MPs (5 μm)	Male C57BL/6 mice MPs+TBT	Gavage MPs: 0.1 mg/per/day TBT: 100 ng/kg 33 days	The combined exposure of MP and TBT attenuated the toxic effects of MP and TBT alone. However, it inhibited BSEP, which induced the accumulation of BAs in the liver and inhibited the excretion of T-α-MCA.	[112]

As: arsenic, Cd: cadmium, EPO: epoxiconazole, CTX: cyclophosphamide, DEHP: di-(2-ethylhexyl) phthalate SMX: sulfamethoxazole, TBT: tributyltin, TCH: tetracycline hydrochloride.

For heavy metals, they can directly adsorb onto MPs and release in gastrointestinal fluids, leading to a Trojan horse effect[59]. For other organic pollutants, MPs upregulated intestinal metabolites containing hydroxyl, carboxyl, and aldehyde functional groups, inhibiting the coprecipitation of iron (Fe) and arsenic (As) in the intestine, thereby increasing the solubility and bioavailability of As[109]. MPs exacerbated tissue damage, oxidative stress, and metabolic disorders in the liver and kidneys by aggravating the accumulation of EPO in tissues through the destruction of the intestinal barrier[106]. The combined intervention of MPs with CTX or DEHP enhanced its toxic effects by disrupting the GM structure and damaging the intestinal barrier, respectively[70,109]. And it was validated that the GM is a potential mechanism by which CTX exacerbates liver damage in mice pre-treated with MPs by FMT[70]. Surprisingly, co-administration of MPs with SMX significantly reduced the bioaccumulation of SMX in mice tissues, but exacerbated the effects of SMX on GM and antibiotic resistance gene (ARG) profiles[111]. This may be due to the size of the MPs in this study prevented mice tissue penetration. Therefore, the remaining MPs were retained in the intestine, resulting in a longer retention time of adsorbed SMX in the intestine compared to free SMX, exacerbating intestinal damage[111].

On the contrary, the combined exposure of MPs with tetracycline hydrochloride (TCH) or tributyltin (TBT) was less than that of single exposure to MPs, TCH or TBT. The MPs+TBT group did not inhibit BAs synthesis like that in the MPs group but rather prevented the efflux of BAs by inhibiting bile salt export pump (BSEP), leading to intrahepatic cholestasis. Additionally, the MPs+TBT group did not significantly increase AST, interferon (IFN) γ, and macrophage-expressed gene (Mpeg) 1 levels, unlike the individual use of MPs or TBT. At the same time, these groups induced changes in the GM in different ways. These differences may be attributed to the adsorption effect of MPs on TBT, resulting in the total content of tin in the liver of the MPs+TBT group being nearly 30% lower than that of the TBT group, thus affecting the different mechanism of BA distribution through the GM[112]. There are distinct spatial differences in physical damage caused by PS MPs and TCH: TCH primarily induced damage to the small intestine, while PS MPs tend to cause damage to the colon. However, co-exposure mitigated toxic effects. PS MPs can adsorb TCH, reducing its impact on the small intestine, while TCH can also enhance the aggregation of PS MPs, reducing the impact of MPs on the colon[69]. Therefore, different interactions between MPs and these pollutants may lead to enhancing or weakening of the toxicity in the body.

7. Mitigation of the toxicity of MPs by bioactive substances

The biological toxicity induced by MPs has garnered widespread attention, while concurrently administering bioactive substances can mitigate or counteract the toxicity of MPs **(Table 5)**. Anthocyanins extracted from bayberries reduced PS MPs-induced inflammation and oxidative stress in the intestine and liver by decreasing the accumulation of PS MPs in organs and regulating disordered GM and its metabolites[58,90]. Melatonin can improve the neurotoxicity of NPs through the circadian rhythm-related pathway mediated by the gut-brain axis[16], and ameliorate the bone marrow hematopoietic dysfunction

caused by NPs by regulating the metabolism of GM[113]. At the same time, the probiotic preparation Bifico (a probiotic mixture containing *Bifidobacterium longum*, *Lactobacillus acidophilus* and *Enterococcus faecalis*) has the same effect as melatonin. However, the difference lies in the fact that Bifico demonstrated a greater beneficial effect than melatonin in hematopoietic toxicity[113], whereas melatonin was more effective against neurotoxicity[16]. Additionally, *Lactobacillus rhamnosus* GG (LGG) reduced PS MPs-induced hepatotoxicity through improved GM dysregulation, enhanced intestinal barrier integrity, and reduced hepatic inflammation, with the regulation of BAs metabolism identified as a key target[83]. As a flavor-enhancer, maltol can improve GM dysbiosis, intestinal barrier damage and intestinal epithelial cell apoptosis caused by PS MPs exposure. Molecular dynamics simulations (MDS) have been used to verify the activation of the AMPK pathway is crucial for maltol improved lysosomal function, promoted autophagy and facilitated autophagic flux[61]. MDS appears to be an effective method for identifying the target of MPs. The pharmacophore modeling was used to screen the target protein of PLA MPs, PLA MPs bound to MMP12 and inhibited its biological activity thereby mediating intestinal inflammation[107]. Meanwhile, PS NPs induced endothelial leakage by causing the dissociation of VE-cadherin dimers which performed with implicit solvent models[114].

Table 5. The effects co-exposure of MPs and bioactive substances

Category of MPs	Mice model	Intervention methods	Collective effect	Reference
PS MPs (5μm)	Male C57BL/6 mice MP+C3G	Gavage MPs: 0.1 mg/per/day C3G: 150 mg/kg/day 6 weeks	C3G alleviated the toxicity of PS MPs to colon and liver	[90]
PS MPs (5μm)	Male C57BL/6J MP+C3G	Gavage MPs: 1 mg/mL C3G: 150mg/kg/day 6 weeks	C3G alleviated PS MPs-induced colonic inflammation	[58]
PS NPs (80 nm)	Male C57BL/6 mice MP+Melatonin/Bifico	Gavage MPs: 60 μg/d Melatonin: 10 mg/kg Bifico: 4.2 g/kg 42 days	Melatonin or probiotics protect mice from neuronal damage induced by PS NPs	[16]
PS NPs (80 nm)	Male C57BL/6 mice MP+Melatonin/Bifico	Gavage MPs: 60 μg/d Melatonin: 10 mg/kg Bifico: 4.2 g/kg 42 days	Melatonin or probiotics alleviated the hematopoietic toxicity caused by PS MPs	[113]
PS MPs (100 nm)	Male C57BL/6N mice MPs+*Lactobacillus rhamnosus* GG	Gavage MPs: 5 mg/kg/day LGG:100 mg/kg/day 4 weeks	LGG alleviated PS MPs-induced colon and liver damage and lipid metabolism disorders	[83]
PS NPs (80 nm)	Male ICR mice MPs+Maltol	Gavage MPs: 100 mg/kg Matol: 50 and 100 mg/kg 28 days	Maltol alleviated PS-induced autophagy-dependent apoptosis and lysosomal dysfunction in the colon.	[61]

Bifico: a probiotic mixture containing *Bifidobacterium longum*, *Lactobacillus acidophilus* and *Enterococcus faecalis*, C3G: Cyanidin-3-O-glucoside.

8. Conclusion and perspectives

Consumption of MPs-contaminated food is the primary source of human exposure, facilitating direct interaction between MPs and GM. Disruption of GM by MPs further affects the health of the intestinal barrier, systemic immunity, and organ tissues. Therefore, GM is a key target for the biological toxicity of MPs. MPs can be biotransformed by GM, which in turn alters the structure of GM. Current evidence suggested that MPs primarily promote the proliferation of pathogenic bacteria. However, due to differences in individual mice from different experimental studies, as well as the length of experimental design, the key bacterial strains involved remain incompletely explored. Only a limited number of studies have preliminarily confirmed through FMT that MPs exerts physiological toxic effects via GM. Further research, including experiments with germ-free mice and co-culture of MPs with key bacterial strains in vitro, is needed to validate the underlying roles of GM. In addition, there is a lack of research on the molecular mechanisms of MPs toxicity. Integrating toxicity studies with specific GM biomarkers could provide targeted prevention and treatment strategies for addressing public health issues caused by MPs.

Biodegradable plastics (BPs) are promoted as environmentally friendly and biodegradable alternatives to traditional plastics. However, the biodegradability of BPs causes it to break down into MPs more quickly than traditional plastics, posing a greater threat to the environment and human health. Currently, research on the harmful effects of BPs on human health is limited, but the growing use of BP necessitates our attention to this potential threat.

Conflict of Interest

No potential competing interest was reported by the author(s).

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Data availability statement

There is no data set associated with this article.

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