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Toxic effects on enzymatic activity, gene expression and histopathological biomarkers in organisms exposed to microplastics and nanoplastics: a review

Indrajit Patra[1], Dinh Tran Ngoc Huy[2], Fahad Alsaikhan[3], Maria Jade Catalan Opulencia[4], Pham Van Tuan[5], Kurbanoy Chorievna Nurmatova[6], Ali Majdi[7], Shehla Shoukat[8], Ghulam Yasin[9], Ria Margiana[10,11,12], Tony R. Walker[13] and Samaneh Karbalaei[14*]

Abstract

Microplastics (MPs) and nanoplastics (NPs) have become an important global environmental issue due to their widespread contamination in the environment. This review summarizes existing literature on the effects of MPs/NPs on three important biomarkers including enzymatic activity, gene expression, and histopathology in various organisms from 2016 to 2021 and suggests a path forward for future research. Application of enzymatic activity, gene expression, and histopathology biomarkers are increasingly used in experimental toxicology studies of MPs/NPs because of their early signs of environmental stress to organisms. Between 2016 to 2021, 70% of published studies focused on aquatic organisms, compared to terrestrial organisms. Zebrafish were widely used as a model organism to study adverse impacts of MPs/NPs. Polystyrene (PS) were the most important polymer used in experimental toxicology studies of MPs/NPs. Fewer studies focused on the histopathological alterations compared to studies on enzymatic activity and gene expression of different organisms exposed to MPs/NPs. There is a growing need to better understand toxic effects of environmentally relevant concentrations of MPs/NPs on enzymatic activity, gene expression, and histopathology biomarkers of both aquatic and terrestrial organisms.

Keywords: Microplastics (MPs), Nanoplastics (NPs), Gene expression, Enzyme activity, Histopathology

Introduction

Plastic is one of the most widely used materials in modern society [161]. However, current production and consumption is unsustainable [13]. Plastics are widely used for a wide range of consumer products [41]. Since the creation of the first commercial plastic polymers in the 1950s, an estimated 9.2 billion metric tons of plastic has been produced and more than 6.9 billion metric tons has ended up in landfills around the world, or worse, 'leaking' into the environment [41]. In 2019, global plastic production reached 368 million metric tons [123], but is estimated to double within 20 years [123]. Synthetic plastic production has increased by 8.3 billion metric tons since the 1950s, and is anticipated to reach 33 billion metric tons by 2050 [132]. Asia is the largest manufacturer of plastic materials (51%,China: 31%, Japan: 3%, rest of Asia:18%, followed by Europe (16%, North American Free Trade Agreement (NAFTA: 19%, Middle East Africa (7% and Latin America (4% [123].

Plastics comprise different polymer types, such as polyethylene (PE), polystyrene (PS), polyvinylchloride (PVC), polyethylene terephthalate (PET), polyamide

*Correspondence: s.karbalaei@alzahra.ac.ir; samaneh.karbalaei@gmail.com

[14] Department of Biotechnology, Faculty of Biological Science, Alzahra University, Tehran, Iran
Full list of author information is available at the end of the article

(PA), polypropylene (PP) and polyhydroxybutyrate (PHB), based on polymer structure and characteristics and have different applications [71]. Over production and use of plastics, followed by waste mismanagement has resulted in increasing amounts of plastic waste leaking into the environment. Borrelle et al. [13] estimated that 19–23 million metric tons of plastic waste generated globally in 2016 entered aquatic ecosystems but is predicted to reach up to 53 million metric tons annually by 2030. Most consumer plastics are designed for single-use with limited recyclability (< 10%), and has resulted in increased global production and consumption leading to unprecedented plastic waste generation and widespread plastic pollution [13, 137]. In 2015, around 60–99 million metric tons of plastic waste globally were produced, and it is expected to reach 155–265 million metric tons by 2060 [79].

Plastic pollution caused by tiny plastic particles are classified according to their sizes. Microplastics (MPs) are particles < 5 mm [134], but even classified from 1 to 1000 µm [118], and nanoplastics (NPs) are particles < 1 µm or 1000 nm [5, 23, 38, 54, 75, 140]. Although a clear distinction between MP and NP size definitions have not been agreed upon [54], this review uses size definitions of < 5 mm and < 1 µm for MPs and NPs, respectively.

MPs/NPs are classified as primary or secondary based on their origin in the environment. Primary MPs/NPs are intentionally manufactured plastics in micro/nano-size ranges (e.g., microbeads) intended for industrial or commercial uses including hygiene and personal care products like scrubbers in cosmetics or clothing drilling fluids and paints that are easily discharged into the environment [70]. Secondary MPs/NPs arise from physical, chemical, and biological degradation of larger plastics discarded in the environment. Sources of secondary MPs/NPs include water bottles, wastewater treatment plants, disposable packaging, and agricultural mulch film [39, 122].

Organisms that ingest MPs/NPs are exposed to a wide range of chemicals from various plastic additives added during production and other pollutants [116]. Plastic additives are plasticizers (e.g., phthalates, bisphenol A) colorants, UV filters, flame retardants. Furthermore, persistent organic pollutants such as polychlorinated biphenyls (PCBs), organochlorine/organophosphorus pesticides, polycyclic aromatic hydrocarbons (PAHs) and metals can be adsorbed onto MP/NP surfaces in the aquatic environments [74, 135]. One recent study reported that combinations of MPs and chlorpyrifos reduced nutritional parameter concentrations in muscle of rainbow trout (*Oncorhynchus mykiss*) [50].

As of 2020 there have been 2500 studies on occurrence of MPs/NPs in the environment, sampling techniques, and impacts on organisms [5, 12]. Exposure of organisms to MPs/NPs produces physical and chemical toxic effects, including enzymatic activity, gene expression, and histopathological effects [1, 52, 58, 69]. Ingestion of MPs/NPs alters expression of immunity-related genes, genes associated with immune function and antioxidant enzyme [30, 109, 164]. Oxidative stress is an important response that induces following interaction between plastic and cellular environment [109]. Reactive oxygen species (ROS) are generated by induction of oxidative stress, which is one of the most well-documented toxicity mechanisms of MP/NP polymers in organisms [109, 117]. Overproduction of ROS is damaging to gut homeostasis and increases lethality of immune regulatory catalase. Thus, antioxidant enzyme activity against ROS is critical [117]. MPs alter digestive enzyme activities and energy acquisition in the marine bivalve (*Mytilus galloprovincialis*) [158].

Vertebrates including fish and mammals are considered suitable model organisms for the investigation of different types of pollution. The potential of various model organisms exposed to MP pollution is dependent on characteristics of individual species such as environmental stress tolerance, their ecological status, type of feeding, behavioral flexibility and life history strategies, and MPs properties such as their type, size and concentration. Zebrafish were one of the most studied groups of fish in toxicological studies [83, 101, 127, 162]. The main characteristics that render zebrafish interesting for toxicological studies are their small size, genetic similarities with humans, ease of breed, short life cycle and inexpensive maintenance. Mollusca and Crustacea are also known as suitable model organisms due to their feeding filtration type, omnipresence, their role in trophic systems, which are primarily primary consumers, and major contribution to human nutrition. According to review of previous studies, Molluscs and Crustaceans were marked as the most studied taxa among invertebrates [4].

Although there has been a dramatic increase in the number of studies on toxicological effects of MPs/NPs on organisms, there has been no comprehensive review of this literature. This comprehensive review examined and analyzed existing literature on enzymatic activity, gene expression, and histopathological effects on terrestrial and aquatic organisms exposed to individual MPs/NPs and their combination with other pollutants. Gaps identified in the literature based on this review will help inform recommendations for future research.

Methodology

Research papers from January 2016 to November 2021 were searched from ScienceDirect, Google Scholar and Web of Science databases using the terms ("microplastic" OR "nanoplastic") and ("enzyme activity" OR "gene expression" OR "histopathology"). The search returned 249 research papers on the effect of MPs/NPs on enzyme activity, gene expression and histopathology with different terrestrial and aquatic organisms used as experimental organisms (Additional file 1: Table S1). Studies on interactive effects of MPs/NPs and other contaminants were also included in this review.

All types of MPs/NPs (i.e., PA, PE, PP, PVC, PET, PHB and PS) particles of different sizes of nano and micro were included in this study. The PE family includes both high density PE (HDPE) and low-density PE (LDPE). Plastic particles of 1 µm to 5 mm were considered MPs, whereas particles of < 1 µm were considered NPs. MP size ranges were assigned according to de Sá et al. [25] into the following classes: < 50 µm (including NPs); 50–100 µm; 100–200 µm; 200–400 µm; 400–800 µm; 800–1600 µm; > 1600 µm; or not specified.

Studies were summarized according to the following criteria: species and common name of organisms, MPs type and size, contaminants absorbed to MPs, MPs and contaminant concentration, duration of the experiment, toxicological effect (enzyme activity, gene expression and histopathology) and organism tissues (Additional file 1: Table S1). Any article that included data from more than one of the above parameters resulted in the same number of studies as the number of elements per assumption. For example, if one article only reported on fish, it was regarded as one study; however, if it reported on both fish and Mollusca, it was regarded as two studies. Therefore, the number of studies examined in the results shows the number of interactions of the parameters (e.g., organism group, MP type, MP size), rather than the total number of publications. Figures were created using Microsoft Excel 2016.

Results and discussion

Reports of organisms exposed to MPs/NPs

MPs/NPs are easily ingested by aquatic and terrestrial organisms and transferred along the food chain [21, 65]. Contamination of MPs/NPs in terrestrial environments is considered potentially more hazardous compared to aquatic environments due to their direct impacts on food chains such as plants, insects, and animals that are directly consumed by humans [157]. Previous reports suggest that soil is a major terrestrial sink of MPs/NPs [112]. Thus, MP/NP pollution in terrestrial environments might be 4- to 23-fold greater than in oceans [56].

This review returned 249 research papers on the effects of MPs/NPs on enzyme activity, gene expression and histopathology of different organisms. Fish (38.15%), Mollusca (17.67%), crustacea (9.64%) and mammals (6.43%) were the most studied groups, whereas limited studies (< 1%) were conducted on amphibians and microbiota (Fig. 1). Most studies focused on aquatic organisms (~ 70%), compared to terrestrial organisms, presumably due to different methods and difficulties in maintaining and handling terrestrial organisms under controlled

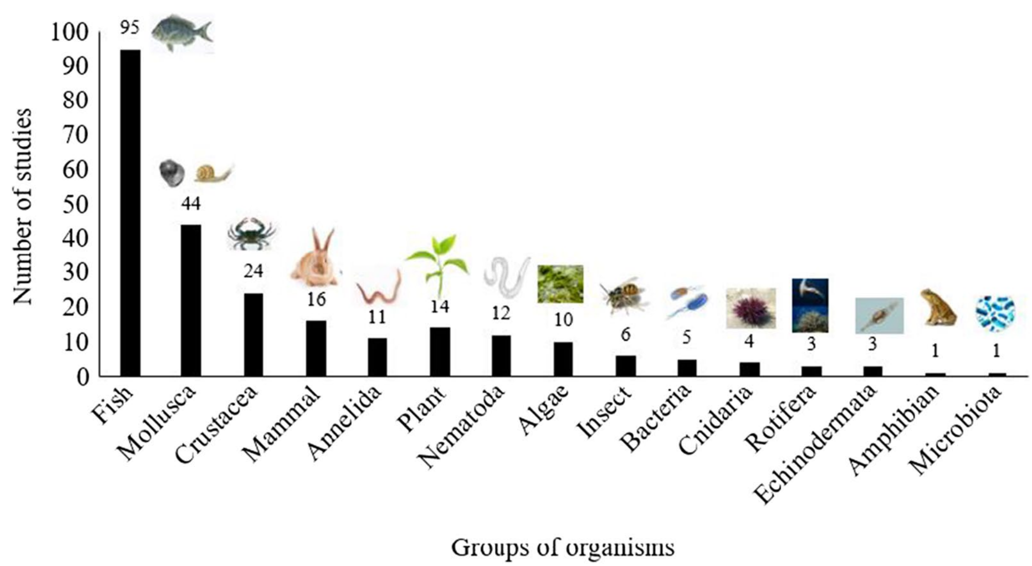

Fig. 1 Number of studies per groups of organisms exposed to MPs/NPs with enzymatic activity/gene expression/histopathological effects in 2016 to 2021

laboratory conditions. Zebrafish were increasingly used as a model organism (43.47%) among fish studies because of their small size, ease of rearing, short life cycle, genetic similarities with humans and cost-effective maintenance. Around 100–200 eggs are produced in a single spawning of zebrafish. In addition, larvae can survive for 7 days on yolk sac contents, providing a reliable and cost-effective method for investigating potentially toxic effects of environmental pollutants [12].

Control groups (negative and positive controls) in toxicological studies play an important role to compare pollutant effects on study organisms. The control group is free of carriers known as a negative control group. For example, in a study on MPs accumulation patterns and transfer of BaP to *D. rerio*, the positive control group of BaP (100 nM waterborne BaP) was analyzed separately against the negative control group to show detectable biomarker response in organisms.

In studies on effects of MPs/NPs on Molluscs, species such as *Mytilus galloprovincialis* [6, 37, 43, 114, 158, 169], *Mytilus coruscus* [44, 48, 139], *Mytilus spp.* [22, 113, 120, 131], and *Mytilus edulis* [104, 105], and clams such as *Corbicula fluminea* [45, 46, 90], *Tegillarca granosa* [150, 154, 189], *Mactra veneriformis* [183], and *Ruditapes philippinarum* [119, 143] are the most studied Mollusca. Previous studies have shown that mussels can easily ingest MPS/NPs via their effective water filtration capacity in natural [184] and laboratory conditions and are considered as reliable model organisms for experimental studies [2, 120, 169]. In addition, MPs/NPs are captured and aggregated in gills and digestive glands or adhere to other organs such as adductor muscles, foot and mantle of mussels that lead to harmful toxicological effects. For example, *M. galloprovincialis* exposed to 3 μm PS-MPs showed modulation of multixenobiotic resistance activity [37]. Among studies on Mollusca organisms, only one other study has considered the impact of PET-MPs on snails (*Achatina fulica*), in which MPs induced significant villi damage in gastrointestinal walls of snails and reduced glutathione peroxidase and total antioxidant activity [146].

Most studies on effects of MPs/NPs from 2016 to 2021 on Crustacea occur in shrimp and *Daphnia* species which are considered model organisms for toxicological research. Studies on shrimp species include *Litopenaeus vannamei* [58, 163, 168], *Penaeus monodon*, *Marsupenaeus japonicas* [164], *Artemia salina* [149], *Artemia franciscana* [32, 47, 160], *Macrobrachium nipponense* [89], and *Artemia parthenogenetica* [167]. Studies on *Daphnia* species include *Daphnia magna* [34, 62, 81, 102, 153, 180], *Daphnia pulex* [97, 98, 171, 182]. In a study by Liu et al. [96, 97], typical environmental NPs concentrations of 1 μg L^{-1} modulated response of antioxidant defenses, gene transcription, vitellogenin synthesis and development in *Daphnia pulex*.

Mice were the most widely studied mammal model organism in experimental studies on effect of MPs/NPs on enzyme activity, gene expression and histopathology [49, 147, 185, 186]. Some studies also used rats [7, 57, 61]. Most research on the biological toxicity of MPs/NPs have been conducted on marine and aquatic organisms (e.g., fish and invertebrates). However, few studies have been performed on the health effects of MPs/NPs on higher trophic level organisms such as mammals (including humans). In medical research, mice and rats are the most commonly studied mammalian model organisms. Jin et al. [68] showed 0.5 μm, 4 μm, and 10 μm PS-MPs cause testicular inflammation and the disruption of blood–testis barrier in mice.

Other groups of organisms including Annelida (4.47%), plants (4.88%), and nematodes (4.88%) were used in some studies on the effects of MPs/NPs on enzyme activity, gene expression and histopathology (Fig. 1). Annelida species such as *Eisenia fetida* [85, 88, 176], *Tubifex* [138], *Lumbricus terrestris* [124] and *Eisenia andrei* [136] were used in different experimental studies. Lettuce (*Lactuca sativa*) [163], Soybean (*Glycine max L. Merrill*) [175], *Vallisneria natans* [165], Sea cucumber (*Apostichopus japonicus*) [108], rice (*Oryza sativa*) [172, 181], maize [121], *Utricularia vulgaris* [178], *Salvinia cucullate* [178], *Allium cepa* [106], cucumber (*Cucumis sativus*) [90], *Vicia faba* [66], wheat (*Triticum aestivum*) [92], radish, wheat and corn [42] were various plants exposed to MPs/NPs.

MP/NP pollution has been recognized as worse in agroecosystems rather than other terrestrial ecosystems because of intensive agricultural activities such as wastewater irrigation, high use of plastic mulch and sewage sludge [112]. MPs have been found in a wide range of agricultural soils around the world, with concentrations ranging from 10 to 12,560 MPs kg^{-1} [20, 42]. Furthermore, plant diversity is an important property of terrestrial environments, and over 300,000 species are the main food source for humans [35, 87]. Therefore, evaluating the ecotoxicology of MPs/NPs to food crops and other soil biota are an essential aspect of risk assessments due to their potentially adverse effects on crop yield and quality and trophic transfer to humans through the food chain. Most studies on the toxicity of MPs/NPs to plants were published in 2021, indicating that this is an emerging issue. However, the limited number of studies and uncertainty of results make it difficult to gain a better understanding of MP/NP effects of on terrestrial plant species and the underlying toxicity mechanisms.

Typical properties of a free-living nematode (*Caenorhabditis elegans*) include translucent body, tiny size, easy cultivation, and short generation cycle allows researchers to use nematodes as model organisms for toxicological studies [84]. In addition, gene expression, enzymatic activities and histopathological effects have been widely used to evaluate toxic effect of MPs/NPs on nematodes [18, 19, 86, 128, 129, 141, 179]. The first study was reported in 2018, which assessed the toxicity of PA, PE, PP, PVC and PS MPs/NPs in *C. elegans* [83].

Few studies were found on MP/NP effects of on algae and limited studies reported on insect (2.44%), bacteria (2.03%), Echinodermata (1.63%), cnidaria (1.22%), and rotifer (1.22%). Various species of algae including *Chlamydomonas reinhardtii* [28, 77, 177], *Euglena gracilis* [174], *Chlorella sp* [111], *Cladocopium goreaui* [148], *Karenia mikimotoi* [185], *Skeletonema costatum* [190], *Phaeodactylum tricornutum* [145], and *Chlorella vulgaris* [77] are applied on experimental studies and enzymatic activities and gene expression are investigated. However, no studies have investigated histopathological effects of MPs/NPs on algae. Microalgae are common in all aquatic environments and occupy lower trophic levels [27]. Microalgae have advantages in environmental purification (e.g., wastewater) and short growth cycles [145].

Studies have used insects including honeybees (*Apis mellifera*) [26, 164], *Chironomus riparius* [17, 110, 142], *E. fetida* as model organisms exposed to MPs/NPs, where enzymatic activities gene expression and histopathological effects were observed. Honeybees are important pollinators of crops, and their presence is critical for preservation of biodiversity within environments [60]. In addition, honeybees are potential sentinel monitors for evaluating environmental pollution, because of their sensitivity they are affected by environmental contaminants (e.g., heavy metals) [8]. Liebezeit and Liebezeit [93] indicated that honey was contaminated by MP fibers (40 μm to ~ 9 mm) and fragments (10–20 μm), which has garnered attention from scientists as well as media.

Microorganisms including heterotrophs, autotrophs, and symbiotic organisms are attached and grow on marine plastics, which may act as vectors [130]. Many resistant bacteria have been detected on MPs in aquaculture environments. *Arcobacter* and *Colwellia* in seafloor sediment can colonize on LDPE [53]. *M. aeruginosa*, a dominant species causes cyanobacterial blooms showed that the activity of superoxide dismutase (SOD) and catalase (CAT) were significantly affected with exposure to PVC, PS and PE MPs [188]. Studies on the effects of MPs/NPs on bacteria began in 2020 and various effects of enzyme and gene expression were observed [80, 96, 103, 166, 188].

Recently, studies have reported hazards caused by MPs/NPs to Cnidaria (1.64%) such as *Tubastrea aurea* [91], *Symbiodinium tridacnidorum*, *Cladocopium sp* [133], and *Pocillopora damicornis* [152] and rotifer (1.23%) such as *Brachionus koreanus* [63, 64], and *Brachionus rotundiformis* [187]. Corals showed stress response [152], or histopathological effect [91] when exposed to the MPs/NPs environment. Little information is available on the impact of MPs/NPs on rotifers and coral species in coral reef ecosystems and underpinning mechanism. Rotifers play key roles to transfer material and energy into aquatic food chains. Also, they are reliable model organisms for MP/NP ecotoxicology studies due to their tiny size, short life cycle, genetic homogeneity, easy maintenance in laboratory, high fertility, and filter feeding behavior [64].

Only single studies have been conducted on Echinodermata [11], amphibians [78], and microbiota [173] organism groups. Sea urchins (*Sterechinus neumayeri*) are the most common echinoid in Antarctic shallow waters and play an important trophic role as predators and grazers. The widespread distribution of *S. neumayeri* across the Southern Ocean, as well as its high trophic flexibility, suggest that this organism could be exposed to MPs/NPs pollution, which could easily be taken up by *S. neumayeri* individuals and cells [11]. Given the worldwide decline in amphibian species, the threat of MPs/NPs to these organisms remains largely unknown [78]. MPs were reported in the gastrointestinal tract of several anuran species (e.g., *Pelophylax nigromaculatus*, *Rana limnochari*, *Microhyla ornata*, and *Bufo gargarizans*), demonstrating that amphibians can ingest MPs [59]. Tadpoles (*Physalaemus cuvieri*) subjected to PE MPs showed locomotor changes, anxiety-like behaviors, as well as antipredatory defensive response deficit after exposing to predators. Recently, Lajmanovich et al. [78] indicated that PE MPs (40–48 μm) significantly affected in enzymatic activities of *S. squalirostris.* No studies have investigated MPs/NPs impacts on gene expression and histopathology of tadpoles. Therefore, we proposed researchers to draw studies on the effects of MPs/NPs on these biochemical parameters. MPs have a significant impact on sedimentary microbial ecosystems [173]. Thus, investigating the influence mechanisms of MPs/NPs on estuarine microbiota is important to improve our understanding the ecological risk of MP/NP pollution in estuarine environments and on marine microbial communities.

MP/NP polymer types

MP/NP polymer types commonly reported include PS (58.48%) and PE (15.92%), followed by PVC (7.27%), PET (3.81%), PP (3.11%), LDPE (3.11%), HDPE (3.11%), PA (1.73%), PHB (0.35%) (Fig. 2), and not specified (3.11%). PS was the most common MP/NP type and was reported in 169 studies. PS and PE polymers are known as one of the most widely used plastics and synthesized for a broad spectrum of applications, including food packaging,

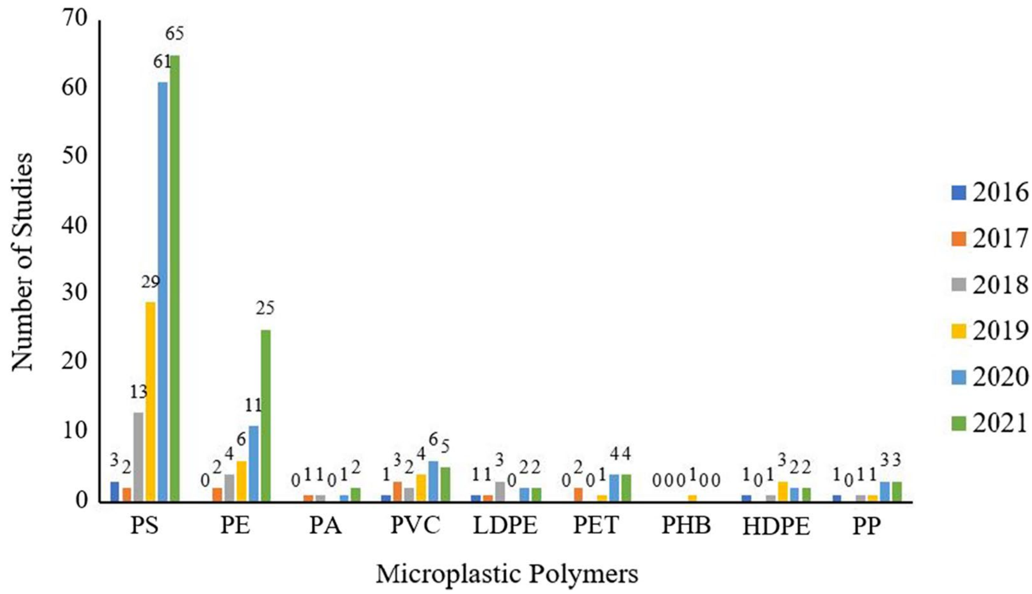

Fig. 2 Percentage of studies under the effects of MPs/NPs on enzymatic activity/gene expression/histopathology of organisms in 2016 to 2021. Different types of microplastics enumerated include PS, polystyrene; PE, polyethylene; PA, polyamide; PVC, polyvinylchloride; LDPE, low-density polyethylene; PET, polyethylene terephthalate; PHB, polyhydroxybutyrate; HDPE, high density polyethylene; PP, polypropylene

personal care products, building insulation. PP and PVC are also widely synthesized for using in different applications [123]. For example, PP is used in food packaging, sweet and snack wrappers, hinged caps, automotive parts, and PVC is used in window frames, profiles, floor and wall covering, and pipes [123]. In 2012, ~ 32.7 million metric tons of PS plastics was generated globally [95]. In Europe, PE comprised 25.31%, PP 19.4%, PVC 10%, and PS 6.2% of total production [123]. MPs/NPs polymers with a wide range of densities could also affect MPs/NPs behavior in the marine environment.

Styrene monomers in PS polymers is a carcinogen in nature and may pose a severe damage to the aquatic organism [149]. According to previous studies in the marine environment, PS, PE, PP, PVC, and PA are a frequently detected form of MPs NPs in the marine and terrestrial environment [12, 31, 83, 149]. PS is lightweight, and therefore it is easily mobile and therefore spreads across in the marine environment. PE and PET have lower and higher densities than water, respectively, that lead to the distribution of these MPs between different compartments [156]. Some studies provided important information for the ecological risk assessment of PP and PVC MPs/NPs in different organisms [16, 25, 85].

Although benthic aquatic organisms are likely to encounter denser polymers, such as PET and PVC, it is primarily dense microfibres that have been documented in benthic invertebrates [29, 125]. In aquatic environments, microbial communities (the plastisphere) can attach to and form a biofilm around MPs [170]. MP ingestion is another mechanism that can alter transport of MPs in the water column. MP ingestion can impact transport of MPs via vertical migration and long-range transport, and the buoyancy of particles can be altered through encapsulation in fecal pellets [125]. Sediments and soils can act as an important sink for MPs following weathering and transformation in the environment. Undisturbed sediments may even provide a useful temporal MP pollution archive [125]. This study showed that despite the wide distribution of PP and PVC in the marine environment, studies on their toxicological effects including enzymatic activity, gene expression, and histopathological effect on various organisms are limited. Given the particulate nature (nano/micro) of PP and PVC, it is crucial to investigate their hazardous effects in organisms. However, more studies are necessary to investigate the impacts of MPs/NPs on enzymatic activity, gene expression, and histopathology on different organisms.

Reports published by PlasticsEurope, [123] showed around 7.9% polyurethane (PUR) was applied in building insulation, pillows and mattresses, insulating foams for fridges. However, studies on the toxicological effects of PUR on different organisms are scarce. For example, combined effects of PUR foam MPs and polybrominated diphenyl-ether (PBDE) on the *E. fetida*, which showed accumulation of chemicals derived from MPs to *E. fetida* [40]. However, we have not found studies on the risk toxicological effects of PUR MPs/NPs on enzymatic activity, gene expression, and histopathology of different organisms. Therefore, more studies are required to providing information for future investigation addressing the effects of PUR MPs/NPs on various terrestrial and marine organisms. MPs/NPs can enter humans via food webs and pose potential health threats [15, 82]. It is estimated that 52,000 MP particles enter the human body per year through diet and an additional 69,000 MPs from inhalation [24]. Thus, the lungs and digestive systems are the first places of contact for MPs/NPs, and MPs/NPs penetrate these barriers before inducing of toxicities [107]. Direct contact of MPs/NPs and various cell types showed subsequent cellular toxicity, which depends on cell types and MPs/NPs physicochemical features. Thus, studies on the toxicological effects of MPs/NPs on human cells are required.

Different shapes of MPs including fragments, pellets, fibers, foam, films are found in aquatic ecosystems, which had different capacities for adsorbing pollutants, which had an impact on different biomarker responses. The MP fragments had various surface features, such as sharp edges with fractures and degraded rough surfaces, demonstrating their potential for internal abrasion, and may show morphological effects on fish gills. Sharp edges of PS MPs increase physical microinjuries of *O. mykiss* on the gill, gut, and skin [69]. Further studies are required to compare the toxicological effects of MPs shape on different tissues of living organisms.

Toxicological effects of MPs/NPs (enzymatic activity, gene expression, and histopathological effect)

Studies on the effects of MPs/NPs on enzymatic activity, gene expression, and histopathological effect of various organisms increased in 2020 and 2021 (Fig. 3). Studies on the effects of MPs/NPs on enzymatic activity (60 studies in 2020 and 53 studies in 2021) were higher than enzymatic activity (41 studies in 2020 and 44 studies in 2021) and histopathological effect (19 studies in 2020 and 41 studies in 2021) of organisms increased in 2020 and 2021.

Biomarkers are increasingly used as worldwide-recognized tools to evaluate the possible biological effects in organisms exposed to environmental contaminants. Biomarkers are also incorporated in environmental quality and environmental monitoring programs [10]. Biomarkers usually occur at the subcellular level of biological organization, and these subcellular responses to environmental stressors could appear before other impacts, such as disease, mortality, or population alteration [3]. The use of enzymatic activity, gene expression, and histopathological biomarkers in toxicology is becoming increasingly important for pollution assessments [17, 58, 94, 115].

This approach is also useful for determining the mechanisms by which environmental stressors induce complex molecular and cellular changes, as well as their interdependence. Among many suggested ecotoxicological biomarkers in the last decade, those biomarkers that show the imbalance between pro-oxidant and antioxidant status and lead to adverse effects such as DNA damage, gene expression, lipid peroxidation and enzyme inhibition as an earlier sign of environmental disturbance [10, 99]. Biomarkers of oxidative stress include alterations in antioxidant defenses and oxidative damage [99]. Genotoxic pollutants alter the

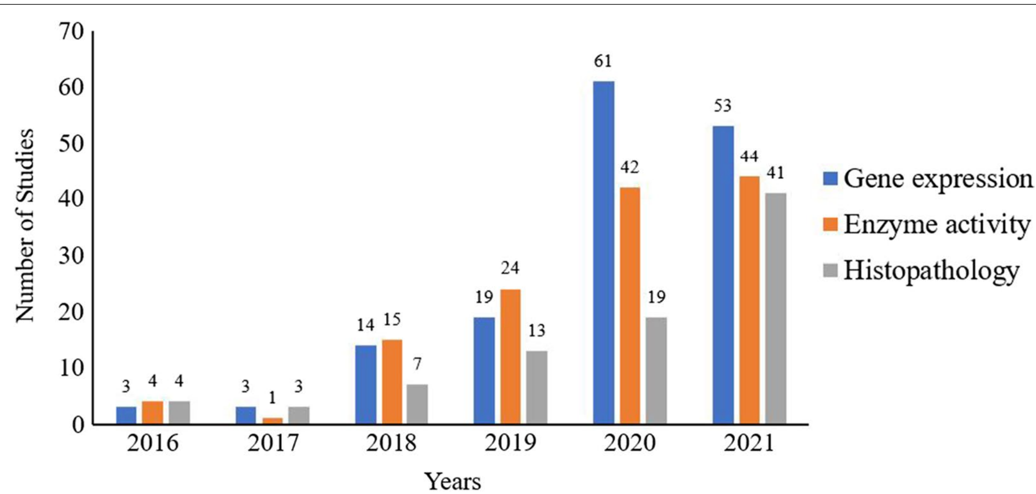

Fig. 3 Number of studies on enzymatic activity, gene expression, and histopathological effects of MPs/NPs on different organism in 2016 to 2021

genetic material of marine organisms, causing DNA damage, genes and chromosomal changes. Assessment and validation of biological markers in sentinel species for biomarker application in environmental monitoring programs is critical under various field conditions. DNA damage and changes in the expression of a gene encoding DNA repair mechanism prepare an important role for measuring the impact of MPs/NPs on organisms [12].

Histopathology is a sensitive biomarker of xenobiotic-induced sublethal stress. In both laboratory studies, histopathological changes have been widely used as biomarkers in the evaluation of the health of fish exposed to contaminants [69]. Histopathological evaluation is widely considered as a potential tool for determining the extent of injury in organisms caused by acute and chronic effects of environmental stressors [155]. Histopathological changes of specific organs show condition and time-integrated endogenous and exogenous effects on the organism resulting from changes at lower levels of biological organization [155]. This study showed that studies on the effects of MPs/NPs on organisms are lower that studies on gene expression and enzymatic activity. Solvents used in histopathological protocols may solve MPs/NPs and effects on results. Considering the importance of histopathological alterations as a valuable biomarker of environmental stressors, more studies are required on the impacts of MPs/NPs on histopathological changes of various organisms.

Some biomarker responses including enzyme activity, gene expression, and histopathological damages are highlighted in Additional file 1: Table S1. Superoxide dismutases (SOD), Catalase (CAT), glutathione peroxidase (GPx), acetylcholinesterase (AChE), glutathione s transferase (GSH), peroxidase (POD), and Cytochrome P450 are commonly analyzed enzymes in toxicological studies. Deregulatory effects of MPs/NPs on hepatic genes, immune genes, stress response and detoxification genes, estrogenic (*vtg1*) or organic (*cyp1a*), genes encoding proteins have been reported in different organisms as well. According to analyzed tissues for histopathological damages in studies inflammation, necrosis, hyperplasia, villi damage, epithelial damage, and MPS/NPs accumulation are reported. Studies showed different size of MPs/NPs, polymer types, and shapes have different response on organisms.

Impact of different plastic sizes

The number of studies related to the effects of individual MPs and both MPs/NPs on enzymatic activity, gene expression, and histopathological biomarkers in different organisms has increased from just three studies in 2016 to 56 studies in 2021 (Fig. 4a). Around 59.04% and 11.75% of publications used plastic particles sizes of < 50 µm and 50–100 µm, respectively (Fig. 4b). Few studies (0.60%) used MPs > 1600 µm.

MP/NP particle size plays an important role in the changes of biomarkers including enzymatic activity, gene expression, and histopathology in exposed organisms [1, 33, 51]. Size-dependent accumulation of MPs/NPs has proven that smaller plastic particles could reach specific tissues such as gut, liver and larger plastic particles were only trapped in gills and the digestive tract of fish [12]. The small size of MPs/NPs facilitates internalization by organisms and, thus, consequent accumulation in the food chain. Trophic transfer of MPs/NPs along the aquatic food chain and implications for human health are important.

Inflammation caused by 0.5 µm PS MPs in zebrafish gut were found to be more severe than that caused by 50 µm PS MPs [68]. The size-dependent toxicity of MPs/NPs has been widely reported in sea organisms. A study conducted by Kinjo et al. [73] showed that larger MPs of PS retained in the digestive tract of *M. galloprovincialis* are longer than smaller particles. In another study, histological changes were observed in the liver, intestine, and gill of goldfish (*Carassius auratus*) exposed to PS MPs and severe changes showed a size-dependent pattern of PS MPs [1].

Until recently, there were few studies on the transfer of MPs/NPs to humans and the potential health consequences. Since humans are the final consumers in the food web, introduction of MPs/NPs into humans is possible, due to consumption of aquatic products that contain MPs/NPs. PS NPs enter in human gastric adenocarcinoma cells through an energy-dependent mechanism. In addition, size and dose are the factors that affect the internalization of NPs in cells. Smaller NPs also significantly change expression of genes involved in inflammation [36]. Similarly, He et al. [55] showed PS NPs with size of 50 nm can be rapidly internalized by human hepatocellular carcinoma (HepG2) cells. As a result, size-dependent toxicity should be considered when assessing the toxicity of MPs/NPs in various organisms.

MPs/NPs as carriers for other contaminants

Around 90 studies were conducted to investigate combined effects of contaminants and MPs/NPs on enzymatic activity, gene expression, and histopathological biomarkers in different organisms (Fig. 5). Most studies used chemical elements, PAH, PCB, pesticides, medication, hormone, triclosan, sewage, and antibiotic as contaminants combined with MPs/NPs. Studies on combined effects of chemical elements, PAH, and pesticides with MPs/NPs are higher than other contaminants (Fig. 5). For example, only a single study has been conducted on sewage and hormones (cite it here).

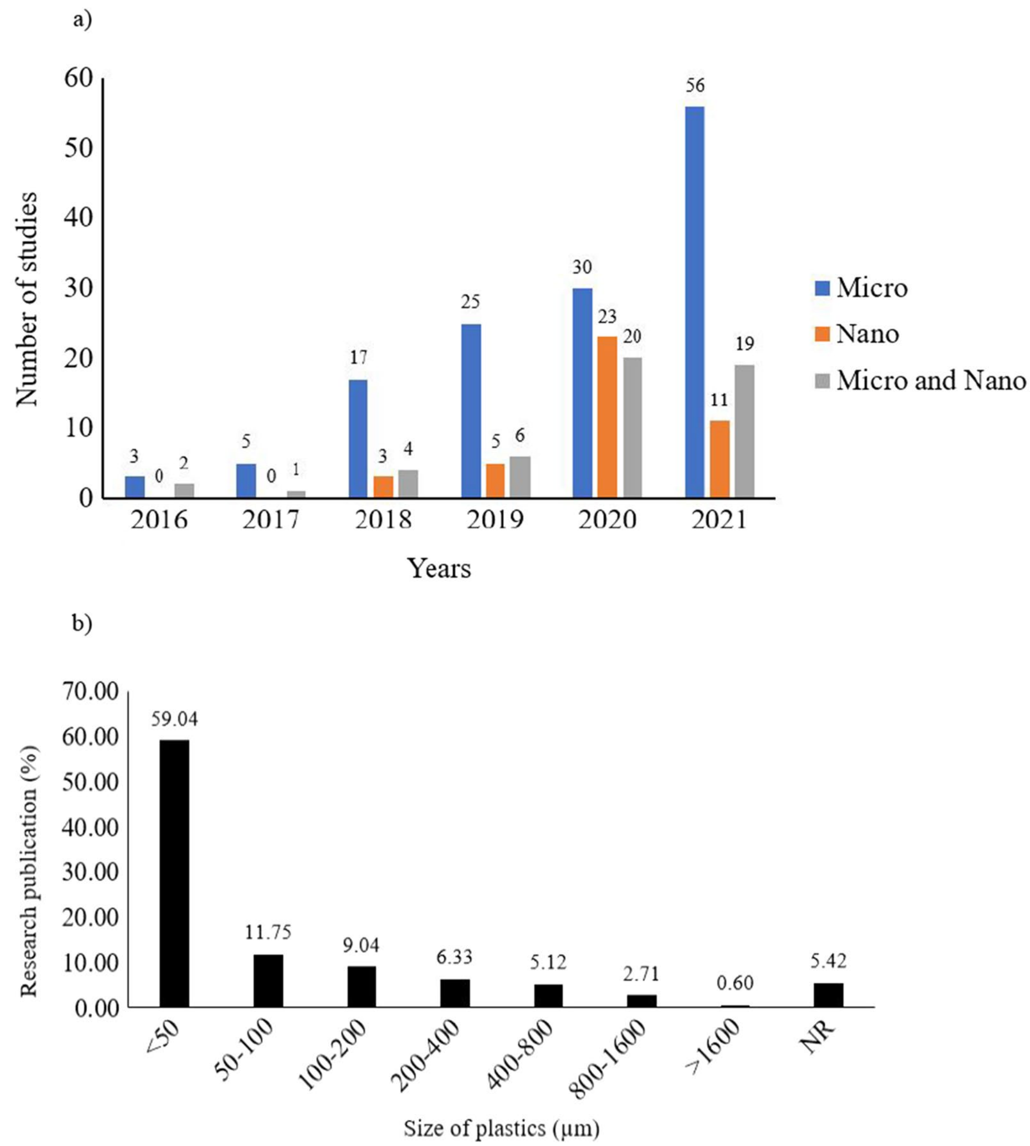

Fig. 4 **a** Number of studies according to micro, nano, and both micro- and nano-plastics and **b** size of plastic particles in research publications (%) with their enzymatic activity/gene expression/histopathological effects on different organisms in 2016 to 2021. *NR* not reported

Environmental MPs/NPs can be regarded as a complex cocktail of contaminants. Plastic-combined with environmental chemicals are readily released in the gut of animals and may subsequently transfer along the aquatic food chain. Interaction of MPs/NPs with other contaminants could affect its uptake by organisms and their combined toxicity. Physico-chemical properties of water are regarded to change the biomarker response of organisms. Thus, the assessment of water quality of exposed water to MPs/NPs is suggested. Many parameters including weathering, salinity, pH, and dissolve organic matter influence the durability and affect interaction of MPs/NPs with other contaminants [72]. For example, higher histopathological damages in combined PS MPs and chlorpyrifos showed were observed in *O. mykiss*, which show increase adverse effects of chlorpyrifos in fish [69]. In another study, induction of cytochrome P450 1A (cyp1a) was indicated when *D. rerio* were fed artemia incubated with a combined of MPs and benzo[a]pyrene (BaP) [9]. PE MPs grow cadmium uptake in lettuce by changing the soil microenvironment [163].

MPs/NPs are hydrophobic in nature and have a large surface area that allows adsorption of heavy metals on

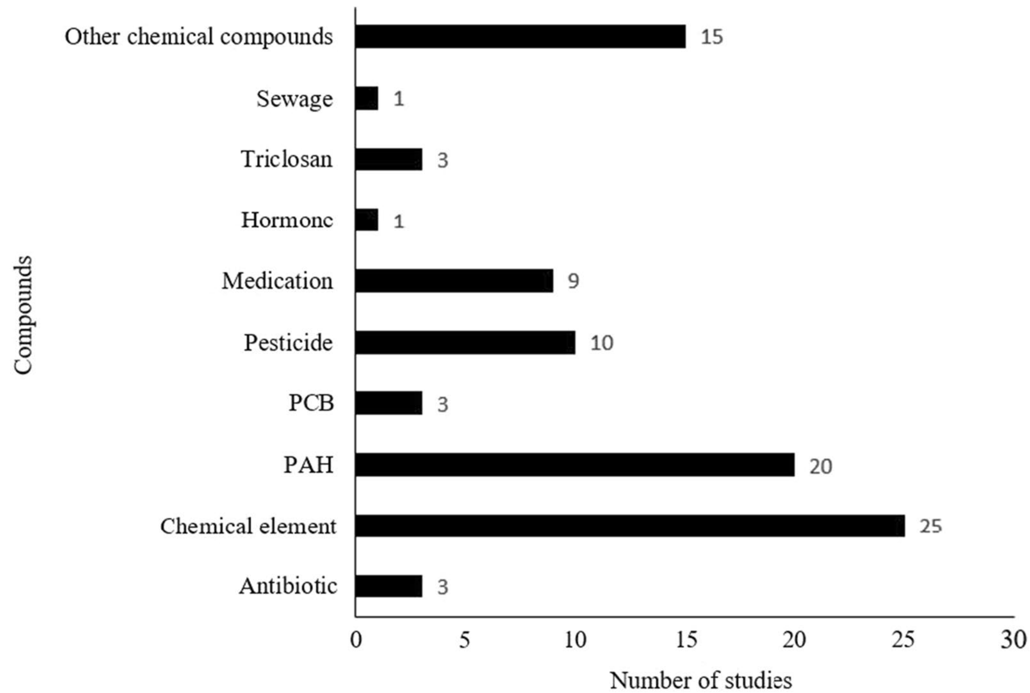

Fig. 5 Combined ecotoxicological effects of MPs/NPs with other contaminants on the enzymatic activity/gene expression/histopathological effects of different groups of organisms

its surface, and play a role to accumulate the pollutants in the body. Several factors influence MPs behaviors, the amount of MPs deposited, retained, and transported, including human activity (e.g., inappropriate waste management), MPs characteristics (e.g., density, shape and size), environmental topography and condition. Size of MPs/NPs, their surface ionic charges, and age of particle affect adsorption capacity of metals. Studies have shown that MPs increase the accumulation and toxicity of cadmium and copper in liver, gut, gills of adult *D. rerio* [100, 126]. Few studies also reported reduced bioavailability and toxicity of MPs/NPs combined with contaminants such as phenanthrene, and PAH [144, 159]. The binding affinity of MPs/NPs with other contaminants also has a significant effect on their bioavailability.

Future considerations

Due to the growing issue of plastic and MPs/NPs pollution, it is becoming critical to solve, and better understand the fate and toxicity of these particles in the environment. In recent years, there has been a dramatic increase in MPs/NPs studies. While most studies have focused on reporting presence of MPs/NPs in the environment and biota, few studies have examined their impacts on biomarkers of organisms including enzymatic activity, gene expression, and histopathology. Early exposure studies used very high concentrations of virgin MPs/NPs in laboratory-controlled experiments that were not considered environmentally relevant, resulting in a shift in recent years to environmentally relevant MPs/NPs concentrations [5, 14, 76, 151, 156]. In the natural environment, MPs/NPs occur in different size combinations and concentrations. Thus, more studies, based on these environmentally relevant parameters, are required to better understand their impacts on enzymatic activity, gene expression, and histopathology biomarkers on organisms. In response, recent research has begun to shift from individual species to focus on multiple species, multi-generational studies [5, 18, 63, 178] (Haegerbaeumer et al. 2019).

The density of MPs/NPs polymers is also an important factor for their distribution in water, which affects their interaction with aquatic organisms. For example, PP and PE pose greater risks for organisms that live near the surface because they float in water, whereas PS, PVC, and PET may impact benthic organisms more, because they sink. In the natural environment, plastics are exposed to degradation via weathering, whereas virgin MPs/NPs are used in most laboratory studies, which affect sorption of other contaminants, aggregations, and even organism toxicity. Both long-term and short-term studies using virgin and weathered MPs/NPs will be required to better understand impacts of weathered and degraded plastics in the environment. Recovery periods of MPs/NPs in laboratory studies should also be examined for future studies.

Conclusions

MPs/NPs contamination in the environment and in biota has been widely recognized as a rapidly emerging pollution problem. This review focussed on 256 studies on the effects of MPs/NPs on enzymatic activity, gene expression, and histopathology biomarkers on organisms from 2016 to 2021. While studies on MPs/NPs toxicity in biota have also increased dramatically to better understand these emerging contaminants, this review found that most studies (~ 70%) have focused on aquatic organisms, and of these, only a few species have been studied. Although impacts of MPs/NPs of biomarkers on terrestrial organisms are less well studied, some researchers consider impacts of MPs/NPs on terrestrial ecosystems may be more harmful to humans due to reliance on agricultural systems for food. Therefore, this was identified as a major knowledge gap that requires further study. Other important knowledge gaps that need to be addressed are that most laboratory toxicology studies use limited size ranges, single polymer categories and virgin MPs/NPs concentrations which are much higher than found in the environment. Thus, measured impacts of enzymatic activity, gene expression, and histopathology biomarkers on organisms are often not environmentally relevant. MPs/NPs occur in different size combinations and concentrations in the natural environment. Thus more studies, based on these environmentally relevant parameters, are required to better understand toxic effects of MPs/NPs on enzymatic activity, gene expression, and histopathology biomarkers of both aquatic and terrestrial organisms.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12302-022-00652-w.

Additional file 1: Table S1. Studies summarizing the following criteria: species and common name of organisms, MPs type and size, contaminants absorbed to MPs, MPs and contaminant concentration, duration of the experiment, toxicological effect (enzyme activity, gene expression and histopathology) and organism tissues.

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Author contributions
IP, SK, DTNH, and FA contributed to the planning and design of the study and writing a draft. MJCO, PVT, KCN, and AM contributed to the interpretation and discussion of the results. SS and GY were contributed in investigation, conclusion, review and editing. Validation, Writing – review and editing were conducted by TRW and RM.

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Availability of data and materials
All data are publicly available, with sources described in the manuscript and supplementary material.

Declarations

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Not applicable.

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Competing interests
The authors declare that they have no competing interests.

Author details
[1] An Independent Researcher, NIT Durgapur, Durgapur, West Bengal, India. [2] Banking University HCM Ho Chi Minh city Vietnam, International University of Japan, Niigata, Japan. [3] Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Alkharj, Kingdom of Saudi Arabia. [4] College of Business Administration, Ajman University, Ajman, United Arab Emirates. [5] National Economics University (NEU), Hanoi, Vietnam. [6] Department of Public Health, Healthcare Management and Physical Culture, Tashkent State Dental Institute, Makhtumkuli 103, Tashkent, Uzbekistan 100147. [7] Department of Building and Construction Techniques Engineering, Al-Mustaqbal University College, 51001 Hillal, Iraq. [8] Department of Plant Genomics and Biotechnology, National Institute for Genomics and Advanced Biotechnology, National Agricultural Research Centre, Islamabad, Pakistan. [9] Department of Botany, Bahauddin Zakariya University, Multan, Pakistan. [10] Department of Anatomy, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia. [11] Master's Programme Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia. [12] Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. [13] School for Resource and Environmental Studies, Dalhousie University, Halifax, NS B3H 4R2, Canada. [14] Department of Biotechnology, Faculty of Biological Science, Alzahra University, Tehran, Iran.

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