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Research Article

MICROPLASTIC-DRUG INTERACTIONS: UNVEILING COMBINED EFFECTS ON BIOLOGICAL SYSTEMS

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ABSTRACT

In our daily life, plastic plays a major role in packaging material, clothing, construction, electrical, transportation, and medical devices because of its affordability, light weight, and availability. The most commonly used plastics are polypropylene, polyethylene, polyhydroxyalkanoates, polystyrene, polyvinyl chloride, and polyamide. Some experts estimate that the total amount of plastics produced worldwide increased at an annual growth rate of 5% from 1950 to 2018, and amounted to 359 million tons; about 10% of that amount is ending up in the ocean through various channels. In 2018, worldwide plastic output hit 360 million tons, with just 6–20% recycled. Regretfully, plastic usage is increasing. Although they are susceptible to ultraviolet light and mechanical wear, they did not wear away. These microplastics (MPs) are abundantly found in the environment, which paved the way to a toxic environment. Because of their tiny size, large specific area, hydrophobicity, and stabilized chemical properties, MPs can endure in the environment for hundreds or even thousands of years. MPs are classified into two types: Degradable and non-degradable. In this review, we demonstrate the interaction between micro- and nano-plastics with drugs and their effect on the environment. Many drugs, such as boron, tetracyclines, methamphetamine, ciprofloxacin, amphetamine, chlortetracycline, procainamide, and doxycyclines with micro and nano plastics, show negative impacts on living organisms directly or indirectly. This review discusses the reported impacts of microplastics and drug interactions on living organisms.

Keywords: Polypropylene, Polyethylene, Polyhydroxy alkanoates, Polystyrene, Polyvinyl chloride, Polyamide.

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INTRODUCTION

The remarkable properties, such as durability, corrosion resistance, light weight, low electrical conductivity, and low thermal conductivity of plastics, have revolutionized them in modern life. Plastics became a ubiquitous material in various industries due to these attributes and their widespread applications. Approximately 300 million tons of plastic are produced every year, which leads to significant environmental challenges. Only 20% of the plastic produced is either recycled or incinerated. The most commonly used plastics are polypropylene (PP), polyethylene (PE), polyhydroxyl alkanoates, polystyrene (PS), polyvinylchloride (PVC), and polyamide [1-3]. In 2018, worldwide plastic output hit 360 million tons, with just 6–20% recycled [4]. The remaining amount of plastic is discarded into the marine environment or ends up in landfills. Because of their tiny size, large specific area, hydrophobicity, and stabilized chemical properties, MPs can endure in the environment for hundreds or even thousands of years [5]. The persistence of plastics in the environment is now a critical concern; particularly, they undergo a series of degradation processes which ultimately result in the formation of microplastics (MPs). MPs are minute plastic particles with a diameter of <5 mm. These particles are pervading and found in various compartments of the environment, such as water, soil, and the atmosphere. MPs can remain in natural environments for extended periods because of their durability and small size. This leads to severe environmental pollution, and its impact extends beyond its mere presence. They act as carriers for chemical pollutants and toxic substances. Ingestion of MPs by various organisms, including humans, leads to health risks. These MPs also effects marine ecosystem as shown in the Fig. 4. Accumulation of MPs in the human body leads to potential hazards such as reduced nutrient absorption, disturbances in the digestive system, and adverse effects on growth as well as on the reproductive system. The major contributors to MPs are synthetic textiles, vehicle tires, city dust, road markings, marine coatings, personal care products and cosmetics, and plastic pellets (first sentier investors (FSI)-and-Mitsubishi United Financial of Japan Financial Group (MUFG)-Sustainable-Investment-Institute-microplastic-pollution-report-may-2021).

Based on size, they can be classified as: MP (>2.5 cm), mesoplastic (5 mm~2.5 cm), MP (large: 1–5 mm, small: 1 um–1 mm), nano plastic (<1 um) [6-9]. MPs are plastic particles smaller than 5 mm in size that result from the ageing of bigger plastic waste [10]. Classification of MPs can be done based on their characteristics and origin. Based on the source, MPs are classified into two different types: primary MPs and secondary MPs. Primary MPs include small-sized microbeads that are found in some cosmetics and cleaning products, which are directly released into the aquatic system. Secondary MPs are formed from the fragmentation of larger plastic items through various degradation processes, including biodegradation, physical degradation, photo degradation, and chemical degradation. Based on morphology, MPs were further classified into several types, which include granules, microfibers, plastic pellets, films, foam plastics., [11]. Another important classification is based on chemical composition, which includes PVC, PS, PE, PP, and PE terephthalate. The diverse origins, types, and degradation processes of MPs result in a wide range of characteristics and properties, which complicates their separation and identification [12,13]. Apart from these synthetic polymers, there are biopolymers from natural sources that considerably helped in biomedicine [14], such as biodegradable nanosized, thermo-reversible buffered gels [15]. The process, such as bioremediation, helps to degrade complex polymers [16].

Developing concordant methods for analysis, detection, and management of MPs remains a significant challenge. To develop effective mitigation

Table 1: The summary of synergistic adverse effects of microplastics with drug combinations *M. anguillicaudatus*

S. No.	Plastic type	Combination drug/ compound	Effect	Organism	Reference
1	Microplastics	Excess boron	• Reduction in chlorophyll-a concentration, oxidative damage, photosynthetic activity, and microcystin.	*Microcystis aeruginosa*	Zhang *et al*. 2023
2	Polystyrene microplastics	Tetracycline hydrochloride	• Reduced gut microbial diversity	Male ICR Mice	Wang *et al*. 2023
3	Microplastics	Methamphetamine	• The oxidative damage of algae, apoptosis, and the filtration rate of snails were significantly increased.	Green algae and snails	Wang *et al*. 2020
4	Microplastics	Heavy metals and Ciprofloxacin	• Acute toxicity	*Photobacterium phosphoreum*	Lv *et al*., 2023
5	Microplastics	Amphetamine	• Acute toxicity, growth suppression, reduced photosynthetic pigment concentration, oxidative stress, and lipid peroxidation.	*Chlorella* pyrenoids (Freshwater algae)	Qu *et al*., 2022
6	polystyrene microplastics	Chlortetracycline	• An increase of *Prevotella*, *Faecalibacterium*, and *Megamonas* abundance was observed at the same time as an increase of total antibiotic resistance genes (ARGs), such as tetracycline ARG subtypes, in the gut microbiota. • *Streptococcus* and *Helicobacter* numbers increase, which may result in intestinal damage improvement.	Muscovy ducks	Liu *et al*., 2023
7	Microplastics	Procainamide and Doxycycline	• Growth rate and chlorophyll a concentration	*Tetraselmis chui* (Marine microalgae)	Prata *et al*., 2018
8	Microplastics	Amitriptyline hydrochloride	• Shortened hatching time, body length, and neurotoxicity in adult zebra fish • Decreased ocular levels of superoxide dismutase, catalase, and glutathione.	Zebra fish	Shi *et al*., 2023. and Zhang *et al*., 2023.
9	Microplastics	Nano ZnO (nZnO) and TiO2 particles	• Growth inhibition	Micro algae (*Tetraselmis helgolandica*	Li *et al*., 2021.
10	Polystyrene microplastics	3,6-dibromocarbazole	• Impacts on zebra fish embryo development.	Zebra fish	Zhang *et al*., 2024.
11	Microplastics	Perfluorooctane sulfonate	• Reproductive, endocrine, neuro, and immunotoxicity in zebra fish • Induced reactive oxygen species in gill and digestive gland tissues in *Scrobicularia plana clams.*	Zebra fish and *Scrobicularia plana clams*	Jian *et al*., 2024. and Islam *et al*., 2021
12	Microplastics	Polyvinyl chloride	• Impede the hatching rate of zebra fish embryos and induce zebra fish mortality.	Zebra fish	Wang *et al*., 2022
13	Microplastics	Triphenyltin	• Increased the immunotoxicity impact of lipid metabolic disruption and immunosuppression.	Common Carp (Cyprinus carpio)	He *et al*., 2023
14	Microplastics	Venlafaxine	• lipid peroxidation damage in liver tissue.	Pond loach (*Misgurnus anguillicaudatus*)	Qu *et al*., 2019

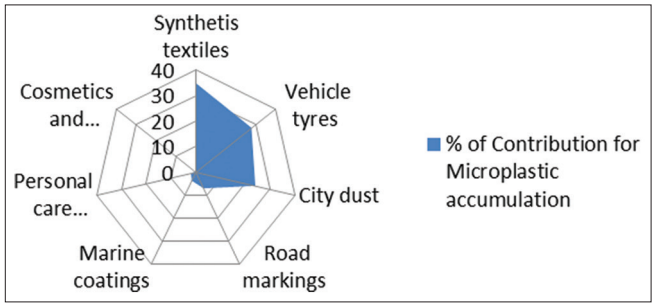

Fig. 1: The percentage contribution of sources for microplastic accumulation

strategies against the effects of MP pollution on the environment and human health, understanding the complexities associated with it is critical. As such, a review article here focused on one of the most critical aspects often ignored or sidestepped when dealing with MP pollution: the interaction between MPs and pharmaceuticals. While extensive research has been conducted on the environmental and health impacts of MPs, their synergistic effects with drugs have not been thoroughly explored. This review will examine how MPs interact with various drugs, including antibiotics and other pharmaceuticals, and the potential consequences of these interactions on the environment. Understanding these interactions is crucial for developing comprehensive strategies to address the multifaceted challenges posed by MPs. Table 1, Figs. 1 and 2 depict the summary and combination effects of MPs with drugs.

METHODS

Literature search and data compilation

Many peer-reviewed publications were searched systematically using online databases such as Google Scholar, Science Direct, Scopus, and PubMed. The data were searched using keywords, abstract, and title. Terms, such as MP, synergistic effect, and adverse effect, were searched in databases. Our extensive search resulted in many papers; of them, the most relevant papers were collected based on criteria such as (1) combination drugs; (2) adverse effects; (3) synergistic effects; (4) living organisms, and (5) types of plastic. Our initial search yielded many papers, and later, based on search criteria, we retained the following studies, which are appropriate to this review.

THEORY AND DISCUSSION

The negative impacts on microalgae are due to both MPs and excess boron. The authors reported that the production of microcystin (MC) in *Microcystis aeruginosa*, oxidative damage, chlorophyll-a content, and photosynthetic activity were all impacted by the combination of excess boron and three kinds of surface-altered MPs: Plain (PS-Plain), amino altered (PS-NH_2), and carboxyl altered (PS-COOH) as shown in the Fig. 3. The greatest inhibition rate of 18.84% in *M. aeruginosa* was demonstrated by the amino-modified polystyrene (PS-NH2), compared to −12.56% and −8.03% for *M. aeruginosa* when using PS-COOH and PS-Plain, respectively. B inhibition was lessened by PS-NH2, but increased by PS-COOH and PS-Plain. The combined exposure of excess boron and PS-NH2 has a more effect on Algal cells, oxidative damage, the structure of the cell, and production of MC than does the combined exposure to PS-COOH and PS-Plain [17].

Fig. 2: The combination effect of microplastics with some drugs

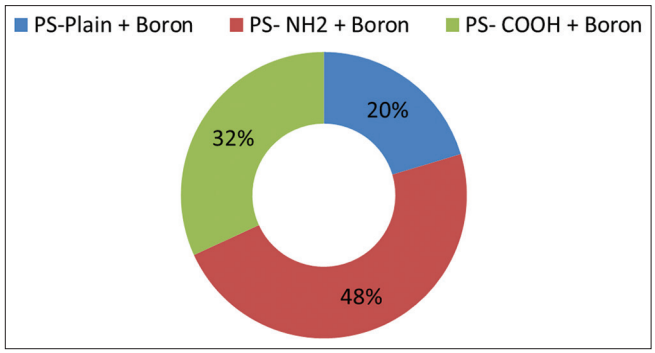

Fig. 3: The extent of the negative impact of microplastics in combination with boron on *Microcystis aeruginosa*

Both polystyrene MPs (PS-MPs) and tetracycline hydrochlorides (TCHs) are environmental emerging pollutants that are harmful to human health. They asserted that exposure to both PS-MPs and tetracyclines results in toxicity to the intestinal segments of mice. Except for the ileum, the combined therapy has an ameliorative adverse effect on the segments of the intestine. The gut microbiota analysis showed that PS-MPs and/or TCH, and especially PS-MPs, decreased the variety of gut microbes. Male ICR mice were chosen, and for 5 weeks, they were subjected to TCH and PS-MPs. Subsequently, the associated issues with intestinal flora and the varying damage to distinct intestinal segments were discovered. In addition, PS-MPs and TCH had an impact on the microbiota metabolic activities, specifically with protein digestion and absorption. One possible explanation for the functional and physical impairment brought on by PS-MPs and TCH could be dysbiosis of the flora in the gut [18].

MPs and chiral illicit drug methamphetamine affect the green algae and snails. They said that, as a rule, racemic methamphetamine caused less toxicity, and similarly, combining exposure to MPs and racemic methamphetamine will bring about acute toxicity in aquatic organisms. They chose non-functionalized PS-MPs (2.5% w/v of 10 mL solution at 700 nm detection) and green algae *Chlorella pyrenoidosa*, as well as freshwater snails Cipangopaludina cathayensis. He chose the snails' average weight of 2.5±0.2 g for this study. *C. pyrenoidosa* showing Shift of EC_{50} from 0.77 to 0.32 mg/L.

and Cipangopaludina cathayensis showing a shift of LC_{50} (lethal concentration) from 4.15 to 1.48 mg/L in combination, in combination with MPs, the acute toxicity of methamphetamine against the two species was elevated markedly. Three different methods of exposure to Cipangopaludina cathayensis and *C. pyrenoidosa* were carried out at 25±10°C in a dark environment. They include (a) exposed to racemic methamphetamine concentrations of 0.01–15 mg/L, (b) exposed to racemic methamphetamine at the same concentrations and to concentrations >20 mg/L of MPs, and (c) exposed to 20 mg/L of MPs. Oxidative damage of algae (19.9–36.8 nmol/mg protein), filtration rate (41.2–65.4 mL/h), and apoptosis (which increased by about 2.17 fold) of snails were significantly higher after exposure to the mixture of methamphetamine with MPs than they were to methamphetamine alone. After secondary ingestion and accumulation of MPs, the distribution, enantioselectivity, and bioaccumulation factor/biomagnification factor

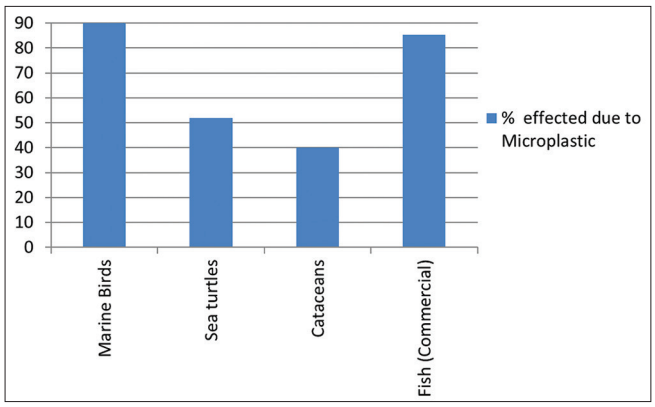

Fig. 4: The percentage of effect of microplastics on different marine dependent animals [55,56]

of methamphetamine were significantly altered [19].

The combination of Mps, heavy metals, and ciprofloxacin causes acute toxicity in *Photobacterium phosphoreum.* The average diameter of the used PE particles was 50 µm, 100 µm, and 150 µm. At various environments (pH and salinity) conditions, the process of drug adsorption of ciprofloxacin on MPs was studied. From Fourier transform infrared spectroscopy, it was analyzed that the drug ciprofloxacin adsorbed physically on PE-MPs. The Freundlich model fits fine at 25°C, indicating that the ciprofloxacin adsorbed on PE-MPs has a multi-layered structure. MP ciprofloxacin adsorption by ciprofloxacin was impacted by heavy metals such as Cu^{2+}, Cd^{2+}, Cr^{3+}, Pb2+, and Cr6, and dependent upon the type of metal ion, concentration, and valence state. Acute toxicity of the MP-ciprofloxacin-Cu^{2+} complex, along with MPs, was studied against *P. phosphoreum*, a luminescent bacterium. Results obtained indicate that the PE toxicity in the MP-ciprofloxacin-Cu^{2+}complex is primarily due to Cu^{2+} and ciprofloxacin rather than MPs [20].

A study was carried out by MPs to evaluate the combined effects of amphetamine and MPs on *Chlorella* pyrenoids, a type of freshwater algae. They observed oxidative stress, lipid peroxidation, photosynthetic pigment content, growth inhibition, and acute toxicity caused by these chemicals. This is an agglomeration test where algae samples were studied in the presence of MPs with a mean size of 150 µm. It went on testing various doses of amphetamine by counting the number of algal cells at the end to detect changes. The results show with reduced algal cell count, to the extent of 18–56%, among those treated with different concentrations of MPs of 5–50 mg/L. Besides, the enantioselectivity of amphetamine, which can normally be degraded by the algae, was drastically reduced by the presence of MPs since it showed an ejection fraction (EF) value of 0.41 as compared to the respective EF value of 0.34 in the pure amphetamine after a 21-day exposure period. Consequently, the review concluded that MPs act as a carrier, enhancing amphetamine toxicity to *Chlorella* pyrenoids [21].

An investigation was done on the impact of chlortetracycline (CTC) bioaccumulation and associated risks in the intestines of Muscovy ducks exposed alone and together with PS-MPs and CTC for a period of 56 days. The ducks exposed to MPs had lower levels of CTC bioaccumulation in their intestines and livers, whereas excretion of CTC in their feces was higher. Exposure to MPs brought disruption in the intestinal barrier, generation of oxidative stress, and an inflammatory response. The incidence of dysbiosis, characterized by an increase in the abundance of *Streptococcus* and *Helicobacter*, which may exacerbate intestinal damage caused by MPs, was reported in the microbiome study. It was evidenced that exposure to MPs combined with CTC altered gut microbiota, leading to the reduction of intestinal damage. In metagenomic sequencing, tetracycline antibiotic resistance gene (ARG) subtypes of total ARGs were more abundant, as well as the abundance of *Prevotella*, *Faecalibacterium*, and *Megamonas* increased in the combination of MPs and CTC. This result provides possible dangers of PS-MPs and CTC for ducks living in aquatic habitats [22].

A bioassay conducted lasting 96 h to assess the toxicity of procainamide (P) and doxycycline (D) to marine microalgae *Tetraselmis chui*, both individually and in mixtures with MPs of 1–5 µm diameter. The parameters monitored were chlorophyll a content and growth rate, with EC10, EC20, and EC50 values determined. Growth rate is not importantly affected up to 41.5 mg/L by MPs alone, but the concentration of chlorophyll a decreased at 0.9 and 2.1 mg/L of MPs; no extra decrease in chlorophyll a could be seen at increased concentrations. The 96-h EC50 values, for chlorophyll concentration and growth rate, were as follows: 104 and 143 mg/L for procainamide alone; 125 and 31 mg/L for procainamide and MPs; 22 and 14 mg/L only to doxycycline; and 11 and 7 mg/L for doxycycline in combination with MPs. The curves of toxicity of each drug alone and in combination with MPs were significantly different for both procainamide (chlorophyll concentration) and doxycycline ($p<0.001$). Hence, both drugs were toxic to *T. chui* at the low ppm range, with combined MP-pharmaceuticals more toxic than pharmaceuticals alone [23].

Amitriptyline hydrochloride (AH) is a well-known tricyclic antidepressant that is found as a pharmaceutical residue in large water bodies such as rivers [24]. Reuptake of serotonin and noradrenaline serotonin into presynaptic nerve terminals was inhibited by AH [25]. Kun Chen *et al.* investigated the toxicity of hydrophilic pharmaceutical residues and MPs in combination in aquatic species. They use Zebra fish (*Danio rerio*) as an experimental organism and evaluate the effects by employing oxidative stress indicator analysis, 16SrRNA amplicon sequencing, and histological analysis. Amitriptyline exposure results in significant toxicity in fish, such as shortened hatching time, body length in zebra fish, and neurotoxicity in adult zebra fish. Adult zebra fish were exposed to MPs (440 µg/L PS), AH (2.5 µg/L), PS+AH (440 µg/L PS+2.5 µg/L AH), and, as a control, dechlorinated tap water was used for 21 days. The zebra fish's stomach is a large target for injury, and any exposure causes harm. Compared to the control group, PS+AH treatment significantly increased superoxide dismutase (SOD) and catalase activity, showing that combined exposure in the zebra fish gut may result in elevated reactive oxygen species (ROS) production. Exposure to PS+AH caused severe injuries in the gut, which included cilia defects, partial presence and rupture of intestinal villi, and gut bacterial communities shifts, increased proteobacteria abundance and actinobacteriota, whereas decreased Firmicutes abundance was observed. Bacteroidota and beneficial bacteria such as *Cetobacterium* cause dysbiosis in the microbiota of the gut and possibly cause inflammation in the intestine [29]. The combination of AH (2.5µg/L)+PS (0.44 mg/L), when exposed for 7 days, affects the vision of zebra fish (*D. rerio*). After 7 days of exposure, some abnormal behaviors are seen in fish, such as elevated locomotor activity significantly, increased frequency and period of shoaling behavior, and a decline in post-stimulation freezing. There are also some adverse effects, such as reduced ocular levels of glutathione, catalase, and SOD [26,27].

MPs can collect and accumulate metal oxides in aquatic environments due to their hydrophobicity and huge specific surface area. Major trace elements, including zinc, were detected on PE pellets recovered from beaches [28,29]. Polymers with different residues or chemical changes exhibit distinct adsorption processes for various contaminant species. For example, non-ionic polymers and metal oxides primarily adsorb via hydrogen bonding [30]. Nano-sized metal oxides, due to their numerous applications found abundantly in the environment, which include nano ZnO (nZnO) and nano TiO2 particles [31,32]. The combination of MPs and metal oxides has a deleterious effect on aquatic species' health, fertilization, cell survival, and growth [33-36]. In an aqueous medium, nZnO interacts more than plastic particles. In aqueous conditions, ZnO interacts with H2O to produce Zn(OH)2, which then releases OH− ion to make Zn(OH)+ and Zn^{2+} ion [37,38]. Moreover, ions can be adsorbed onto nZnO particles, forming surface groups, which may impact the degree of their adsorption onto polymers [39]. Specifically, with polymer segments including fluorinated ethylene-propylene, polycarbonate, polytetrafluoroethylene, and polychlorotrifluoroethylene, the -OH

groups on the surface of nZnO can form hydrogen bonds [40]. However, both PE and PS can only establish hydrogen bonds at oxidised sites. Scientists predicted that Mps and metal oxide affect the growth of microalgae and tested this hypothesis using *Tetraselmis helgolandica* and nZnO as microalgae and metal oxide, respectively. The study of the adsorption of nZnO on MPs was done by the use of a scanning electron microscope, whereas inductively coupled plasma mass spectrometry was used to measure the Zn levels and the compound form of Zn, which is on the surface of PE MPs via the use of X-ray diffraction analysis. The evaluation showed that 5.53–7.16% of the Zn in the suspension was adsorbed during the process of adsorption of nZnO on MPs, which were examined by scanning electron microscope, their Zinc levels were evaluated by Inductively Coupled Plasma Mass Spectrometry, and X-ray diffraction analysis was used to determine the compound form of Zn on the PE MPs surface. It has been reported that within the first 24 h of exposure, about 5.53–7.16% of the introduced Zn is adsorbed, and after adsorption, the Zn exists in the form of ZnO. Before preparing ten test suspensions ranging from 0.10 to 20.00 mg/L, an ultrasonically prepared stock suspension of nZnO (62.31 mg/L) was made using artificial seawater. Microalgae (104 cells/mL) were introduced to 20 mL of each mixture in 50-mL flasks four times. Growth inhibition was measured over 4 days. After 4 days of exposure, nZnO, PEMP/nZnO, ZnSO4, and PEMP/ZnSO4 decreased microalgae growth by 65.1±2.3% (61.2–67.5%), 55.7±3.9% (51.2–61.0%), 76.3±3.3% (72.5–81.2%), and 66.0±3.1% (60.0–68.7%), respectively. Compared to combined exposure, nZnO alone showed much higher growth inhibition ($p<0.05$). This also applies to Zn^{2+} and its combined exposure with polyethylene microplastics. Finally, they found that the presence of PEMP lowers the inhibitory impact of nZnO by 14.4% and Zn^{2+} by 13.5% [41].

Scientists find that the adverse consequences of combined exposure of PS-MPs and 3,6-dibromocarbazole (3,6-DBCZ) on zebra fish. Investigations have indicated significant effects on zebra fish embryo development when exposed to single or combination concentrations of PS-MPs (10 mg/L) and 3,6-DBCZ (0.5 mg/L), resulting in noticeable abnormalities without impacting mortality or hatching rates. Notably, treatment with either 3,6-DBCZ or PS-MPs increased ROS levels in zebra fish embryos, resulting in apoptosis caused by oxidative stress. Surprisingly, the combined exposure to 3,6-DBCZ and PS-MPs had an antagonistic effect in zebra fish embryos, lowering both oxidative stress and apoptotic levels. Fluorescence tracing and 3,6-DBCZ enrichment analysis showed that the chorion effectively inhibited PS-MPs (5 and 50 μm) from entering zebra fish embryos at 55 h after fertilization (hpf). However, at the later stages (96–144 hpf), PS-MPs worked as carriers, allowing 3, 6-DBCZ to accumulate in zebra fish larvae and cause dioxin-like toxicity by consumption. 50-μm PS-MPs significantly increased the accumulation and dioxin-like toxicity of 3,6-DBCZ in zebra fish larvae compared to 5-μm PS-MPs. These findings highlight the substantial significance of microplastics as carriers of persistent hydrophobic pollutants, modifying their toxicity and bioaccumulation in aquatic species [42].

Per- and polyfluoroalkyl substances (PFASs), ubiquitous in industrial applications since the mid-20th century, pose environmental challenges due to their widespread use and persistence. Notably, perfluoro octane sulfonate (PFOS) emerges as a prevalent PFAS found in various environmental compartments worldwide. Its bioaccumulative nature adds to a number of negative impacts on organisms, including. Understanding the intricate interplay between MPs and organic pollutants, such as PFOS and its alternative, 6:2 chlorinated polyfluorinated ether sulfonate (F-53B), holds crucial implications for aquatic ecosystems. Despite extensive knowledge of their individual toxicities, research into their combined effects with MPs remains limited. To address these gaps, scientists, adult female zebra fish were exposed to PFOS/F-53B and MPs, alone or in combination, over 14 days. The presence of MPs in the exposure scenario reduced the amounts of freely dissolved PFOS and F-53B, but did not affect their bioaccumulation in zebra fish tissues. However, combined exposure to PFOS and MPs resulted in significant liver oxidative stress, immunoinflammatory responses, and abnormalities in energy metabolism. Surprisingly, the study of gut microbiota using *16SrRNA* gene sequencing indicated significant changes following simultaneous exposure to F-53B and MP. Functional enrichment analysis further elucidated the potential interference of these microbiota alterations with immune and energy metabolic pathways, indicating their significant role in host health. They discovered associations between alterations in gut microbiota and immunological and energy metabolism indices, highlighting the complex interplay between microbiota dysregulation and negative health consequences. Collectively, these findings highlight the exacerbated liver immunotoxicity and energy metabolism disturbances resulting from combined PFOS/F-53B and MPs exposure in adult zebra fish, implicating gut microbiota dysregulation as a potential mediator of these effects [43].

In marine ecosystems, MPs pose a widespread threat, causing adverse reactions upon ingestion by organisms. Acting as carriers for contaminants, they challenge marine life, influenced by factors such as size, shape, and composition. Researchers investigated the accumulation and toxicity of MPs, both virgin and PFOS-contaminated, in *Scrobicularia planaclams*. Clams were subjected to low-density PE MPs (4–6 μm and 20–25 μm) with or without PFOS for 14 days. Assessments included MP ingestion, PFOS accumulation, filtration rates, and biomarker analyses. Results showed size-dependent MP ingestion and PFOS accumulation, while PFOS levels did not affect accumulation rates. Filtration rates decreased post-exposure, indicating potential physiological impacts. Both virgin and PFOS-laden MPs induced ROS in gill and digestive gland tissues, disrupting antioxidant defences. Larger virgin MPs had stronger effects, as confirmed by biomarker responses. In addition, an anti-apoptotic response was observed in digestive glands across all MP treatments. These findings emphasize the need for comprehensive assessments to understand and mitigate MP pollution's impact on marine ecosystems [44].

MPs have a high specific surface area, high hydrophobicity, and surface charge that enable the mixing of MPs with other contaminants to exert dangerous effects on aquatic organisms. Based on real MP conditions, the researchers established a model for PVC-MPs fragmentation. The composition, shape, particle size, and zeta potential of PVC-MPs were therefore well explored. Single and combination exposures of PVC and di (2-ethylhexyl) phthalate (DEHP) were studied to find their effects on the hatchability of zebra fish embryos, mortality rates, toxicity caused by oxidative stress, and the development of hearts in the larvae of zebra fish. The PVC-MPs delayed the rate of hatching of zebra fish embryos but increased the mortality of zebra fish. DEHP, on the other hand, reduced the mortality but had no effect on the rate of hatching. Single exposure to PVC-MPs or DEHP resulted in the generation of ROS and activation of the antioxidant defense signaling pathway; however, feedback auto-regulatory action resulted in the Nrf2 signaling pathway from combined exposure, which could indicate the compensatory mechanism. The expression of genes related to cardiovascular development was also affected by the presence of single pollution, which made it lower. Mixed pollution, however, exerted the opposite effect on the expression of genes linked to cardiovascular development. Their findings offer valuable insights into the ecotoxicology of MPs in their natural state. By elucidating the complex interactions among PVC-MPs, DEHP, and zebra fish embryos/larvae, this study advances our understanding of the multifaceted impacts of MP pollution on aquatic ecosystems. Moreover, the identification of antagonistic effects in combined pollution scenarios underscores the importance of assessing pollutant interactions in ecotoxicological studies. Overall, the study will create a solid theoretical framework for biomonitoring and an ecological risk assessment of MPs in aquatic ecosystems [45].

Zhang *et al.* discovered that the combined exposure to triphenyltin and Mps to aquatic organisms has negative impacts. To investigate these findings, Common Carp (Cyprinus carpio) were subjected for 42 days. For this purpose, they set the triphenyltin and MPs concentrations to 1 mg/L and 0.5 mg/L, respectively. The effects of MPs and triphenyltin on the carp gut–brain axis were investigated by evaluating gut physiology and

biochemical parameters, gut microbial 16S rRNA, and brain transcriptome sequence. Their findings show that a single triphenyltin caused lipid metabolic disturbance, while a single MP caused immunosuppression in carp. When MPs were combined with triphenyltin, the latter exacerbated the former's immunotoxicity. They also explored the gut-brain axis connection of carp immunosuppression, which provided fresh insights into the combined toxicity of MPs and TPT. At the same time, their research lays the theoretical groundwork for analyzing the coexistence risk of MPs and TPT in the aquatic environment [49].

Venlafaxine, a selective serotonin norepinephrine reuptake inhibitor, is a common antidepressant medication found in aquatic ecosystems such as rainbow trout, Daphnia magna, and hybrid striped bass [46-49]. Venlafaxine is licensed and prescribed as a racemic mixture of two enantiomers [50]. The ecological effect of rac-venlafaxine on aquatic species was assessed, and it was concluded that venlafaxine may affect zebra fish egg production and kidney tubule morphology after 6 weeks of exposure. Chiral medicines such as ibuprofen, propanol, and venlafaxine have been used as chiral signatures to determine the function of biological attenuation and distinguish between abiotic and biotic components in surface water [51-53]. They discovered that the racemic combination of venlafaxine and metabolite has a deleterious impact on the loach *Misgurnus anguillicaudatus*. They undertake the following experiments on *M. anguillicaudatus*, which provide unexpected findings. (1) Sorption experiment, in which venlafaxine and O-desmethylvenlafaxine were absorbed into MPs in 6 days with the addition of sodium azide. (2) Oxidative stress assay, they conducted this over 4 days in two scenarios: One in which the loaches are exposed to a racemic mixture of venlafaxine and O-desmethylvenlafaxine at the desired concentrations, and another in which they are exposed to the same mixture along with MPs. After the duration, they extract liver tissue from the organism and test the levels of SOD and malondialdehyde. Venlafaxine and O-desmethylvenlafaxine have quite distinct effects on the loach liver. SOD concentrations were higher in the same concentration treatments than in O-desmethylvenlafaxine, showing that O-desmethylvenlafaxine may produce more oxygen radicals than the parent medication. This finding is congruent with venlafaxine treatment, which indicated that the R-enantiomer produced more oxygen radicals in liver tissue. Oxygenic radicals can promote lipid peroxidation, which exacerbates liver tissue damage. At the same exposure level, MDA levels in O-desmethylvenlafaxine were higher than in venlafaxine treatments. MDA levels in venlafaxine and O-desmethylvenlafaxine treatments were higher in R-enantiomers compared to S-forms and racemate, showing that R-enantiomers may induce more lipid peroxidation damage in liver tissue. As a result, they found that the combination of MPs, venlafaxine, and their metabolite has a negative impact on *M. anguillicaudatus* [54].

CONCLUSION

This review reveals that MPs, in combination with some drugs, adversely affect living organisms individually. Various studies depict that the pollution of MPs and unused drugs in the environment, especially in the aquatic environment, disturbs the biological system. This combination became a curse to some organisms as they altered their natural phenomenon. There is a need for extensive study on the combination of MPs with drugs and other chemical compounds that commonly pollute the aquatic environment. Immediate measures should be taken to control the pollution of MPs with drugs and their combined toxicity. This review provides a foundational understanding of the hidden risks posed by MPs and pharmaceutical interactions, highlighting critical research gaps. It guides future experimental studies on toxicity, bioaccumulation, and environmental persistence, fostering a deeper investigation into long-term health and ecological effects. Policymakers and environmental agencies can use the findings to develop stricter regulations on plastic and pharmaceutical waste management. The review also promotes interdisciplinary collaboration, bridging environmental science, toxicology, and pharmacology to address this complex issue.

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AUTHOR'S CONTRIBUTION

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