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REVIEW
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Influence of Functional Group Modification on the Toxicity of Nanoplastics

Haihong Zhang[1], Haodong Cheng[1], Yudi Wang[1], Zhenghua Duan[1], Wenjie Cui[1], Yansong Shi[1] and Li Qin[2]**

[1] Tianjin Key Laboratory of Hazardous Waste Safety Disposal and Recycling Technology, School of Environmental Science and Safety Engineering, Tianjin University of Technology, Tianjin, China, [2] Agro-Environmental Protection Institute, Ministry of Agriculture and Rural Affairs, Tianjin, China

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***Correspondence:**
Zhenghua Duan
duanzhenghua@mail.nankai.edu.cn
Li Qin
ql-tj@163.com

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Nanoplastics (NPs) are ubiquitous in harvested organisms at various trophic levels, and more concerns on their diverse responses and wide species-dependent sensitivity are continuously increasing. However, systematic study on the toxic effects of NPs with different functional group modifications is still limited. In this review, we gathered and analyzed the toxic effects of NPs with different functional groups on microorganisms, plants, animals, and mammalian/human cells *in vitro.* The corresponding toxic mechanisms were also described. In general, most up-to-date relevant studies focus on amino ($-NH_2$) or carboxyl ($-COOH$)-modified polystyrene (PS) NPs, while research on other materials and functional groups is lacking. Positively charged PS-NH_2 NPs induced stronger toxicity than negatively charged PS-COOH. Plausible toxicity mechanisms mainly include membrane interaction and disruption, reactive oxygen species generation, and protein corona and eco-corona formations, and they were influenced by surface charges of NPs. The effects of NPs in the long-term exposure and in the real environment world also warrant further study.

Keywords: nanoplastic, functional group modification, surface charge, toxic effect, mechanism

INTRODUCTION

Plastics discarded into the environment has become a global concerned pollution (Alak et al., 2021; Zhang et al., 2021). Microplastics, especially nanoplastics (NPs, smaller than 1 μm), could more likely to penetrate the cell membranes and impose adverse impacts on living organisms (Shen et al., 2019). However, due to limitations in quantitative detection, the varying effects of their environmental concentrations are still unclear, although Schirinzi et al. (2019) reported traces of nano-sized polystyrene (PS) in estuarine and surface waters of the West Mediterranean Sea. Toxicities of NPs on development, behavioral alterations, and oxidative stress have attached great importance in various organisms (Duan et al., 2020). Ultimately, they may cause hazards to human health (Sun M. et al., 2021).

The aged plastics through photo-degradation, biodegradation, hydrolysis, and mechanical abrasion in the environment, will result in different surface modifications in NPs. Negatively charged NPs, such as the carbonyl groups (−COOH), are expected to be the most common ones due to surface oxidation and acquisition of functionalities during the weathering (Luan et al., 2019). Positively charged NPs, such as amino modification ($-NH_2$), may also consider as an important counterpart due to the hydrolyzation of polyamides (Wang et al., 2019). However, compared with morphology and size (Aznar et al., 2019; Cheng et al., 2020), the presence of functional groups on the surface modifications of plastic polymers working on their toxicological effects remains to be systematically studied.

Thus, the toxic effects of NPs, with different functional groups or without modification (bare NPs), were reviewed and compared on microorganisms, plants, animals, and mammalian/human cells *in vitro* in the present study. We aim to provide some new information concerning on the health risk of NPs in the environment.

BIBLIOMETRIC ANALYSIS

The keywords used in the bibliographic search were as follows: "nanoplastics, toxic mechanism, toxic effects, surface modification, and functional group" or "nanoplastics, toxic mechanism, toxic effects, and amino-modified" or "nanoplastics, toxic mechanism, toxic effects, and carboxyl-modified" in Science Direct database and Web of Science database from January 2012 to December 2021. A total of 477 references were obtained, including review articles and research articles. Abstracts of the retrieved publications were reviewed separately to screen the relevant literature. Only studies that involved the toxic effects and/or toxic mechanisms of NPs researched on organisms were selected for further analysis. Literature that did not specify whether NPs were modified, or the information of NPs was incomplete, or the toxic mechanisms were not assessed based on organisms, were excluded. In addition, a manual review of the reference lists of the selected publications was conducted to recover articles not included in the bibliographic search. Eventually, 6 review articles and 59 research articles (summarized in **Table 1**) were screened, accounting for approximately 13.6% of the total. The numbers of manuscripts talked about the functional groups including: $-NH_2$ (48), −COOH (40), −COC (1), $-SO_3H$ (3), $-CNH_2NH_2{}^+$(1), and bare NPs (19).

Cite Space software (5.8.R2, 64 bit) and Origin Pro 9.0 (Origin Lab Corp., Northampton, MA, United States) were used to perform visualization and bibliometric analysis, mainly for the number of annual publications and keyword co-occurrence analysis. As shown in **Figure 1**, the number of published articles on NPs increased from 2 in 2012 to 272 in 2021, which indicated that the toxicity of NPs played important roles in relevant studies. However, only 11 studies compared the toxicities of NPs with different functional groups in 2021. The co-occurrence network (**Figure 2**) showed that *Caenorhabditis elegan*, *Artemia franciscana*, *Daphnia magna*, mussel, oyster, and algae were the main species used in the previous studies. The main toxic effects included growth, behavior, apoptosis, and cytotoxicity. The main toxic mechanisms discussed involved oxidative stress, accumulation, activation, adsorption, ingestion, surface charge, size, aggregation, and extracellular polymeric substance.

TOXIC EFFECTS OF NPS WITH DIFFERENT FUNCTIONAL GROUP MODIFICATIONS

Microorganisms

Microorganisms play important roles in the biological chain as decomposers for the ecosystem (Liu et al., 2020). NPs can penetrate into cells through microbial cell membranes and destroy cell functions (Ning et al., 2021). The toxicity is greater when the particle size is smaller (Miao et al., 2019). For example, PS NPs of 100 and 200 nm had no effect on the growth of *Escherichia coli*, whereas PS NPs of 30 nm had an increased inhibition on bacterial growth (Ning et al., 2021).

Amino-modified NPs are usually positively charged, which make it easier for them to get into the negatively charged bio-membrane due to the electrostatic interaction (González-Fernández et al., 2018; Tallec et al., 2018). Therefore, the toxicity of amino-modified NPs was supposed to be higher than that of carboxyl-modified NPs and bare NPs. However, to our knowledge, only five manuscripts compared the toxicity of NPs with different functional groups in microorganisms to date. PS-NH_2 NPs more strongly inhibited the growth of *Synechococcus* and damaged the membrane integrity of *Synechococcus* than PS-SO_3H NPs (Feng et al., 2019). PS-NH_2 NPs of 50 nm produced a higher reactive oxygen species (ROS) level in *Halomonas Alkaliphila*than that bare PS NPs of 55 nm, and the generated ROS may cross extracellular polymers (EPS) and cause great damages (Sun et al., 2018). PS-NH_2, bare PS, and PS-COOH NPs caused cell membrane damage and induced oxidative stress in activated sludge and biofilms, and PS-NH_2 NPs induced the highest effect among them (Miao et al., 2019; Qian et al., 2021). NPs inhibited the bacterial growth of *Escherichia coli* in the order of PS-NH_2 > PS-COC > PS-COOH (Ning et al., 2021).

Algae and Plants

Algae-adsorbed NPs might be ingested by aquatic animals and transmitted through the food chains, and ultimately result in health risk to human beings (Heddagaard and Møller, 2019; Huang et al., 2020; Mateos-Cárdenas et al., 2021). The potential risks of NPs to the algae in freshwater and seawater have been well documented recently. The toxicity of NPs to the algae was affected by exposure doses, particle sizes, and types of functional groups (González-Fernández et al., 2019). Exposure to carboxyl-modified NPs inhibited the growth of *Raphidocelis subcapitata*, diatom, *Chlorella Vulgaris*, *Phaeodactylum tricornutum*, and *Rhodomonas baltica*, which was manifested in morphological changes, interference

TABLE 1 | Summary of toxicity assessment of NPs with different functional groups.

Species	NPs type	Particle size	Exposure concentration	Toxic effects	References
Microorganisms					
Biofilms	PS-bare PS-NH_2 PS-COOH	100 and 500 nm	5–100 mg/L	Oxidative stress	Miao et al., 2019
Activated sludge	PS-bare PS-NH_2 PS-COOH	100 nm	100 mg /L	Cell membrane damage and oxidative stress	Qian et al., 2021
Halomonas alkaliphila	PS-bare PS-NH_2	55 nm 50 nm	20–320 mg/L	Inhibit growth and oxidative stress	Sun et al., 2018
Synechococcus	PS-NH_2 PS-SO_3H	50 nm 52.03 nm	2–9 µg/mL	Inhibit growth; damage the membrane integrity; changes in metabolic; and oxidative stress	Feng et al., 2019
Escherichia coli	PS-bare PS-NH_2 PS-COC PS-COOH	30–200 nm 200 nm	4–32 mg/L	Inhibit growth; oxidative stress; and DNA damage	Ning et al., 2021
Algae in freshwater					
Pseudokirchneriella subcapitata	PS-NH_2 PS-COOH	20 nm 110 nm	10 mg/L	Inhibition of photosynthesis and/or cell wall disruption	Nolte et al., 2017
Raphidocelis subcapitata	PS-COOH	88 nm	0.5–50 mg/L	Interfere with mitosis and cell metabolism	Bellingeri et al., 2019
Microcystis aeruginosa	PS-NH_2	50 nm	3.4 and 6.8 µg/mL	Inhibit photosystem II efficiency; reduce organic substance synthesis; induce oxidative stress; and enhance the synthesis of microcystin	Feng et al., 2020
	PS-SO_3H	–	100 µg/mL		
Algae in seawater					
Diatom	PS-NH_2	50 nm	0.05 and 5 µg/mL	Inhibit photosynthesis and destroy lipid structure	González-Fernández et al., 2020
	PS-NH_2	500 nm	2.5 µg/mL	Decrease in esterase activity and diminished neutral lipid content	Seoane et al., 2019
Dunaliella tertiolecta	PS-NH_2 PS-COOH	50 nm 40 nm	5–50 µg/mL	Inhibit growth and photosynthesis	Bergami et al., 2017
Phaeodactylum tricornutum	PS-COOH	60 nm	1–100 mg/L	No toxic effects	Grassi et al., 2020
Chlorella vulgaris	PS-NH_2	90, 200, and 300 nm	25–200 mg/L	Inhibit photosynthesis and algal growth	Khoshnamvand et al., 2021
Rhodomonas baltica	PMMA PMMA-COOH	50 nm 50 nm	0.5–100 µg/mL	Cell cycle injury; loss of membrane integrity; inhibition of photosynthesis; and decrease cell viability	Gomes et al., 2020
Chlorella sp.	PS-bare PS-NH_2 PS-COOH	217 nm 217 nm 220 nm	1 mg/L	Eco-corona formation and decline the oxidative stress	Natarajan et al., 2020
	PS-NH_2 PS-COOH	200 nm	5 mg/L	Reduced bioavailability of TiO_2 and decrease oxidative stress and enhance photosynthetic yield	Natarajan et al., 2021
Terrestrial plants					
Arabidopsis thaliana	PS-NH_2 PS-SO_3H	200 nm	10, 50, and 100 µg/mL	Induced a higher accumulation of ROS and inhibit plant growth and seedling development	Sun X. D. et al., 2020
	PS-COOH	40 nm	0.029 g/L 8.3×10^{11} n/mL	Accumulation of plastics at root surface and cap cells	Taylor et al., 2020
Maize	PS-NH_2 PS-COOH	22 nm 24 nm	10–500 ng/spot	Inhibit photosynthesis; inhibit growth; oxidative damage; and upset metabolic balance	Sun H. et al., 2021
Wheat	PS-COOH	40 nm	0.029 g/L 8.3×10^{11} n/mL	Accumulation of plastics at root surface and cap cells	Taylor et al., 2020
Aquatic animals in freshwater					
Daphnia magna-Zooplankton	PS-bare PS-n-NH_2	100 nm 50 and 100 nm	75 mg/L 40 mg/L	Stimulate the antioxidant system	Lin et al., 2019

(Continued)

TABLE 1 | (Continued)

Species	NPs type	Particle size	Exposure concentration	Toxic effects	References
	PS-COOH	300 nm	70 mg/L		
	PS-p-NH_2	110 nm	100 mg/L		
	PS(-CNH_2NH_2 $^+$)	200 nm	50 and 150 mg/L	Acute toxicity	Saavedra et al., 2019
	PS(-COO-)				
Caenorhabditis elegans-Zooplankton	PS-bare	35 nm	1–1000 μg/L	Reproductive and gonadal developmental toxicity and genotoxicity	Qu et al., 2019
	PS-NH_2				
	PS-bare	35 nm	1–100 μg/L	Reproductive and gonadal developmental toxicity and genotoxicity	Sun L. et al., 2020
	PS-NH_2				
	PS-COOH	200 and 500 nm	100 nm/L	Reduce survival rate	Yilimulati et al., 2020
	PS-bare	50 and 60 nm	1–50 mg/L	Effects on survival, growth, and reproduction	Schultz et al., 2021
	PS-NH_2				
	PS-COOH				
	PS-bare	116.2 nm	1 and 10 μg/mL	Change cellular behavior	Kim et al., 2020
	PS-COOH	110.6 nm			
	PS-NH_2	120.2 nm			
Brachionus calyciflorus-Zooplankton	PS(-CNH_2NH_2 $^+$)	200 nm	50 and 150 mg/L	Acute toxicity	Saavedra et al., 2019
	PS(-COO-)				
Coregonus lavaretus	PS-COOH	50 nm	100 and 10000 pcs	Decrease sperm motility and reduce offspring body mass and impair swimming ability	Yaripour et al., 2021
Aquatic animals in seawater					
Brachionus plicatilis-Zooplankton	PS-NH_2	50 nm	0.5–50 μg/mL	Increase mortality rate	Manfra et al., 2017
	PS-COOH	40 nm			
Ciona robusta-Zooplankton	PS-NH_2	50 nm	2–15 μg/mL	Developmental toxicity and induced oxidative stress	Eliso et al., 2020
	PS-COOH	60 nm	5–100 μg/mL		
Artemia franciscana-Zooplankton	PS-NH_2	50 nm	1 and 10 μg/mL	Exfoliation; increase mortality rates; inhibit growth; inhibit activity; and regulate *clap* and *cstb* gene expressions	Bergami et al., 2017
	PS-COOH	40 nm			
	PS-NH_2	50 nm	0.1–10 μg /mL	Inhibit growth; inhibit gene expression; neurotoxicity; and higher mortality rate	Varó et al., 2019
	PS-NH_2	50 nm	5–100 μg/mL	Impair feeding, motility and multiple molting	Bergami et al., 2016
	PS-COOH	40 nm			
Mytilus galloprovincialis Lam.	PS-NH_2	50 nm	1–50 μg/mL	Stimulate increase in extracellular ROS and NO and induce lysosomal damage and a dramatic decrease in phagocytosis	Canesi et al., 2015
			0.001–20 mg/L 0.15 mg/L	Induce malformations and a delay in development dysregulation of transcription of genes and decrease in shell length	Balbi et al., 2017
			1–50 μg/mL	Increase cellular damage and ROS production and induce lysosomal damage and a dramatic decrease in phagocytosis	Canesi et al., 2016
			10 μg/L	Induce lysosomal release and a dramatic decrease in phagocytosis	Auguste et al., 2020a
			10 μg/L	Dysregulation of transcription of genes and affect immune function	Auguste et al., 2020b
Meretrix	PS-NH_2	100 nm	0.02–2 mg/L	Inhibit growth; disrupt energy homeostasis; Digestive tubule atrophy and necrosis; induce lysosomal damage; and inhibit phagocytic activity	Liu et al., 2021
Sea urchin	PS-NH_2	50 nm	1–50 μg/mL	Increase the appearance of malformations and undeveloped embryos and effects on gene expression	Della Torre et al., 2014
	PS-COOH	40 nm	2.5–50 μg/mL		
	PS-NH_2	50 nm	1 and 5 μg/mL	Induce lysosomal damage and a dramatic decrease in phagocytosis	Bergami et al., 2019
	PS-COOH	40 nm			
	PS-NH_2	50 nm	5–25 μg/mL	Induce lysosomal damage	Marques-Santos et al., 2018
Euphausia superba	PS-NH_2	50 nm	2.5 mg/L	Increase molting and inhibit swimming activity	Bergami et al., 2020

(Continued)

TABLE 1 | (Continued)

Species	NPs type	Particle size	Exposure concentration	Toxic effects	References
	PS-COOH	60 nm			
	PS-COOH	40 nm			
Crassostrea gigas	PS-bare	50 and 500 nm	0.1–25 μmg/L	Developmental toxicity and cytotoxicity	Tallec et al., 2018
	PS-NH_2	50 nm			
	PS-COOH	50 nm			
	PS-NH_2	100 nm	0.1–100 mg/L	ROS generation	González-Fernández et al., 2018
	PS-COOH	100 nm			
Mammalian animal					
Mice	PS-bare PS-NH_2 PS-COOH	100 nm	10 mg/mL	Weight loss induce cell apoptosis; inflammation; structural disorder; damage to the blood system; and lipid metabolism disorders	Xu et al., 2021
	PS@Bap	192 nm	0.5 mg/mL	Protein corona and inhibit cell viability	Ji et al., 2020
	PS-bare	188 nm			
Mammalian cells *in vitro*					
Neonatal rat ventricular myocytes	PS-NH_2 PS-COOH	50 nm	25 μg/mL	Damage contractility, glycolytic homeostasis and the mitochondrial activity of neonatal cardiomyocytes	Roshanzadeh et al., 2021
Human cells *in vitro*					
HepG2	PS-bare PS-NH_2 PS-COOH	50 nm	10, 50, and 100 μg/mL	Inhibit cell viability; destroy cell morphology; and damage the antioxidant structure	He et al., 2020
Caco-2/HT29-MTX-E12/THP-1	PS-bare PS-NH_2	50 nm	1–50 μg/cm^2	Reduce cell viability; cytotoxicity; and decrease metabolic activity	Busch et al., 2020
	PS-COOH	50 and 500 nm	0.01–100 μg/mL	No effect on cell viability	Hesler et al., 2019
BEAS-2B	PS-bare PS-NH_2 PS-COOH	60 nm	1–40 μg/mL	Inhibit cell viability; increase ROS production; lead endoplasmic reticulum stress; and induce Lysosomal, autophagic cell death, and protein misfolding	Chiu et al., 2015
Calu-3	PS-bare PS-NH_2 PS-COOH	50 nm	0.3–32.3 μg cm^{-2}	Decrease cell viability; induce genotoxicity; and increase ROS production	Paget et al., 2015
Caco-2, HT29-MTX-E1, RajiB co-culture	PS-bare PS-NH_2 PS-COOH	50 and 100 nm	250 μg/mL	Shift the translocation rates; protein corona; and membrane integrity	Walczak et al., 2015
Caco-2, HT29 and LS174T monocultures	PS-bare PS-NH_2 PS-COOH	60 nm	20–100 μg/mL	Inhibit cell viability; induce apoptosis; and induce mucin interaction and cell apoptosis	Inkielewicz-Stepniak et al., 2018
THP-1	PS-NH_2 PS-COOH	120 nm	1–100 μg/mL	Inhibit cell viability and polarization and induce inflammation	Fuchs et al., 2016
THP-1	PS-bare PS-NH_2 PS-COOH	50 nm	0.3–32.3 μg cm^{-2}	Decrease cell viability; induce genotoxicity; and increase ROS production	Paget et al., 2015
Human erythrocytes	PS-COOH	200 nm	50–2000 particles cell^{-1}	Sensitivity to osmotic, mechanical, oxidative and complement lysis	Pan et al., 2016
Astrocyte 131N	PS-NH_2 PS-COOH	50 nm 40 nm	100 μg/mL	Induce apoptosis and lysosomal cell death; cell membrane damage	Wang et al., 2013
Brain capillary endothelial cells	PS-COOH	40, 100, and 200 nm	25–100 μg/ mL	Affect cell viability; particle uptake; induce inflammation; and no cell death	Raghnaill et al., 2014
Human endothelial	PS-COOH	20, 40, 100, 200, and 500 nm	10–100 μg/mL	Cell viability, particle localization, lysosome function and integrity	Fröhlich et al., 2012
Alveolar cells	PS-NH2 PS-COOH	50 nm	100 μg/mL	Interfere the mechanoadaptive capacity of alveolar cells; cyclic stretch induces higher ROS levels in alveolar cells treated with PS-NPs; and upregulate pro-apoptotic gene expressions	Roshanzadeh et al., 2020

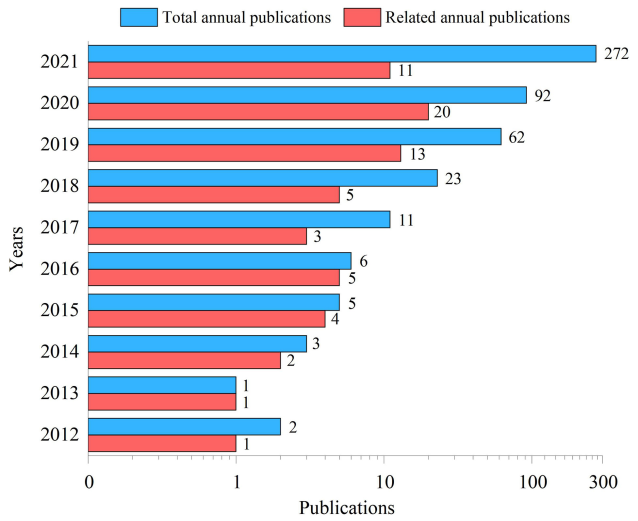

FIGURE 1 | Total annual publications and publications from 2012 to 2021 related to this manuscript indexed in Science Direct and Web of Science.

with mitotic cycle, reduction in chlorophyll content, and photosynthetic efficiency (Bellingeri et al., 2019). PS-NH_2 NPs with diameters of 90 and 200 nm decreased the biomass and the content of chlorophyll a in *Chlorella Vulgaris*, and mall-sized PS-NH_2 NPs were more toxic than large-sized ones (Khoshnamvand et al., 2021).

Positively charged NPs induced higher toxicology on the algae than negatively charged NPs, which was also due to the electrostatic interaction with bio-membrane. For example, PS-NH_2 NPs had higher adsorption ratios on the cell surface of the algae than bare PS and PS-COOH NPs, which limited the material transfer, gas exchange, and energy transfer in diatom (Seoane et al., 2019; González-Fernández et al., 2020). PS-NH_2 NPs more significantly inhibited the photo-system efficiency than PS-COOH NPs in *Pseudokirchneriella subcapitata* (Nolte et al., 2017) and PS-SO_3H NPs in *Microcystis aeruginosa* (Feng et al., 2020). Poly methyl methacrylate (PMMA) caused a higher impact on cellular and physiological parameters than PMMA-COOH (Gomes et al., 2020).

Land-based sources have been considered an important long-term sink for NPs (Rochman, 2018). NPs could accumulate and aggregate on the leaves of land-based plants, transfer from leaves to stems, and finally to roots (Yu et al., 2021). However, the toxicity of NPs to land-based plants was poorly understood although three relevant studies were reported recently. PS-COOH NPs mainly accumulated on the root surface and cap cells of *Arabidopsis thaliana* and wheat, rather than in roots (Taylor et al., 2020). Compared with PS-COOH NPs, PS-NH_2 NPs were more present in roots, which resulted in a stronger inhibitory effect on photosynthesis and growth of maize leaves; they also activated a more obvious oxidative defense mechanism (Sun H. et al., 2021). PS-NH_2 NPs induced a higher accumulation of ROS in *Arabidopsis thaliana*, and they inhibited the plant growth and the seedling development more strongly than PS-SO_3H NPs (Sun X. D. et al., 2020).

Animals and Mammalian/Human Cells *in vitro*

The functional groups of NPs influenced their toxicities to zooplankton in fresh water and seawater (Saavedra et al., 2019; Kim et al., 2020; Gola et al., 2021). PS-NH_2 NPs enhanced the gonad development, the reproductive capacity, and the genotoxicity to nematode (*Caenorhabditis elegan*) compared with bare PS NPs and PS-COOH NPs (Qu et al., 2019; Kim et al., 2020; Sun L. et al., 2020; Yilimulati et al., 2020; Schultz et al., 2021). Compared with PS-COOH NPs, PS-NH_2 NPs induced higher mortality in rotifers (*Brachionus plicatilis*) (Manfra et al., 2017); PS-NH_2 NPs caused more effects on the molting amount, the developmental toxicity on larval *Artemia franciscana* (Bergami et al., 2016, 2017; Varó et al., 2019), larval *Ciona robusta* (Eliso et al., 2020), and *Daphnia magna* (Lin et al., 2019); they also more significantly reduced the swimming activity of *Euphausia superba* (Bergami et al., 2020).

As for other aquatic animals, pre-fertilization exposure of sperm to PS-NH_2 NPs decreased offspring size and swimming performance in the European whitefish (*Coregonus lavaretus*) (Yaripour et al., 2021). PS-NH_2 NPs stimulated the increase in extracellular ROS, induced lysosomal damage, and decreased shell length in two kinds of mussels, *Mytilus galloprovincialis* (Canesi et al., 2015, 2016; Balbi et al., 2017; Auguste et al., 2020a,b) and *Meretrix* (Liu et al., 2021). Compared with PS-COOH NPs, PS-NH_2 NPs induced severe developmental defects and genetic regulations in the development of sea urchin (*Paracentrotus Lividus*) embryos (Della Torre et al., 2014). Nevertheless, the controversial joint effects were obtained in some cases. PS-COOH NPs had a significant increase in ROS production in sperm cells of *Crassostrea gigas*, whereas PS-NH_2 NPs did not (González-Fernández et al., 2018). In contrast to PS-COOH, positively charged PS-NH_2 seemed to affect the antioxidant and immune genetic responses differently and to a lesser extent in coelomocytes of the Antarctic sea urchin (Bergami et al., 2019).

Few studies have been conducted on their toxic effects on mammals except Xu et al. (2021) reported that PS-NH_2 NPs significantly affected the body weight of mice compared with PS-COOH NPs. Several *in vitro* studies on mammalian and human cells have also confirmed the high toxicity of positively charged NPs. PS-NH_2 NPs were more highly internalized in neonatal rat ventricular myocytes when compared with PS-COOH NPs, which resulted in decreased myocardial contractility (Roshanzadeh et al., 2021). PS-NH_2 NPs accumulated more than bare PS NPs in human hepatocellular carcinoma (*HepG2*) cells, and caused greater oxidative damage than PS-COOH NPs in *HepG2* cells (He et al., 2020). PS-NH_2 NPs increased the cytotoxicity and induced cell apoptosis of human *BEAS-2B* (Chiu et al., 2015), *Calu-3* (Paget et al., 2015), *Caco-2* (Walczak et al., 2015; Busch et al., 2020), *HT29-MTX-E12* (Inkielewicz-Stepniak et al., 2018), *THP-1* cell lines (Fuchs et al., 2016; Hesler et al., 2019), and human alveolar cells (Roshanzadeh et al., 2020). On

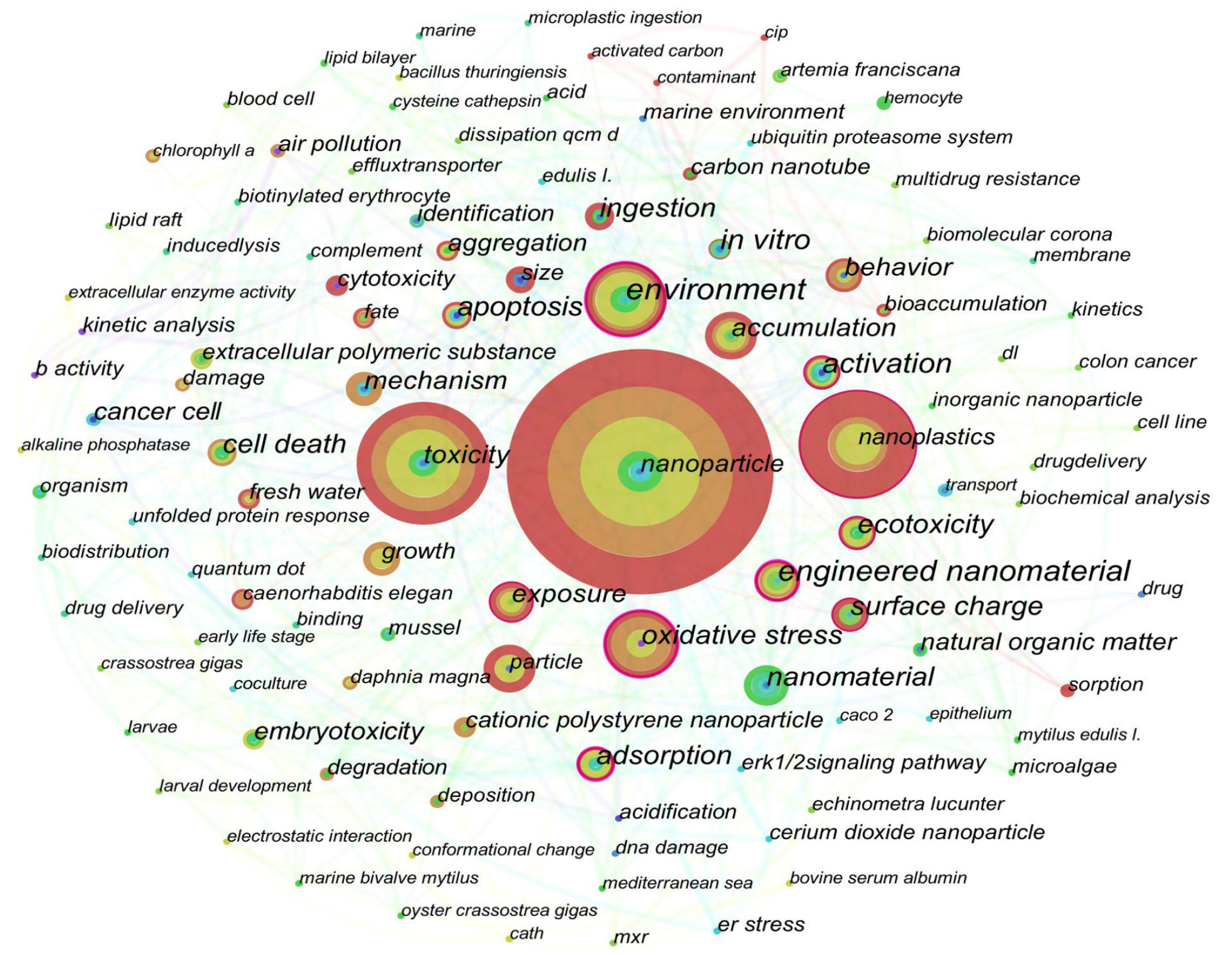

FIGURE 2 | Co-occurrence network of keywords extracted from the obtained literature. The size of each node represents the occurrence frequency of the corresponding keyword.

the contrary, bare PS NPs and PS-COOH NPs did not or were in a lesser extent.

TOXIC MECHANISM OF NANOPLASTICS WITH DIFFERENT FUNCTIONAL GROUP MODIFICATIONS

This manuscript summarizes the toxic effects of NPs with different functional groups in various organisms. Most studies focus on PS NPs, while research on other materials of NPs is lacking. The above mentioned studies show that NPs with different functional groups greatly impact on the toxicity of NPs, but most groups are concentrated in amino ($-NH_2$) and carboxyl ($-COOH$) groups. Only a few studies have been performed on the toxic effects of other functional groups. The surface charge of NPs considerably contribute to the toxic mechanisms of NPs (Banerjee and Shelver, 2020; Zhao et al., 2020). Positively charged NPs (PS-NH_2) usually induce stronger toxicity than bare NPs and negatively charged NPs (PS-COOH, PS-SO_3H NPs, and PS-COC).

In general, the stimulatory effect of exogenous particles causes granulocytosis to generate ROS in organisms (Qin et al., 2021). Significant decreases in the cell viability and the changed membrane integrity due to the generation of ROS and other cellular parameters are common toxic mechanisms in the microorganisms, algae, plants, animals, and mammalian/human cells *in vitro* we reviewed above. Positively charged NPs are more likely to interact with the cell membranes due to the negative charges of cell surfaces and cell walls; thus, they will generate more ROS (Sun X. D. et al., 2020), which will result in more effects on oxidative stresses, changes in membrane permeability, and destruction of cell function; they even induce cell apoptosis (Pan et al., 2016; Ning et al., 2021).

Nevertheless, the differences of toxicity mechanisms affected by charged groups of NPs still exist among different species. For microorganisms, the toxic mechanism is limited to the membrane disruption via the generated ROS (Sun et al., 2018), because larger particles cannot be internalized. Algae and plant cells are affected mainly by the adsorption of NPs to the surface through disrupted/damaged membrane, aquaporins, and cell pores, and further cause ROS generation and sequentially damage to the photosynthesis system (Sun H. et al., 2021). As for animal/human cells, the cellular processes of NPs internalized into lysosomesis are also related to their different surface charges (Fröhlich et al., 2012; Raghnaill et al., 2014). Negative NPs can escape from lysosomes and interact with cellular components to trigger cellular stress (Wang et al., 2013; Marques-Santos et al., 2018; Matthews et al., 2021), whereas Positive NPs destabilize lysosomes and initiate a cascade of cellular damage via ROS generation due to the proton sponge hypothesis (Nel et al., 2009). Thus, the cellular process of NPs in animals and human beings might be more complicatedly affected by their charged groups.

The eco-corona on the surface of NPs will be stimulated through coating different components of natural organic matters (NOMs; Grassi et al., 2020). The eco-corona formation enhances the aggregation of the NPs and accompanied with the decreased effective surface area, which will reduce the toxic impact of NPs (Bergami et al., 2017). The formation of the eco-corona is also influenced by the surface charge of NPs (Saavedra et al., 2019). Negatively charged NPs are more effective to form the eco-corona in the presence of EPS than positively charged NPs, which helps them in more significantly lessening the oxidative stress and cytotoxic impact on biological cells (Natarajan et al., 2020, 2021). However, the characteristics of the surrounding environment will significantly influence the biological effects of eco-corona on NPs. For example, PS-NH_2 NPs are usually better dispersed than PS-COOH NPs in nature seawater (Della Torre et al., 2014; Bergami et al., 2019). Yet the abundance and composition of NOMs vary significantly across different seawater bodies. Humic acids (HA), one of the main compositions of NOMs in seawater, was found to stabilize negatively charged NPs due to electrostatic repulsion between negative charges and steric effect, whereas it induced PS-NH_2 NPs to agglomerate (Wu et al., 2019). Thus, the controversial joint effects might be obtained in marine organisms in some cases (González-Fernández et al., 2018; Bergami et al., 2019).

In addition, the types and charges of surface chemical modification will affect the formation of the protein corona on NPs (Ji et al., 2020). The protein corona might be formed on the surface of NPs when they enter the physiological environment (Li et al., 2020). The formation of the protein corona in the serum is considered as a general protective effect from the potential cytotoxicity of NPs (Coglitore et al., 2019), because they reduce NP surface energy by non-specific adsorption, which leads to the lowered membrane adhesion and uptake efficiency (Lesniak et al., 2013). Positively charged NPs usually adsorb more plasma proteins than negatively charged NPs, which cause more opportunities for them to form the protein corona (Liu et al., 2019). Thus, positively charged NPs are hypothesized to weaken their toxicity more than negatively charged NPs. However, the formation of a PS-NH_2-protein corona in hemolymph serum (HS) increased the short term cellular damage and ROS production of PS-NH_2 toward immunocytes (Canesi et al., 2016), because NP-protein complexes were hypothesized to function as recognizable molecular patterns to be cleared by phagocytic cells (Hayashi et al., 2013). In addition, the enhanced formation of the protein corona on positively charged NPs will promote their "Trojan-horse effect" on other pollutants (Matthews et al., 2021). The studies on the biological effects of NPs with the protein corona are still in the initial stage. Most of recent results obtained were *in vitro*, which do not entirely reflect a realistic exposure scenario *in vivo*. More efforts should be contributed on the specific cell biological behavior of various NPs in the real environment, not limited to their effects on cell uptake efficiency and biocompatibility (Qin et al., 2021).

CONCLUSION AND RESEARCH PROSPECTS

In sum, amino-modified polystyrene nanoparticles (PS-NH_2) usually induce stronger toxicity than modified NPs, due to their positively charge characteristics. Positively charged NPs are more likely to interact with the cell membranes and generate more ROS than negatively charged NPs, which is mainly due to the negative charges of cell surfaces and cell walls. Nevertheless, there are still some differences existed among different species in the toxicity mechanisms of NPs affected by charged groups. The biological effects of NPs with the eco-corona and protein corona also contribute a lot to their differentiate toxic mechanisms. The exact environmental distributions of these functional group-modified NPs are unclear to date due to the limitations of quantitative detection. The mass balance of NPs between intake and excretion in organisms is also far from being established. Thus, the transmission of these modified NPs on organisms needs to be further researched. Reducing the inherent toxicity of NPs will be an urgent topic due to the substantial environmental problems they induced. The effect of NPs in the long-term exposure and in reality should also be explored.

AUTHOR CONTRIBUTIONS

HZ: data curation and writing—original draft preparation. YW and HC: data curation. YS and WC: data collection. ZD: supervision, writing, reviewing, editing, and resources. LQ: conceptualization, writing, reviewing, and editing. All authors contributed to the article and approved the submitted version.

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