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Review Article

Nanoplastics as an Invisible Threat to Humans and the Environment

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The consequence of the unstoppable growth of plastic production and inadequate waste disposal is plastic pollution, which is becoming a global challenge. Large quantities of discarded plastics in the environment are under the direct influence of biotic and abiotic factors, leading to the fragmentation of particles and the formation of tiny particles of plastics or nanoplastics. Nanoplastics are a fast-growing pollutant that, due to ubiquity in the environment, causes great public concern. It also attracts the attention of scientists in detecting harmful effects on health and the environment. This review is aimed at summarizing all adverse effects of nanoplastics on human health and the environment. Due to their toxic effects, it is necessary to reduce the disposal of plastics in the environment, develop or improve existing methods, and implement legislation that would reduce the release of nanoplastics into the environment. A possible ban or reasonable regulation of nanoplastics in cosmetics or food can be expected only after a critical mass of scientific objections has been created.

1. Introduction

Environmental pollution and its far-reaching consequences are two of the main problems facing today's modern society [1, 2]. Globalization, a dramatic increase in human population in the 20th century, and mass consumption of various products, followed by inadequate disposal of waste, have led to the worrying situation in which both land and water areas of our planet are affected today [3]. More importantly, such changes affect the animal communities that live in them. Marine pollution, as a part of this problem, is a subject of research by many scientists and societies for environmental protection, as many believe that environmental pollution is the most dangerous factor for human health [4–6]. The main component of environmental pollution is plastic [7], which is continuously disposed of, in substantial quantities, as a by-product of human consumption. By plastics, we mean hundreds of different plastic polymers obtained from organic compounds. In today's society, plastic is an indispensable part of most everyday items. Since the creation of the first plastic polymers in the midtwentieth century, plastic production has increased dramatically, from 1.5 million tons in 1950 to 280 million tons of plastic produced in 2011, with an annual growth rate of 8.7 percent [8]. It is estimated that about 5.25 trillion pieces of plastic are currently circulating in the sea alone [9]. While a small portion of plastic waste ends up in the sea due to maritime activities, it is estimated that 80 percent comes from land-based sources [10]. Improperly

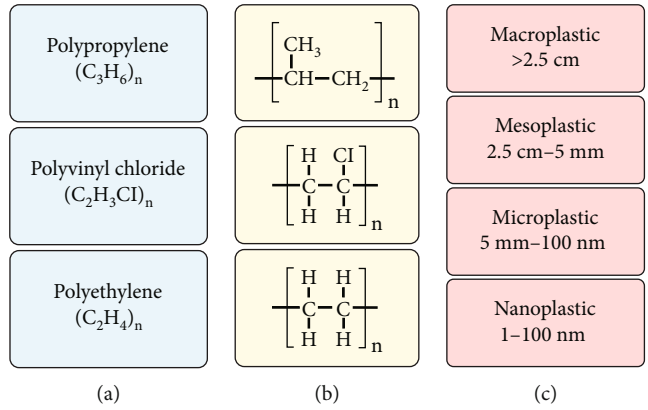

Figure 1: The most common forms of plastics for human consumption (a), structural formulas (b), and plastic pollutants are categorized by size (c).

disposed plastic waste accumulates in large quantities in the environment and comes under the influence of wind as well as river currents, which eventually reach the shores and enter the sea. The monitoring and "transport" of waste are proportionally connected and are inevitably associated with economic development, industrialization, and local infrastructure [11, 12].

The most common forms of plastics produced for human consumption and thus found in the sea are polymers polypropylene (PP), polyvinyl chloride (PVC), and polyethylene (PE) (Figure 1) [13]. The negative impact of larger pieces of plastic waste, better known as "macroplastics," on the marine environment is manifold. The effects on the human economy are most pronounced in many types of marine industries including fishing, aquaculture, and energy production, as well as maritime affairs, as plastics can greatly damage the equipment used in them. Another branch of the economy that is negatively affected by this problem is tourism, the main source of income for some countries [14]. However, the most severe and far-reaching consequences of marine pollution by plastics are borne by the ecosystem itself and all living organisms in it [15]. Some of the many consequences that plastic waste brings into the sea include injury and death of seabirds, mammals, and fish, occurring as a result of their interference with plastic parts, the introduction of plastic into the body by feeding, and transport of marine organisms from their natural habitat to new floating parts, as well as "choking" the seabed by preventing alteration gases due to deposits of plastic waste on it [16, 17]. Perhaps, the most shocking fact is that even if plastics were no longer disposed of in the sea, nanoplastic pollution would continue to grow as a result of the decomposition of preexisting plastic waste in the environment [18].

Nanoplastics can be defined as really small plastic parts, smaller than 1 μm in size. It includes a wide range of plastic particles, which vary in size, color, shape, and origin. The problem of nanoplastic pollution has become the subject of attention and concern of many scientists in recent years [19–21]. However, nanoplastics in the environment are not a completely new phenomenon. Namely, recent research has shown that nanoplastics have been actively accumulating in the seas and oceans around the world for the past 40 years. Due to their extremely small dimensions, nanoplastics are introduced into marine organisms through the food they eat and cause various blockages of the digestive and respiratory systems and other health problems [22, 23]. Nanoplastics can also be carriers of resistant organic pollutants which, due to the large ratio of surface to volume, as well as the hydrophobic surfaces of nanoplastics, are adsorbed on it. Intake of nanoplastics can thus also lead to the uptake of toxins into the food chain [24]. What worries scientists, even more, is the fact that marine organisms with accumulated nanoplastics in their bodies are being used in human nutrition. Thus, it is essential to study each aspect of nanoplastics individually.

2. The Invisible Spectrum of Plastic

Visible plastic can be removed from the environment, while micro- and nanoplastics remain an integral part of nature. Therefore, the toxic profile of micro- and nanoplastics is worse than that attributed to visible plastic [25]. Appropriate environmental clean-up actions relate to the removal of visible plastic, but not micro- and nanoplastics. Until recently, even microplastics were not the focus of the public debate, for the simple reason that they were not visible and detectable. Today, microplastics are a measurable quantity, a parameter of environmental plasticization that can be quantified [26]. Thus, in some ocean areas, there are more than a million microplastic fragments per square kilometer of the sea surface.

Just as microplastics are a bigger environmental problem than visible "bags and bottles," nanoplastics are, as already known, an additional and even greater risk to the environment and human health [27]. However, it is less known that microplastics can also be further converted into even smaller components. When the size of the resulting particles is less than one hundred nanometers, scientists talk about nanoplastics. Thus "small" (Greek: "micro") turns into "dwarf" (Greek: "nano"). However, until recently, that was just a guess. Apart from being invisible to the naked eye, like microplastics, nanoplastics are still difficult to access with analytical instruments [28]. Detection, quantification, and characterization of nanoplastic particles are too great of a

methodological challenge for many scientists. Therefore, nanoplastics are stuck in the realm of the hypothesis, not laboratories.

2.1. Nanoplastics. Plastics appear in the environment in visible and invisible forms. The visible form refers to common scenes, such as bags "flying" on tree branches or PET bottles floating in rivers, lakes, and seas. The visible form of plastic in the environment is an aesthetic mockery and a reminder of the socially indiscriminate reception of all offers from the petrochemical industry. The invisible form of plastic is called nanoplastic.

Plastic particles of different sizes can be found in the natural environment, so plastics are divided into macroplastics (particles larger than 2.5 cm), mesoplastics (particles between 2.5 cm and 5 mm), microplastics, and nanoplastics (Figure 1) [29]. The upper limit of microplastic particle dimensions is usually 5 mm, and the lower limit has not yet been determined [30]. The European Commission defines the dimensions of microplastic particles between 5 mm and 100 nm, while the particle size of nanoplastics ranges between 1 and 100 nm [31].

Nanoplastic can be obtained from primary or secondary sources [32]. These are plastic fragments invisible to the human eye such as filaments, granules, and flakes. There is a so-called secondary nanoplastic that is formed by the decomposition of larger plastic pieces and packaging [33]. By the action of ultraviolet rays and chemical and biological processes, visible plastic is crushed into invisible nanoplastic. However, there are also the so-called primary or synthetic nanoplastics that are targeted in the polymer industry and inserted into various products, such as cosmetics or textiles [34].

For example, researchers at McGill University in Montreal recently published a study showing that nanoplastics are found in many cosmetic products, especially those filled with microplastic granules [35]. Cosmetic nanoplastics are formed during the production process of shampoos, shower gels, or facial care products. These are polyethylene and polystyrene microgranules that are inserted into cosmetic products, which also create nanoplastic by-products. Using special detection and isolation techniques, Canadian scientists have proven that nanoplastics are a regular cosmetic supplement.

2.2. Sources of Nanoplastics. In the scientific community, there is still a debate related to the classification of plastic waste in relation to the size of the particles and their chemical composition. However, we can say that nanoplastics are polymer-based particles in the nanometer size range. By primary particles of nanoplastic we mean particles of a defined size and composition that are intentionally produced for use in industry, while secondary particles are regarded as particles created by the decomposition of larger plastic waste. Nanoplastics can originate from several sources, but the most important are tires, synthetic textiles, marine coatings, road markings, personal care products, plastic pellets, city dust, and nanoplastic from industrial suppliers. To date, plastic pollutants have occurred in oceans [36, 37], lakes [38, 39], soils [40], and sediments [41, 42]. However, nanoplastics have even been found in isolated places with rare or without human activity, such as the Arctic [43, 44] and the Antarctic [45]. Under the influence of external factors such as UV rays from sunlight, wind, and waves, the formation of nanoplastics could be formed if the mentioned pollutants have been found in the natural environment. Pollutants are subjected to mechanical fragmentation, and then, the small particles become even smaller and further transform into microplastic. At the moment of microplastic formation, the nanoplastic is also formed. This process cannot be stopped because it happens in nature [46]. It is a long and lasting process of the plastic lifecycle in the environment. Generally, poorly managed plastic matter leads to the formation of macro- and microplastic particles that further can be transformed into nanoplastic particles (e.g., polyethylene terephthalate (PET) or polystyrene) [47–50]. Compared to terrestrial ecosystems in the aquatic environment, plastic waste is significantly easier to fragment in the aquatic environment predominantly due to high salinity and the presence of microorganisms [51]. When microplastics are formed in environmental areas, the physicochemical factors affect further degradation of nanoplastics. The main factors are UV radiation, temperature, and pH. The presence of other contaminants (e.g., heavy metals and their oxides) can accelerate this process. Nonbiodegradation and biodegradation are key pathways in the mechanism of nanoplastic formation. The first path implies physical, thermal, oxidative, and photodegradation or even hydrolysis [52]. Thermal degradation is controlled by humans and cannot be reached in the environment. This process is followed by the oxidative transformation -C-C- bonds into -C=O and/or -C-O, thus significantly changing the hydrophobic properties of the plastics. Therefore, physical, oxidative, and photodegradation or hydrolysis of plastic matter have occurred in nature. Physical degradation is the first stage in the mechanism of nanoplastic formation. It implies the fragmentation of robust plastics into smaller pieces dependent on weathering conditions and sea waves. Different shapes are usually formed, e.g., flakes, discs, rectangles, cylinders, and spheres [53]. In this way, the contact surface is changed, which is important for the next steps in the degradation cycle. These formed species could be photodegraded via bond-breaking reactions that are dependent on UV rays, and consequently, the hydrolysis is processed. These associated abiotic processes convert a high to a low polymer. During this fragmentation process, significant changes will occur, such as structural differences, mechanical properties of the polymer, and increased surface area as the crucial property for their interaction with microbes [54].

Therefore, biodegradation is often a mechanistic path in the environment for converting plastic waste to nanoplastics [24, 55]. Biodegradation is slower compared to the nonbiodegradable path. Moreover, smaller pieces, as well as low polymers formed in nonbiodegradable paths, can be recognized by different microorganism populations that in combination with pH value, ions, oxygen, UV light, and temperature can produce nanoplastic particles.

2.3. Nanoplastics in the Environment. Nanoplastics are ubiquitous and are found all over the Earth: in the oceans, on the coasts, and inland [56], brought by wind from various

sources, nanoplastic sediment on the ground, from where they easily travel through the soil, ending up in aquifers and ultimately contaminating drinking water. The path of nanoplastics in the environment is interconnected with all three components, and in each of these, their harmful effects are found [57]. However, the biggest problem is the organisms that live in aquatic systems.

In aquatic ecosystems, nanoplastics are found in all parts of the water column [58]. Due to their structure, polymers have a specific density (0.9-2.3 g/cm^3) that is lower than the water density (1.02 to 1.03 g/cm^3), which leads to the floating of plastics and nanoplastics on the water surface [59]. However, on the surface of nanoplastics, organisms (e.g., algae) can colonize and increase the weight of particles, i.e., change the density, and thus reduce buoyancy, which allows immersion. Algae overgrow plastic waste that ends up in the sea, so much waste under the influence of sea currents transfers the species to places where they were originally absent [60]. Chemicals adsorbed on microplastics can have a toxic effect, and nanoplastic particles are small enough to pass through cell walls and membranes and reduce population growth and chlorophyll concentration, as studied in green algae *Scenedesmus obliquus* [30]. Fragmentation does not affect particle density because it does not change the chemical composition. Furthermore, the concentration of plastics, therefore nanoplastics, in the oceans depends on the period in which it is sampled. For example, if the coastal winds are low, the concentration is higher. Water that flows at a lower speed has lower energy, and the plastic that is denser than its environment will sediment. In areas of faster water flow, the plastic is easier to carry and resuspend. Furthermore, the areas of lower salinity show an increase in the plastic deposition as a result of an increase in plastic density [61].

Finally, the sum of the actions of coastal winds, the colonization of nanoplastic particles, and the exact distribution of nanoplastics in the water column remain unknown. Nanoplastics from cosmetic products, cleaning products, medicines, and mostly from washing machines that emit microfibers end up in municipal wastewater [35, 61]. Microfibers come from synthetic fabrics from which much of the garment is made, and it is estimated that 1900 synthetic microfibers are released during a washing cycle [61]. Furthermore, due to the very small size of the particles, they pass through filters in wastewater treatment facilities and end up in rivers or soil through direct discharge of treated water or using waste sludge, from where they travel to other parts of the environment. According to Mason et al., between 50000 and 15 million microplastic particles pass through wastewater treatment facilities daily [62].

2.4. Surface Toxicity. Just as microplastics are a bigger environmental problem than visible "bags and bottles," nanoplastics, according to scientists, are an additional and greater risk to the environment and human health. Nanomaterials, including nanoplastics, have a special property: although their size is on the scale of ordinary molecules, the (relative) surface area of nanomaterials is extremely large and active. Moreover, most of the biological, chemical, and technological properties of nanomaterials are attributed to this new dimension or parameter—the surface.

Nanoplastic size corresponds to the size of cell membranes, and due to hydrophobicity, it is easily absorbed into cells. This is sufficient for the mechanism of cellular toxicity (cytotoxicity) proven in nanoplastics [63, 64]. Unfortunately, the regulation of nanoplastics in cosmetics and food is unclear, which gives room to the industry to "hunt in the dark". In Table 1 are presented some *in vitro* and *in vivo* studies impaling the threats of nanosized plastics in the marine environment.

2.5. Cellular Responses to Nanoplastics. The toxicity of nanoplastics is a subject of discussion throughout the scientific community and has been attracting attention for many years. The cellular response depends on the way and route of absorption of nanoplastics and the location in the body where they are stacked (Figure 2). It is considered that gastrointestinal and airway cells are the most exposed places to nanoplastics.

Intra- and extracellular responses could be significantly different mainly because of the various physical properties of the nanoplastics particles. Effect of particle size and dose, the effect of particle charge, and time of exposition are the key factors that can induce different cellular responses if nanoplastics are found in the cell. Due to the enormous use of plastic in food packaging, the largest number of studies is focused on the effect of nanoplastics on the cells of the gastrointestinal tract [71]. The intestinal epithelial tissues primarily contain enterocytes, mucus-producing goblet cells, and microfold or M cells. There are two trafficking lines for polystyrene nanoparticles by Caco-2 cells. Primarily and the literally accepted mechanistic line was discovered and interpreted *via* micropinocytosis-mediated uptake [72]. Every few days (4-5), trapped nanoplastics might be excreted *via* epithelial cell shedding. A limited mechanistic path of the administration implies diffusion across the cell membrane. The process of elimination is followed by basal exocytosis. For instance, phagocytic M cells in the gut epithelia can significantly make nanoparticles transport better [73]. Furthermore, some types of adenocarcinoma cells are treated with nanoplastics sized from 44 to 100 nm. Experiments lasted one day while the tested concentrations were 1, 2, and 10 μg/mL [74]. During 1 h exposure, any morphological changes in cells have not occurred. The important fact is that all sized particles during 1 h increased the level of interleukin-1β, interleukin-6, and interleukin-8 proinflammatory cytokines. Going forwards, few studies showed low toxicity of nanosized plastics in Caco-2 intestinal cells. In that way, Cortés and coworkers demonstrated that after the treatment with 50-100 nm size particles, no increases of the ROS have been detected [75]. However, the authors have noticed the increase of mitochondrial membrane potential in a dose-dependent manner (0-100 μg/mL). In addition, the DNA cleavage or oxidative damage has not been approved after the treatment. Even though the gastrointestinal toxicity of nanoplastics of different sizes has not been proven in many studies, still, it is the subject of debate in the scientific community [76–79]. Knowing that the cell membrane has its

Table 1: Toxicity of nanoplastics to marine species and animals.

Study	Marine species	Potential toxicity/damage/threats
Wegner et al. [65]	Blue mussel (*Mytilus edulis*)	Extended exposure to nanoplastic can harm *Mytilus edulis* due to producing pseudofeces; it consumes energy, while reduced filtering activity can finally take to starvation.
Brandts et al. [66]	Mediterranean mussel (*Mytilus galloprovincialis*)	Significant alterations in the expression of genes associated with biotransformation, DNA repair, cell stress-response, and innate immunity have been discovered. Genotoxicity in hemocytes has been noticed.
Canesi et al. [67]	Mediterranean mussel (*Mytilus galloprovincialis*)	Increased cellular damage and ROS production.
Cole and Galloway [68]	Pacific oyster (*Crassostrea gigas*)	Exposure to nanoplastic concentrations greater than those meshured in the marine environment showed no measurable effects on the development or feeding capacity of the pacific oyster larvae.
González-Fernández et al. [69]	Pacific oyster (*Crassostrea gigas*)	The increase of relative cell size and ROS production was observed.
Besseling et al. [70]	Algae (*Scenedesmus obliquus*)	Nanoplastics inhibited the growth and development of this species. It also had an impact on increased mortality.

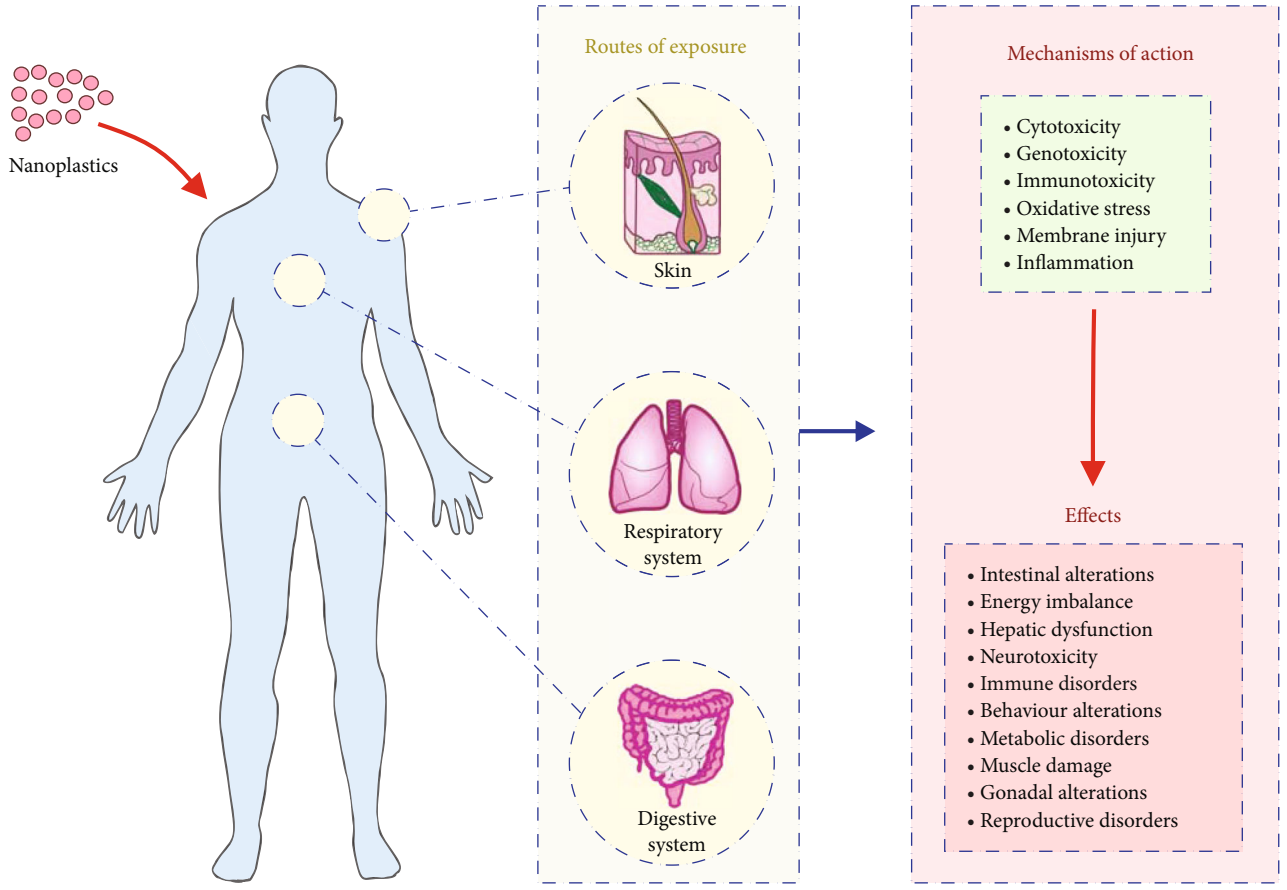

Figure 2: The most important routes of exposure, mechanisms of action, and effects of nanoplastics on the human organism.

own potential, it is very important to examine the effect of the nanoplastic surface charge on toxicity. For example, Walczak and collaborators investigated the effects of particle charge on the translocation efficiency across Caco-2/HT-29-MTX coculture. The highest translocation has been denoted for negatively charged particles [80, 81]. Mucin is a negatively charged glycoprotein with high molecular weight. Positively charged nanoplastics could smoothly bind to mucin resin *via* electrostatic forces and as consequence make changes within rheology [82, 83]. Similar conclusions have been obtained by Rieux and colleagues [84] who have investigated the effects of the absence of mucin. The study also

showed that the transport of nanoparticles with amine resin has been higher in comparison with the carboxylated. Apoptosis was induced in the presence of catalase and nanoplastics with carboxylate resins. Thubagere and Reinhard suggested that this intracellular event was caused by nanoplastics particles and hydrogen-peroxide [85]. On the other hand, amine resins were capable to pass the mucin layer. Some investigations showed that after treatment with polystyrene nanoplastic beads, Caco-2 does not produce mucin, HT-29 produced a limited quantity of mucin, and LS174T produced abundant mucin cells [86]. In all treated cells, apoptosis was triggered after treatment with a high concentration (100 μg/mL), whereas the lowest concentration (20 μg/mL) caused higher cytotoxicity.

Besides, the inhaled nanoplastics can be responsible for plenty of respiratory problems such as irritation, dyspnea, decreased lung capacity, interstitial fibrosis, and granulomatous lesions [87, 88]. In one study [89], bronchial epithelial BEAS-2B cells were treated with different sizes of nanoplastics. Oxidative stress with significant ROS accumulation has been noticed upon 24 h. Cytokines interleukin-6 and interleukin-8 were also overexpressed. The nanoplastics with negatively charged resins and 60 nm size similarly generated oxidative stress in BEAS-2B cells [90]. Dose-dependent autophagy has also been provoked after the treatment. Namely, TCA cycle intermediate, pyruvate, and lactate were detected in nanoplastic-treated cells. All these facts implied that autophagy was caused by oxidative stress, due to the exposure of the cells to nanoplastics. The effects of different sizes of nanoplastics (25 and 70 nm) to A549 cells have also been investigated in the study by Xu and coworkers [91]. Namely, toxic effects and dose-dependent apoptosis were noted after 24 h for 25 (25–30 μg/mL) and 70 nm (160–300 μg/mL) particles. BEAS-2B cells were taken to investigate the effect of nanoparticles charge [92]. The aminated and carboxylated 60 nm particles have been used. After one day of incubation, the aminated particles caused the necrosis, most probably because of mitochondrial injury that is followed by fast ATP consumption. Higher toxicity of aminated compared to carboxylated nanoplastics has been discovered by Chiu and collaborators [93]. The higher toxicity has been proven in the *in vivo* study, where aminated nanoparticles caused up to 40-fold higher flux than carboxylated particles [94].

2.6. Nanoplastics in Food. Significant amounts of nanoplastics are found in aquatic species that are intended for human consumption, which allows nanoplastics to end up in the human body through the food chain. Nanoplastics are found in a variety of foods and beverages: seafood, beer, honey, sugar, salt, and drinking water [95]. 1000 particles of microplastics per person are introduced through sea salt. According to research by Orb Media on tap water samples from around the world, data show that a large proportion of drinking water is contaminated with microplastics, and the amount of microplastics ingested per person each year is 4,000 particles. Moreover, nanoplastic particles have been found in bottled drinking water, plastic, and glass bottles [96]. After being taken into the body, the nanoplastic particles are distributed into various tissues (testicles, liver, blood, gills, and intestines). Numerous pieces of evidence are emerging indicating that nanoparticles affect the connection between the gastrointestinal and nervous system, gut-brain axis (Figure 3). Nanoparticles can cross the blood-brain barrier, a highly selective barrier necessary for neuronal functioning and crucial for maintaining necessary homeostasis and protecting the brain from toxins [97]. There are numerous ways of communication between the gut and the brain. The core of the gut-brain axis consists of the vagus nerve, which via afferent fibers sends information about the state of the internal organs to the brain and connects the CNS with the enteric nervous system. The sensitivity of the vagus nerve affects various responses in the brain, stimulating regions associated with feeding behavior and numerous psychological functions including emotions [97–99]. Efferent vagus activity affects the intestinal immune system and metabolism [97, 99, 100]. The CNS also interacts with the gastrointestinal tract through the hypothalamic-pituitary-adrenal axis (HPA axis) [99]. In response to hypothalamic and pituitary gland stimulation, adrenal glands produce the primary stress hormone, cortisol, which can modulate various processes in the gastrointestinal system [98]. The rare but consistent evidence shows that exposure to plastic nanoparticles can affect both the digestive and the nervous systems. The main effects include microbiota alterations, intestinal barrier permeability, oxidative stress, inflammation, neurotoxicity, and behavioral disturbances [97]. To supplement the information on the impact of nanoplastics on humans, it is important to summarize the potentially harmful effects of nanoplastics.

2.7. Side Effects of Nanoplastics. Numerous studies have shown that nanoplastic particles can lead to several side effects such as increased free radicals, activation of oxidative stress pathways, oxidative stress, DNA damage, lipid peroxidation, dysfunction of certain cellular organelles, and overactivation or inhibition of certain enzymes (Figure 4).

Our recent study investigated, in an animal model, the effects of oral uptake of polystyrene nanoparticles, a material that is widely present for human consumption. We demonstrated that after oral uptake, fluorescent polystyrene (PS) nanoparticles pass through the digestive system of mice, accumulate and aggregate in different organs, and induce functional changes in cells and organs. Apart from the increased accumulation in the inner ear, our results showed that PS effects were also gender-dependent. Male mice had significant accumulation in testicular tissue, which was associated with a decrease in testosterone levels. In addition, male mice showed a broad range of anxiogenic responses to PS nanoparticles, while hippocampal samples from treated females showed an increased expression of Bax and Nlrp3 genes, indicating a proapoptotic/proinflammatory effect of PS treatment [101].

A lysosome is a one-layer cytoplasmic organelle with high sensitivity to xenobiotics, including natural toxins. Consequently, lysosomal layer stability can be utilized as a biomarker to determine the potential effect of environmental contamination [102]. The lysosome capability disturbance was tracked down in blue mussel (*M. galloprovincialis*) [66,

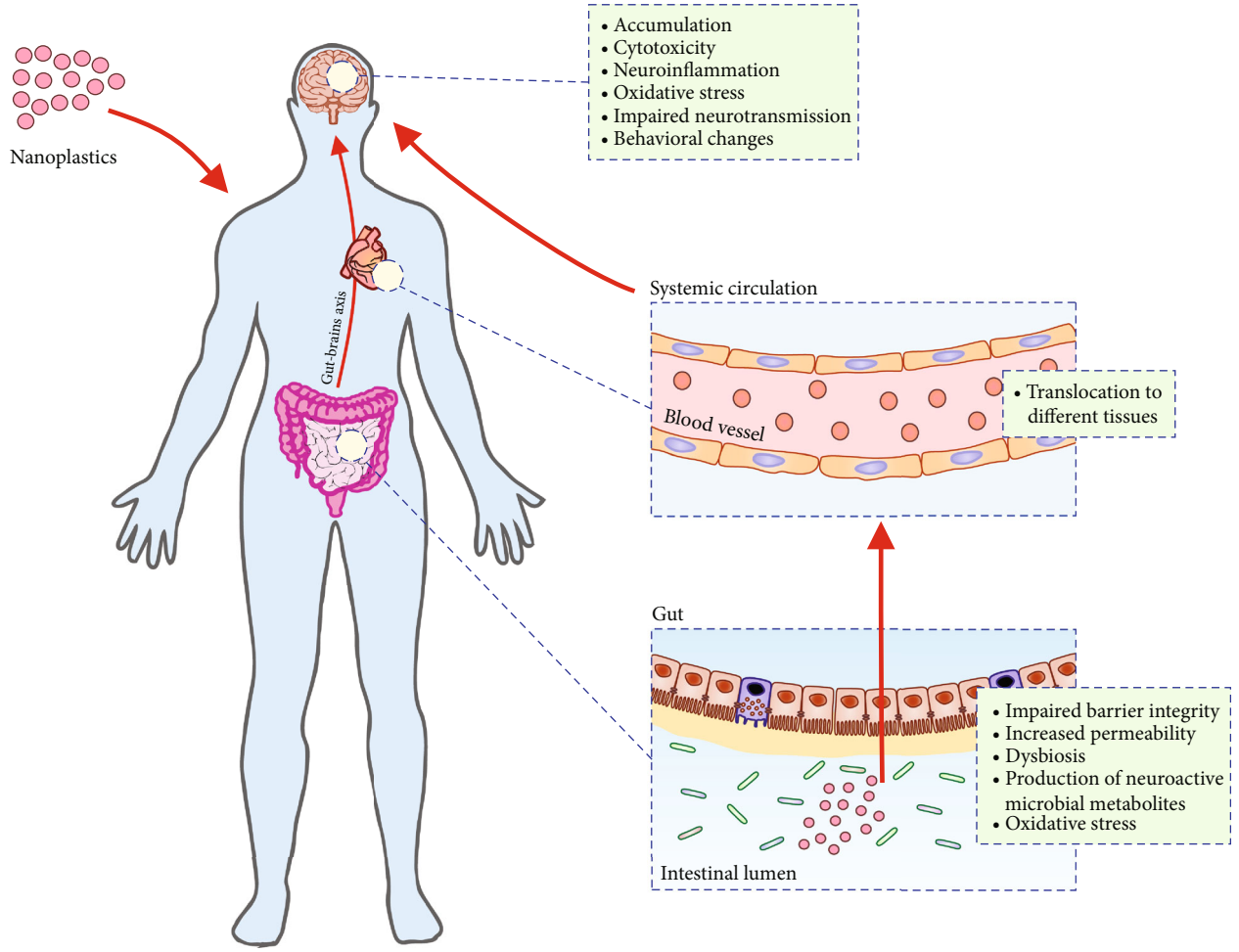

Figure 3: The effects of nanoplastics exposure on the gut-brain axis.

103]. These toxicological studies proved significant genotoxicity after treatment with micro- and nanoplastics. Similar results were achieved after treatment of marine bivalve hemocytes with polystyrene nanoplastics in a physiological environment [104]. The presence of the mentioned nanoplastics increased cellular damage and reactive oxygen species (ROS) production compared to the control medium. Dysregulation of p38 mitogen-activated protein kinase (MAPK) signaling was also noted. Moreover, the connection between oxidative digestion and ROS generation and induced stress was established, including the harmful influence of nanomaterials on the lysosome function. Nanoplastics can prompt lysosomal harm following the following mechanism of action: (1) direct harm after ingestion of plastic particles in the cell through endocytosis or permeation (<50 nm) and attempts to process an unfamiliar body which might bring about lysosome interruption [105, 106]. The creation of ROS induced by the presence of nanoplastics impacts lysosomal membranes that are very sensitive to the oxidative effects of released ROS. However, the exact pathway within the mechanism of nanoplastics action on lysosome function has not yet been discovered and demands more toxicological studies (*in vitro* and *in vivo*).

Mitochondria are organelles in which most of the intracellular creation of ROS happens. Mitochondrial layer potential instability can lead to excessive generation of ROS through single-electron transporters (for example, cytochromes and iron-sulfur protein) and other oxidases [107].

From a mechanistic point of view, excessive exposure to oxidative stress results in a critical level of ROS, thus making the mitochondrial channels open. Consequently, mitochondrial membrane potential will collapse. Furthermore, the authors reported mitochondrial brokenness during the treatment of monogonont rotifer (*Brachionus koreanus*) with nanoplastics. During this process, the charge collapse has been denoted as a critical point [107, 108]. These results require further investigation as nanoplastics cannot directly accumulate in mitochondria. The mentioned studies in rotifer *B. koreanus* revealed that 0.5 μm polystyrene microbeads decreased the mitochondrial layer potential significantly. Furthermore, it was suggested that nanoplastics might influence the mitochondrial external layer (membrane) by implication through expanded ROS presence in cellular compartments beyond nearby mitochondria [107]. Exposure of mitochondria to unnecessary oxidative stress in the cytosol can trigger the activation of several mitochondrial Na/K

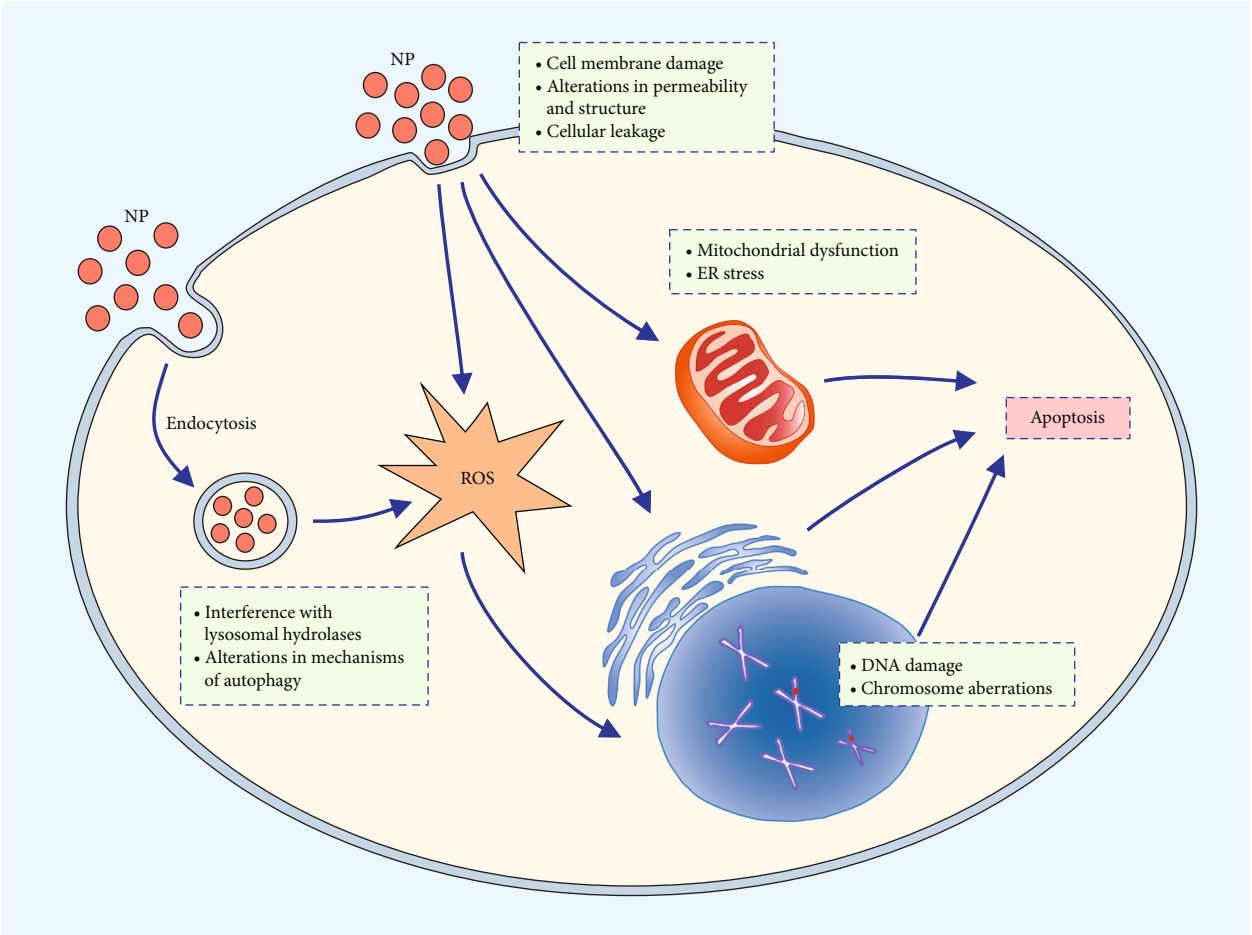

Figure 4: The intracellular side effects of nanoplastics.

transmembrane channels. Ion transition *via* an expanded membrane channel may further promote the breakdown of the mitochondrial layer potential and deliver ROS through a stimulated ROS scavenging mechanism [107].

Mitochondrial layer harm caused by nanoplastic presence is also related to the particle size. Nanoplastics could be less than 5 nm, implying that nanoplastics could force more extreme harm on mitochondria [108]. In that regard, nanoplastics activated mitochondria interruption in *D. magna* and an assortment of human cell lines [109, 110]. In addition, amine-functionalized polystyrene nanoplastics prompted essentially more extreme mitochondrial damage than the nonchanged ones. Therefore, this implies that the surface charge of nanoplastics takes on a significant role in causing adverse effects on mitochondrial function [110].

DNA strand damage might happen over the oxidative path. There is a current debate on whether nanoplastics are prompting DNA harm generally since just two articles to date have revealed that DNA damage happens in aquatic living models [103]. DNA strands could be broken down by polystyrene nanoparticles (20 nm) in the hemocytes of *S. plana*. Additionally, it was detected in mussels treated with polyethylene nanoparticles [111]. The two reports proposed that the noticed DNA harm could be related to the oxidative damage caused by nanoplastics.

Genotoxicity caused by nanoplastics, including damage to DNA strands, has also been under investigation. Nevertheless, an illustration from more extensive nanotoxicological research has shown that some nanoparticles (such as nanoplastics, titanium dioxide) can cause DNA damage through two systems: (I) direct interaction among nanoparticles and DNA and (II) aberrant DNA harm brought about by nanoparticle-produced ROS. An intracellular unique imaging study showed that cationic functionalized PS nanoplastics could result in a delayed G0/G1 work in the cell cycle during mitosis in NIH 3T3 cells [112]. The results demonstrated the potential for DNA harm. Paget and coworkers indicated that unmodified PS nanoplastics did not induce genotoxicity after 8.1 μg/cm discharge during one hour of exposure [113]. There is proof that nanoplastics can prompt DNA strands to break down predominately depending on the nanoplastics size and their surface charge.

Lipid peroxidation (LPO) is a self-sustaining reaction chain triggered by excessive ROS generation; the result is antioxidant damage to cell membranes and other fatty structures [114]. It has now become a topic of discussion as to

whether the reaction and cell membranes in the exposure of nanoplastics are triggered on this human scale. In a study by Barboza and coworkers [115] in European countries, a significant increase in LPO in brain and muscle tissue has been noted to occur naturally after the release of nanoplastics in 0.69 mg/L doses within 24 hours. Another review showed that LPO was not essentially induced in hemocytes of the sea mussel Mytilus spp. after 7 days of nanoplastic exposure. Moreover, in *S. plan*, LPO levels in gills and stomach-related organs were either decreased or not substantially increased after 7 days of exposure to polystyrene nanoparticles. The authors proposed that such an outcome could be explained by an adequate limitation of antioxidant systems to defend the form of the organism against LPO damage. But it would be at least prudent to consider this molecular event as the main event induced by the nanoplastics [15]. This approach would be additionally upheld with nearly 10% of surveyed examinations showing that LPO and resulting harms were prompted by nanoplastic openness, subsequently proposing the likelihood that LPO might be a harm endpoint shared by the plastic particles in both the miniature and nanosize ranges.

2.8. Effects of Nanoplastic on Oxidative Stress. Oxidative pressure happens when there is unevenness between the creation of ROS and cancer prevention agent-based detoxification/balance. The antioxidant process is very complicated and includes different antioxidant compounds such as C, E, and D3 vitamins, respectively. Different enzymatic pathways are occupied by several manufacturers to remove oxidants, or antioxidants, as well as reactive nitrogen species and ROS. This goes past the extent of the previous framework review, and this translation is past the extent of the antioxidant system framework survey. Sies and colleagues explored oxidative pressure pathways after exposure to nanoplastics [116].

Antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), play an important role in protecting tissues against ROS damage [117]. For example, a complex ROS scavenging framework in natural resistant cells uses SOD and CAT enzymatic systems to catalyze the conversion of superoxide anion radical (O_2^-) and hydrogen peroxide (H_2O_2) into water (H_2O) and oxygen (O_2) as metabolites, respectively [118]. CAT and SOD-based antioxidant mechanisms play a significant cellular role in the adverse effects of ROS that could be used as a sensor of xenobiotic-mediated oxidative stress [119, 120]. Exposure to nanoplastics could expand the grouping of ROS in the live form as we recently described, and the SOD and CAT antioxidative enzymes would respond to such a signal.

The determination of antioxidant properties related to nanoplastics was found in different animal models, such as water fleas (*Daphnia magna*) [121], rotifers (*B. koreanus*), mammals (*M. musculus*) [122], and fish (*D. rerio*) [122, 123]. This peculiarity proposes the presence of initial factors to start the disturbance of oxidative status induced by microplastic openness. Because of nanoplastic particle entry, an increase in oxidative stress parameter levels of approximately 50% was observed both in *in vitro* and *in vivo* studies. Those levels of oxidative imbalance have been reported to set the oxidative damage as one of the most decisive factors accompanied by adverse effects among all nanoplastic-induced poisonousness endpoints.

It was plainly shown that ROS can instigate or intervene in the enactment of the MAPK pathways [124]. However, definite instruments of MAPK downstream pathway guidelines remain unclear. Some studies revealed that activation of MAPK signaling could activate antioxidant response element-interceded quality articulation through the simultaneous component increase Nrf2 (nuclear factor erythroid 2-related factor 2) activity, and apparently, MAPK enactment by ROS can be downregulated by concurrent expansion in Nrf2 action [125]. In contrast, the drawn-out initiation of MAPK framework with expanded ROS generation can activate different adverse pathways (such as autophagy), basically connected with the hindrance of extracellular-signal-regulated kinase (ERK) and enactment of p38 MAPK parts. It was recently detailed that brominated fire-resistant prompted oxidative pressure in two copepod species enacted the MAPK pathway [126], and it was concluded that MAPK pathways assume a synergistic part with the Nrf2/Keap1 pathway in the oxidative pressure reaction in the scallops presented to benzo(a)pyrene [127].

In the following stage in the oxidative pressure occasion series, it has been seen that nanoplastic openness additionally enacts redox-sensitive signaling pathways such as MAPKs. MAPK downstream pathways were started post-nanoplastic openness in the marine copepod *P. nana* and Mitten crab *E. sinensis* [27, 53]. Jeong and colleagues showed that the phosphorylation level increment of ERK and p38 kinase had a positive relationship with intracellular ROS age-level post-microplastic openness in *P. nana* [127]. The factor Nrf-2 was extended after openness to nanoplastics. As a consequence, nanoplastics set off breath bursts plausibly acted using ERK and p38 MAPK pathways activated by Nrf-2 [128].

The activation of the MAPK pathway is related to the size of a nanoparticle. Going forward, the MAPK pathway is activated after exposure to nanoplastics [66, 109, 129]. It was recommended that plastics with a size of 50 nm could create more serious oxidative pressure in comparison to 6 μm plastic, causing higher phosphorylation levels of p38 MAPKs in both *P. nana* and *B. koreanus* [130]. Furthermore, the surface charge of nanoplastic particles seems essential in the enactment of MAPK overflow, as plain/local polystyrene nanoparticles prompted the activation of p38 and c-Jun N-terminal kinase (JNK) alongside ROS enlistment, while adversely charged polystyrene nanoparticles activated p38 and JNK autonomously [109].

A free radical is a group of atoms with more than one unconnected electron. Generally, in the biological system, various radicals are synthesized from oxygen and are together referred to as ROS [131]. Several reports pointed out that the generation of ROS happens at release time, after exposure to the nanoplastics of different sizes and characteristics [108, 132, 133]. The remarkable nanoplastic process of ROS generation has two stages; intracellular and

extracellular. Electrocellular ROS generation induced by nanoplastics connects with the level of enduring (maturing) process during plastic polymers' openness to the components in the environment [134, 135]. Enduring cycles of nanoplastics include the concurrent or individual activity of photooxidation and warm oxidation, as well as UV radiation prompting synthetic changes on the outer layer of plastic polymers [136]. Photooxidation and/or UV light radiation can prompt the development of free radicals on nanoplastic surfaces as essential items through various pathways: deduction of a hydrogen atom from the macromolecular chain, or through cross-linking response (expansion to an unsaturated carbon chain bunch) [137]. Consequently, with the creation of free radicals in the polymer series chain, the second type of polymer chain is created due to appropriate conditions in the atmosphere [138]. This enduring prompted extracellular free radical release could be one of the potential mechanisms regarding the substantial increment of ROS amount observed after the cellular entry of the matured nanoplastics [67].

Nevertheless, the most primitive nanoplastics can trigger the abundant intracellular ROS production. This peculiarity was accounted for by utilizing a wide cluster of model frameworks, from mammalian cell lines to marine invertebrates and living fish models [134, 138]. Nanoplastics can be immersed by a cell through the processes of endocytosis or pinocytosis [132]. When inside a phagocyte, these nanoplastics seem to set off the natural insusceptible protection systems and are treated as unfamiliar substances [139]. Moreover, when a microplastic debases into nanosized particles, their surface-to-mass proportion increases and enables the nanoplastics to enter directly through the lipid layers. Changes in surface charge potential and mass/surface proportion in nanoplastics likewise empower simpler retention of free revolutionaries as well as more straightforward movement through the films, introducing areas of strength between the molecule size and ROS age potential: the more modest the molecule, the higher ROS age potential [135]. Size-subordinate contrasts in the harmfulness of nanoplastics are upheld by a few examinations [136].

3. Conclusions

In recent years, the problem of nanoplastics has gained importance both in the scientific community and in the general public. Numerous studies have revealed that nanoplastics are a ubiquitous pollutant of the human environment, which, in addition to environmental pollution, poses a serious threat to the organisms in them. Namely, numerous studies examining the organisms living in those ecosystems have revealed that nanoplastics can cause blockage of the digestive tract, inhibition of growth, reproduction disability, and ultimately cause death.

The presence of nanoplastics in fish and many other marine species has shown that nanoplastics can easily reach the human body through the food chain. The impact of nanoplastics, however, cannot be observed only at the level of a particular organism. Namely, nanoplastics can completely change the population structure of a particular species and ultimately lead to a change in the dynamics of the entire ecosystem. What is even more worrying is the potential impact of nanoplastics on humans themselves. By consuming marine organisms that contain accumulated nanoplastics, a human takes nanoplastic particles into his body. Depending on the concentration ingested, nanoplastics can have various negative consequences on human health as listed above. Many studies have shown that nanoplastics in the human body can cause an inflammatory response and disruption of the intestinal microbiome and cause many other side effects including oxidative stress.

Finally, it can be concluded that nanoplastics in the human environment have multiple negative impacts, and this problem should be approached with extreme seriousness and attention. A strategic plan should be made to solve it, including individuals, as well as local and global communities.

Conflicts of Interest

The authors confirm that this article content has no conflict of interest.

Authors' Contributions

Nenad Joksimovic and Dragica Selakovic contributed equally to this work.

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