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Immunotoxicity by Microplastics

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Abstract: In today's modern environment, microplastics have become pervasive, infiltrating ecosystems on a global scale. This widespread distribution has raised substantial concerns regarding their potential repercussions on human health. Given their persistence in diverse habitats, it is imperative to comprehend the immunotoxic effects of these minuscule plastic particles, not only for safeguarding human well-being but also for preserving the integrity of ecosystems worldwide. This comprehensive review aims to shed light on the origins of microplastics and their detrimental impact on the immune system. While considerable attention has been devoted to investigating the environmental ramifications of micro and nanoplastics, there exists a notable gap in our understanding of their effects on the human body at the subcellular or molecular levels. Specifically, the intricate pathways through which micro and nanoplastics traverse the gastrointestinal tract, respiratory system, and various layers of the skin to induce harm remain largely uncharted territory. Mounting evidence suggests that microplastics possess the capacity to provoke a range of immune responses, including triggering inflammation, inducing oxidative stress, and disrupting the normal functions of immune cells. Despite the accumulating data linking microplastics to immune system dysfunction, substantial knowledge gaps persist regarding their long-term consequences for human health and ecological equilibrium. This review underscores the critical importance of further exploration into the mechanisms and impacts of microplastic-induced immunotoxicity. Such endeavors are essential for developing effective mitigation strategies aimed at curbing the adverse effects of microplastics on both ecosystems and human health. By deepening our understanding of these processes, we can work towards safeguarding the well-being of present and future generations and preserving the delicate balance of our planet's ecosystems.

Keywords: Microplastics, Nanoplastics, Immune response, Immunotoxicity, BPA, Heavy metals, Phthalates, Probiotics

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Introduction

Plastics, a group of synthetic materials derived from polymers, exhibit remarkable versatility in being molded into various shapes, rendering them indispensable across industries such as transportation, packaging, automotive, construction, healthcare, and electronics (Ferreira *et al.*, 2020). Serving as vectors for transporting diverse chemicals, the widespread distribution of plastics

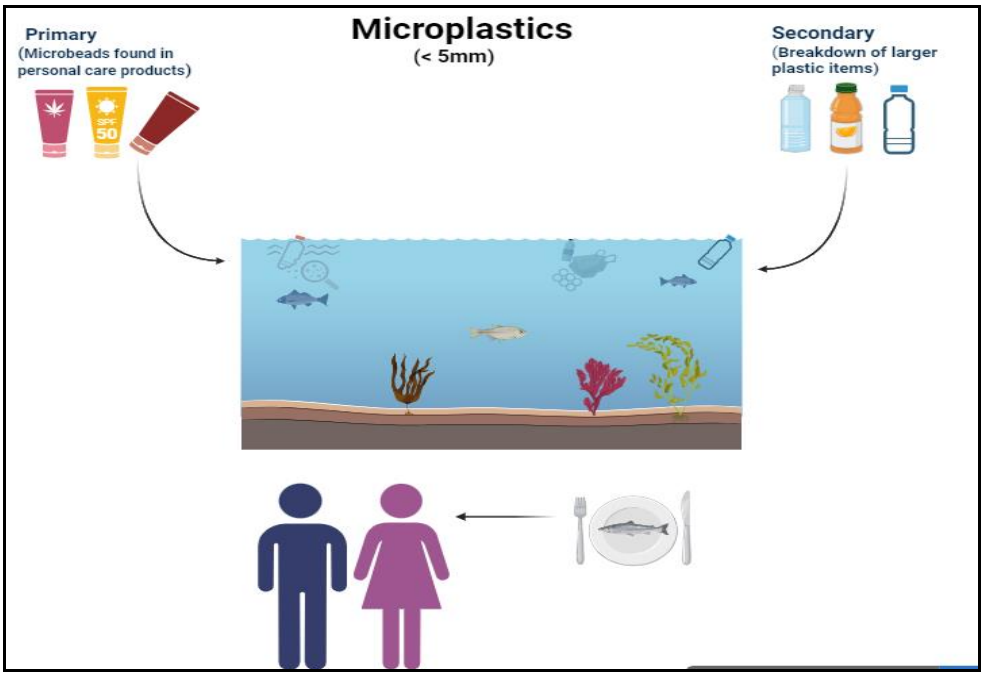

Fig. 1: Types of microplastics and introduction of microplastics in food chain.

serves as a defining feature of the Anthropocene era, according to many scientists (Jambeck *et al.*, 2015). While their durability and convenience have revolutionized modern life, the inherent lack of biodegradability has spurred significant environmental concerns, impacting both marine ecosystems and human health (Geyer *et al.*, 2017).

The inception of artificial plastic traces back to 1862 with Alexander Parkes' introduction of "Parkesine," later modified by John Wesley Hyatt into "celluloid," capable of mimicking horn, linen, and tortoiseshell (Rao, 2018). Presently, global plastic production stands at an estimated 390.7 million metric tons annually, with plastic waste production exceeding 350 million metric tons. China leads in plastic production, generating 85 million metric tons in 2018, while India's plastic consumption reached approximately 21 million tons in 2021 (PlasticsEurope, 2022).

The term "Microplastics" was coined in 2004 by Professor Richard Thompson, referring to tiny plastic particles typically measuring less than 5 mm in length (Thompson *et al.*, 2004). They are categorized into primary microplastics, intentionally manufactured to be small (e.g., microbeads in personal care products), and secondary microplastics, resulting from the breakdown of larger plastic items due to environmental factors like sunlight and wave action (Fig. 1)(Galloway, 2015). Microplastics may contain chemicals originating from plastics' additives, monomers, or oligomers, as well as absorbed environmental chemicals. Additives, incorporated during plastic production, imbue plastics with properties like transparency, color, and resistance to degradation. Nanoplastics, ranging from 1 to 100 nanometers, are even smaller particles resulting from the breakdown of larger plastic products. Their minute size allows them to penetrate cellular structures, raising concerns about their impact on human immunity and the environment (Hartmann *et al.*, 2019).

The pervasive presence and toxic effects of Microplastics and Nanoplastics on human health, marine life, and the environment underscore their status as a global issue in need of urgent attention (Hermabessiere *et al.*, 2017).

Sources and routes of exposure of Microplastics:

Microplastics can be derived from various

plastic items such as plastic carry bags, plastic water and cold drink bottles, food containers, many kitchenware and household appliances, many medical devices such as syringes and various construction and electrical materials. Micro-plastics are also found in the air. City dust, synthetic textiles, tires are some sources of microplastics in the air. A study found that 83% of tap water in metropolitan areas contained microplastics, the rate was higher in bottled water (Hirt *et al.*, 2020).

Microplastics are formed from degradation of large plastic items which can occur through various process such as weathering, abrasion, photodegradation (breakdown due to sunlight). These events contribute to the generation of microplastics which then spread in various environment and eventually enter human body and aquatic lives. As fish is an important protein source for human, it can enter the human body through consumption of fishes also (Fig. 1). Microplastics are also found in sugar, salt, honey and other edible things. Nine types of microplastics have been found in human feces. Microplastics has also been detected in sea salt from various countries. These events proves that food chain is an important source of microplastics that enters the human body (Yang *et al.*, 2022). Microplastic contamination is also widespread in various soil settings such as agricultural, farmland, coastal, home garden, industrial and floodplain soil. Agricultural practices contribute to the introduction of microplastics into the soil with the use of plastic mulches and sewage sludge application (Hirt *et al.*, 2020).

Microplastics can exposed to human by dermal contact as microplastics are used in many personal care products such as facial cleansers, exfoliating scrubs, toothpastes, soaps, moisturizers, shampoos. A Chinese study reported that around 7% of facial cleansers contains microplastics. Most of these microplastics are made of PE (polyethylene). Alvarez-Roman *et al.* (2004) conducted an experiment using fluorescent polystyrene particles ranging 20-200 nm in diameter and skin tissue of pig. Confocal laser scanning micrograph of the skin showed that mostly 20 nm polystyrene particles concentrated in the follicles but they cannot penetrate the stratum corneum in order to sink themselves deeper into the skin tissue. Vogt *et al.* (2006) conducted an experiment with 40 nm fluorescent polystyrene particles in the perifollicular tissue of skin and discovered that when particles were applied transcutaneously, they were absorbed by the Langerhans cells (Yee *et al.*, 2021). Overall, in case of human microplastics are exposed by multiple ways (e.g. ingestion, inhalation, dermal contact). Internalization of microplastics depends on some factors such as their size, surface charge etc. After exposure those microplastics translocate to different tissues where cells uptake them depending upon their size. Microplastic internalization process increases with decreasing microplastic size. Positively charged microplastics can easily enter the cell membrane compared to negative and neutral microplastics (Panariti *et al.*, 2012).

Immuno-toxic agents:

Toxicity of any substances is its ability to cause harmful effects. These effects can be seen within single cell or group of cells, tissues, an organ or the entire body. Most harmful chemicals are those which cause DNA mutation, cancer, hormone disruption, toxic reproductive effects and capable of building up in the food chain. Endocrine disrupting chemicals (EDCs), substances external to the human or animal body, exhibit hormonal activity, disrupting the endocrine system's equilibrium, raising significant concerns. They disrupt endocrine system development and performance of the organs that rely on hormonal cues. The adverse effects on endocrine and reproductive functions results from their ability to: (a) replicate natural hormones, (b) counteract their functions, (c) modify synthesis and metabolism patterns, or (d) influence specific receptor expressions. The liver, kidneys, heart, nervous system are among the most commonly affected internal organs by certain compounds

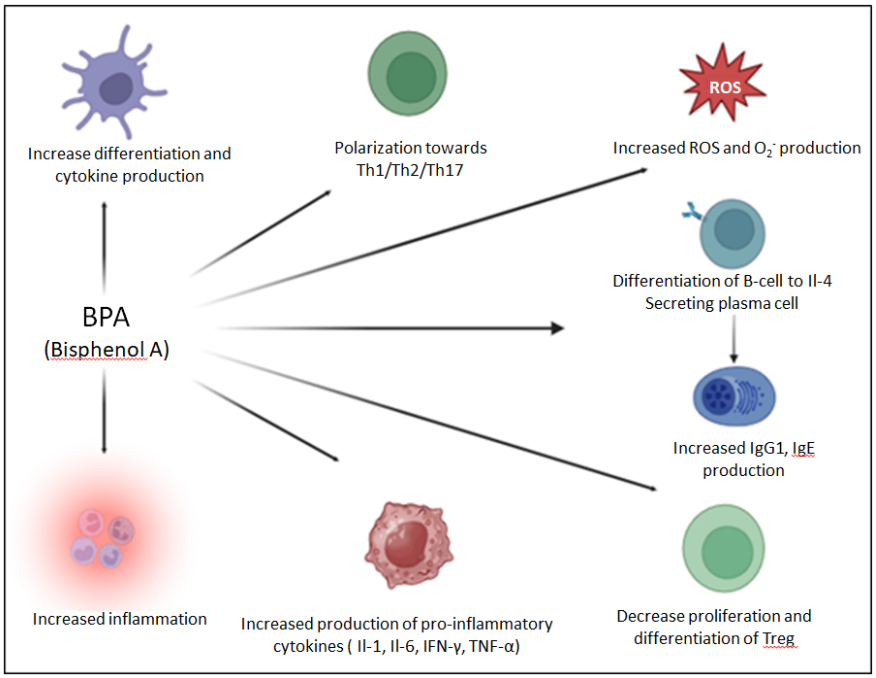

Fig. 2: Effects of BPA on different types of immune cells.

(Campanale *et al.*, 2020).

(i) *Bisphenol A*

BPA (Bisphnol A), phthalates, some heavy metals and some brominated flame retardants are used to make various products including food packaging, and have been proven to disrupt the homeostasis of the endocrine system if ingested or inhaled (Fig. 2). Recent studies have associated Endocrine-disrupting chemicals (EDCs) with various health problems such as cancers (breast, prostate), diabetes, obesity, asthma, autism and reproductive problems such as infertility. Dodds and Lawson (1938) discovered that BPA was estrogenic and recently the General Court of the EU confirmed that BPA is a 'substance of serious concern' for its hormonal disrupting properties on human body (Deutschle *et al.*, 2008). Main source of BPA exposure in human occurs through the consumption of food and beverages packed in containers made from polycarbonate plastics. The European Food Safety Agency calculated that daily intake of 50 µg/kg/day of BPA can be tolerable. BPA exposure through food packaging is 0.185 µg/kg/day in adults and around 2.42 µg/kg/day in children (Mendoza *et al.*, 2020). BPA food contamination has been estimated to be responsible for 12,404 cases of obesity and 33,863 cases of coronary heart disease in 2008 (Campanale *et al.*, 2020).

(ii) *Heavy Metals*

Heavy metals are naturally present in environment. According to USEPA (United States Environmental Protection Agency) and IRAC (International Agency for Research on Cancer), arsenic, chromium, cadmium, mercury and lead are classified as "known" or "probable" carcinogens for human based on evidences of some studies that have shown correlation between exposure of those elements and cancer incidence on humans (Deutschle *et al.*, 2008). As, Al, Cd, Cu, Cr, Pb, Co, Ni, Se, Sn and V are those heavy metals that have high affinity to estrogen receptors so they are considered very harmful and are linked with breast cancer. Cadmium has been shown to be involved in DNA methylation, cellular apoptosis, changes in calcium metabolism and increasing bone fractures in post-menopausal women (Engwa *et al.*, 2019). Lead is responsible

Table 1: Types of heavy metals and their effects on human

Heavy Metals	Types of Polymers	Effects on Human
Arsenic (As)	PVC and polyesters	Carcinogen: liver, lung, skin, kidney; gastrointestinal damage
Aluminum (Al)	PVC, PE, PET	Breast cancer
Bromine (Br)	PE, PS, PP	Apoptosis (Hahladakis *et al.*, 2018)
Cadmium (Cd)	PVC	DNA methylation, apoptosis, bone fractures in post-menopausal women, lipid peroxidation, changes in calcium metabolism, carcinogenesis (Sharma *et al.*, 2005)
Chromium (Cr)	PVC, PE, PP	Respiratory, cardiovascular, gastrointestinal effects; risk of lung cancer (Engwa *et al.* 2019)
Lead (Pb)	PVC	Hypertension, oxidative stress, effects on central nervous system (Byrne *et al.*, 2013)
Mercury (Hg)	PU (Polyurethane)	Carcinogen, brain damage, disruption of DNA molecular structure (Hansen *et al.*, 2013)
Titanium (Ti)	PVC	Cytotoxicity on human epithelial lung and colon cells (Gandamalla *et al.*,, 2019)

for producing ROS (Reactive oxygen species), hypertension, oxidative stress and many effects on the CNS (central nervous system). Mercury affects two target organs: CNS and the kidney. Titanium oxide is responsible for cytotoxicity on human epithelial lung and colon cells. Therefore, Microplastics with various additives and heavy metals (Tables 1, 2) can affect human health and marine organisms in many ways (Goyer *et al.*, 2004).

(iii) *Phthalates*

Phthalates are chemicals which are often used in plastic and personal care products. Phthalates are known as endocrine disruptors. Research suggests that exposure to phthalates may be linked to various health issues such as hormonal disruption, reproductive issues, as well as prenatal and postnatal developmental problems. They are also carcinogenic (Jobling *et al.*, 1995). Di-(2 ethylhexyl) phthalate (DEHP) has been shown to increase IL-4, IFN-γ production, antibody production (IgE) and pulmonary inflammation. Children born to women with elevated urinary levels of BBP and DBP during their pregnancies show a 70% increased risk of asthma diagnosis between the age of 5-11 years. In adults allergic to dust mite, inhaling dust containing DEHP resulted in altered expression of GCSF (Granulocyte Colony-Stimulating Factor), IL-5 and IL-6 with variations depending on the concentration. At high concentration GCSF and IL-6 level decreased, while at low concentration cytokines increased (Fig. 3) (Deutschle *et al.*, 2008). Also, exposure to MEHP and DEHP has inhibited neutrophil chemotaxis in both neonatal and adult cells (Mendoza *et al.*, 2020).

Immunological Effects of microplastics

Researchers pay more attention to biological and immunological effects of microplastics. Amino modified Polystyrene microplastics (NH2-PSMPs) have been used to study the effects of microplastics on marine shellfish. After 24 h of exposure acidification of lysozyme and membrane destabilization decreased in circulating hemocytes. Serum lysozyme activity increased inducing degranulation. During second exposure, absorption rate of NH2-PSMPs by cells is much lower and expression of other genes are reduced.

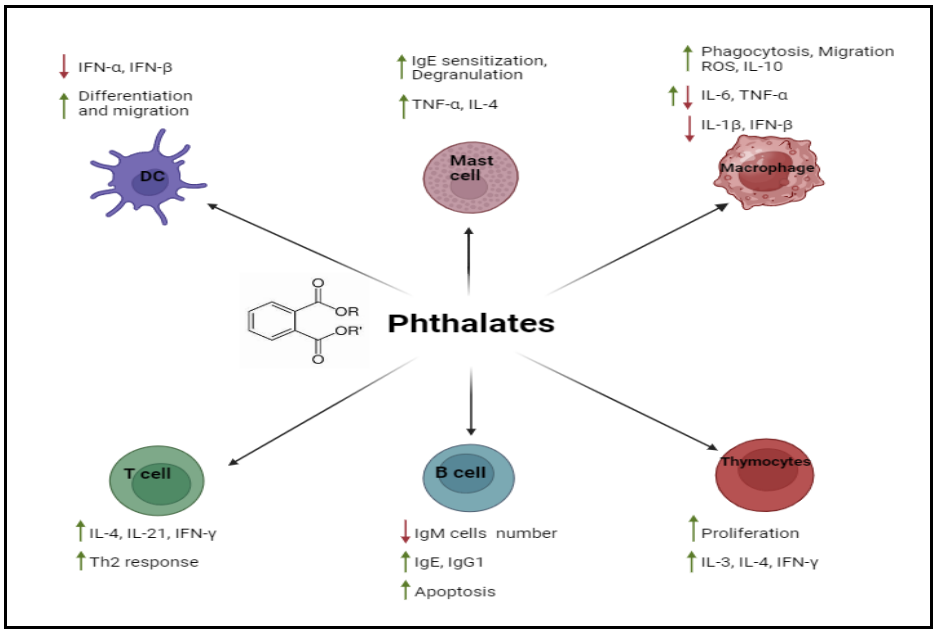

Fig. 3: Effects of Phthalates on different types of immune cells.

The result indicates that immune response of shellfish towards microplastics is established.

In case of human, PVC and ABS (acrylonitrile butadiene styrene) are used to study the effect of microplastics on human immune cells. These plastic particles inhibited the release of histamine. Upon increasing PVC concentration, TNF-α and IL-2 production decreased. ABS and PVC both induce the production of IL-6 and TNF-α. Green *et al.* (1998) found that larger Polyethylene micro-plastics promote development of inflammatory cytokines (IL-6, TNF-α). Microplastics disrupt the immune response including Ca^{2+} signaling and NF-kB pathway (Yang *et al.*, 2022).

Neutrophils play an Important role in immune system to prevent immunotoxicity. Microplastics like polystyrene, polyethylene induces the release of Neutrophil extracellular traps (NETs) and increases the degranulation of primary granules of neutrophils. *In vitro*, Neutrophil function assay showed engulfing 7.3 µm microplastic resulted in around 50-97% of total neutrophil death within 45 min and phagocytosis results in re-release of microplastics from dead cells. Phagocytosis of immune cells from intestine, kidney, brain, blood is dissimilar for different microplastics. Phagocytic ability is related to types of microplastics. Polyethylene microplastic is more accessible to uptake and accumulate compare to Polystyrene microplastic. However, polystyrene particles of the size 50 nm in diameter have cytotoxic and genotoxic effects on macrophages and pulmonary epithelial cells. The use of metal nanoparticles and polystyrene, polyethylene microplastics has induced cytotoxic effects on human brain and epithelial cells (HeLa cell lines). Use of polypropylene (PP), depending on their size and different concentration has shown various harmful effects on various cell lines. The interaction between positively charged polystyrene particles and the secretion film of gastrointestinal epithelium was analyzed in a study. Polystyrene particles showed strong ability to influence cellular vitality and induce apoptosis in the intestinal epithelial cell lines (Caco-2, HT-29 and LS174T) (Campanale *et al.*, 2020). Macrophages, monocytes, NK cells are reported to induce memory which is called "Innate immunity memory". Microplastics and Nanoparticles have the potential to induce the generation of innate immunity memory (Yang *et al.*, 2022).

Some studies have shown that micro and

nanoplastics cause harmful effect on human health such as oxidative stress, apoptosis, inflammation, disrupt homeostasis, and cancer.

- *Oxidative Stress*

In inhalation exposure experiments, the primary effects of microplastics were believed to stem from oxidative stress resulting in inflammatory and cytotoxic effects. Microplastics have the potential to trigger oxidative stress by generating oxidizing substances that adhere to their surfaces. Additionally they can contribute to reactive oxygen radicals produced by the host during inflammation. In experiments utilizing nanoparticles to elicit pro-inflammatory responses in A549 lung cells and human gastric cells, it was observed that larger polyethylene particles promote the production of cytokines like IL-6, IL-1b, TNF- α, some of which serve as inflammatory agents (Bhuyan *et al.*, 2022). Amine modified polystyrene particles were shown to interact and aggregate with mucin, leading to apoptosis in both mucin-secreting and non mucin-secreting intestinal epithelial cells, Conversely, unmodified or functionalized polystyrene demonstrated apoptosis induction across various human cell types including primary human alveolar macrophages (MAC), alveolar type 2 epithelial cells (AT2), immortalized alveolar epithelial type 1 cells, monocytic leukemia cell lines (THP-1), colon carcinoma cells (Caco-2) and lung cancer cells (Calu-3) (Thubagere *et al.*, 2010; Reunraroengsak *et al.*, 2015).

- *Inflammation*

In an in-vitro study, diverse sizes of polystyrene particles were examined, revealing that larger particle induced inflammatory effects on human A549 lung cells. Lung cells treated with larger particles exhibited higher IL-8 expression compared to those exposed to smaller (64nm) particles (Brown *et al.*, 2001). Additionally unaltered or carboxylated polystyrene nanoparticles triggered a significant upregulation of IL-6 and IL-8 genes in human gastric adenocarcinoma, leukemia and histiocytic lymphoma cells. This suggests that the heightened inflammatory reactions to polystyrene particles may stem from the particle's constitution or particles presence rather than the particle charge (Forte *et al.*, 2016). Previous studies suggest that the use of polyethylene components in prostheses can lead to fragmentation due to wear and tear, resulting in debris formation in joints. These polyethylene wear particles can activate pro inflammatory factors such as TNF-α and IL-1 along with the pro-osteoclastic factors, including the receptor activator of NF-kB ligand. This cascade contributes to periprosthetic bone resorption, potentially leading to prosthesis failure. Notably, high levels of plastic particles in the range of 0.2-10 μm have been identified in the periprosthetic tissue of implants based on high molecular weight polyethylene. Moreover, the existence of macrophages in the surrounding tissue near the implant area suggests the activation of the inflammatory response (Nich *et al.*, 2014; Koelmans *et al.*, 2019).

- *Homeostasis*

Microplastics exert their influence on metabolism through direct alterations to metabolic enzymes or indirect disruption in energy balance. This dual impact manifests as changes in energy consumption, shift in nutritional intake and modulation of crucial metabolic enzymes. Nanoparticle interaction with the cytoplasmic membrane of airway epithelial cells, particularly those composed of negatively charged carboxy-lated polystyrene measuring 20 nm lead to significant effects on signaling systems. In human lung cells, exposure to these nanoparticles activates basolateral k^+ ion channels. This activation results in persistent and concentration dependent enhancements in short circuit currents driven by stimulated efflux of Cl^- and $HCO3^-$ ions (McCarthy *et al.*, 2011). 30 nm polystyrene nanoparticles extend the induction of large vesicle-like structure within the endocytic pathway observed in macrophages and human cancer cell lines A549, HepG-2 and HCT116. This interference disrupts vesicle transport and alters

the distribution of proteins crucial for cytokinesis, ultimately promoting the formation of binucleated cells (Xia *et al.*, 2016). Additionally acute oral exposure to positively charged polystyrene nanoparticles carries the potential to interfere with intestinal iron transport and cellular uptake (Mahler *et al.*, 2012).

Probiotics and their probable effects

Baralić *et al.* (2021) conducted an experiment where mice were exposed to a combination of BPA and phthalates, common toxins found in daily human diets. They also administered polybiotics (different species of lactobacillus) to investigate how these probiotics might mitigate the toxicity of these compounds. The results indicate that the probiotics had a positive impact on the endocrine system, as well as the hepatic, renal and splenic tissues. Additionally, it was observed that at the cellular level, probiotics could potentially possess antioxidant properties (Baralić *et al.*, 2021).

Probiotics are live microbial supplements that individuals can ingest. They have advantageous effects in host by enhancing microbial equilibrium in the gut and modulating host's immune system. Studies indicate that these microorganisms, particularly lactic acid bacteria (LAB) can help control hypertension, hyperglycemia, modify lipid profiles and also mitigate oxidative stress (Arani *et al.*, 2019).

Gut microbiota is composed of good as well as pathogenic bacterial species, gut dysbiosis occur when pathogenic bacteria dominate over the beneficial species. Gut dysbiosis has been associated with worse gastrointestinal damage after oral exposure to micro and nanoplastics, which leads to more pronounced inflammatory immune response, increases oxidative damage. Several studies have reported the use of probiotics to modulate the gut microbiome and normalize immune responses for the prevention of intestinal dysbiosis. Clinical trials have also shown that probiotic strains effectively reduce the side effects of microbial dysbiosis induced by different diseases or medical treatments. The consumption of a complex mixture of probiotics (*Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Bacillus ceresus*) demonstrated significant restoration of gut and oral microbial diversity. The use of probiotics can improve the gut microbial population, increase mucus secretion and prevent the destruction of tight junction proteins by decreasing the lipopoly-saccharides level. Furthermore, the decrease in gut dysbiosis and intestinal leakage after probiotic therapy may lower the release of inflammatory biomarkers and attenuate unnecessary activation of the immune system. Probiotic microorganisms, whether they are indigenous to the gastro-intestinal tract or consumed as supplements, may interact with PS particles to mitigate their harmful effects on various tissues (Jin *et al.*, 2019). The specific mechanisms of how probiotics might alter PS hematotoxicity remain unclear. One potential explanation could be that probiotics generate particular small molecule metabolites or initiate signaling pathways that enhance the organism's immune system or mitigate inappropriate inflammatory reactions. Introduction of probiotic bacteria such as LAB strains into gastrointestinal tract has the potential to reduce or eliminate the harmful effects of heavy metals or toxic fungi. Bacterial components like mannan oligosaccha-rides or peptidoglycans found in the cell wall of these organisms facilitate the binding of cells to these toxins. Certain probiotic bacteria and yeasts possess the ability to adsorb diverse heavy metals such as cadmium, copper, lead and mercury. Moreover, probiotics can bind to molecules and toxins like BPA (Bisphenol A) or phthalates, further contributing to their detoxification properties. The association between gut dysbiosis and heightened gastrointestinal damage following oral exposure to micro and nanoplastics has been documented in various studies. Microbial dysbiosis exacerbates inflammatory responses, increases oxidative stress, and promotes cancer progression. Numerous studies have explored the efficacy of probiotic strains in modulating the gut microbiome and restoring immune balance to prevent and manage intestinal dysbiosis (Bazeli *et*

Table 2: Possible effects of Micro and nanoplastics on human health

Effects	Types of Particles	Changes in Body
Oxidative stress	Amine modified polystyrene nanoparticles	Interaction and aggregation of mucin. In all intestinal epithelial cells apoptosis was induced.
	Unmodified or functionalized polystyrene	Induction of apoptosis in all human cell type. Induction of ROS production and ER stress. Cell viability reduced due to increasing ROS levels and decreasing ATP. (Stepniak *et al.*, 2018)
Inflammation	Polystyrene particles Unmodified/Carboxylated polystyrene particles	Induction of inflammation in human A549 lung cells. Higher IL-8 expression. IL-6, IL-8 expression increased
	Polyethylene particles from prosthetic implants Polystyrene microplastic particles	Increased secretion of IL-6, IL-1, TNF-α in murine macrophages. Periprosthetic bone resorption. Inflammation occurs at the implant area. As a result, neurotransmission harmed. (Deng *et al.*, 2017)
Homeostasis	Cationic polystyrene nanoparticles Anionic carboxylated polystyrene nanoparticles Polystyrene nanoparticles Microplastics	Disruption of intestinal iron transport and cellular uptake. Energy metabolism deficiency. Basolateral k^+ channels activated. Induced Cl^- and $HCO3^-$ ion efflux. Metabolic condition associated with gut microbiota dysbiosis and dysfunction of gut barrier. Increased risk of metabolic disorder in children. (Luo *et al.*, 2019)

al., 2023).

Probiotics have shown potential in reducing the carcinogenic and genotoxic effects of heterocyclic aromatic amines by binding to toxins. Another study using Caco-2 cells demonstrated that *Lactobacillus acidophilus* could mitigate DNA damage and cell death caused by phthalates. This effect was primarily achieved through modulation of gene expression levels associated with P53, MAPK, and mTOR pathways (Zhao *et al.*, 2021).

Conclusion

Plastic, a versatile and indispensable material, constitutes the majority of everyday items, contributing significantly to modern life. Nonetheless, the contemporary world witnesses extensive mismanagement, inadequate disposal and overexploitation of plastics, culminating in the pervasive presence of microplastic pollution across aquatic ecosystems. While extensive research has been conducted on microplastics and nanoplastics within the marine environment, we have only recently begun to acknowledge the potential pathways for human exposure. Once exposed, uptake of microplastics and nanoplastics can occur through ingestion or inhalation. Assessments of the toxicity of micro and nanoplastics on humans primarily concentrate on gastrointestinal and pulmonary effects, encompassing oxidative stress, inflammatory

responses, metabolic disruptions. This analysis delves into the potential impact of microplastics and other plastic additives on human immunity and immunotoxicity. Nonetheless, the precise immunological processes and pathways following brief and extended exposure to microplastics remain elusive. Further investigation is needed to grasp the potential adverse impacts of micro and nanoplastics on human well being and to unravel the immunological mechanisms our body employ in response to these plastic particles.

Ethical Statement

This is a review article hence no Ethical Approval needed.

Conflict of Interest

The author declares no conflicts of interest.

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