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Review Article

Microplastic Pollution: The Escalating Environmental and Health Hazards Threatening Ecosystems and Human Well-being

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ABSTRACT

Plastic is found with its wide applications worldwide to fulfil our domestic and industrial needs. Its vast diversified usability and unscientific disposal patterns cause tireless accumulation of various forms of plastic waste materials in our surroundings. Anthropogenic waste is causing an increasing threat to the environment and to the public. The global production of plastic waste is expected to increase from the current 350 million metric tons to 1200 million metric tons per by the year 2050. Its poor biodegradability and improper and unscientific disposal methods lead to its undue environmental segregation and bioaccumulation due to its constant contact and exposure. Based on their particle size they are classified as macroplastic, microplastic, mesoplastic, nanoplastic, etc. Smaller the particle size greater will be the potential to breach into the bio/ecosystem and can cause environmental discrepancies and threaten the food chain system which involves the chain of creatures that are consumed in an orderly manner for their survival. Inevitable human exposure towards diversified varieties of plastic polymers causing severe health and environmental hazards. It's improper and inadequate recycling cause undue infiltration and vast accumulation in various layers of the ecosphere. They enter human biological system through various pathways through inhalation, ingestion, and dermal contact of plastic pollutants, can produce hazardous impacts. These pollutants jeopardize the lives of billions of living beings directly or indirectly. Micro plastic pollution and its constraints in disposal is a great challenge to the modern era; if they once released into the environment, it is almost impossible to retrieve them back. Their constant and subtle dissemination into the biological system causing subtle to grievous impacts on all living beings. Microplastics are currently being considered intensely from the point of their potential hazardous health effects. Its diversified consequences threatening various body systems like respiratory, digestive, nervous, endocrine, skin, etc., along with its effect during early foetal life also will be highlighted in the present review

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INTRODUCTION

The ecotoxicological effects of plastic pollutants are very much a concern at the time. It has a wide impact on the different strata of the ecosystem (Song *et al.*, 2018). Plants and animals are constantly exposed to plastic particles; hence they are the ultimate victim of plastic emission, contact, and improper disposal. The pollutants are categorized broadly into air pollutants, water pollutants, soil pollutants, etc. They include smoke, ash, pharmaceutical chemicals/drugs, medicines, plastic materials, etc. Micropollutants once released into the environment are almost impossible to retrieve them back. They keep on disseminating into the environment causing subtle to grievous impacts on all living beings in various components of the ecosystem. Plastic is a most inevitable, and its indispensable utility and an inevitable supporting element required for human life; it is blended with our lifestyle in and out. The plastics are of two types, thermoplastics, and thermosets. The thermoplastics can undergo reversible changes when encountering the temperature ex; polycarbonate, polypropylene, polystyrene; thermosets, etc. But thermosets will not change in contact with the temperature. The thermoplastics may change by creating a grid. This plastic undergoes natural fragmentation leading to the formation of many microplastic particles (Verla, 2019). Microplastics are synthetic polymers of micronized fragments less than 5mm in

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size, having heavy molecular weight. They strongly resist natural degradation and stay in the environment for an indefinite time frame. Its dissemination into the environment can easily ingested into various creatures ultimately threatening different levels of human interactions. Primary plastics are deliberate creations for human use, and secondary plastics are products with plastic fragments or plastic fibers. Additives are chemicals that increase various qualities of plastic materials in their sustainability against temperature, radiation, colour, transparency, etc., and it is used to increase the mechanical, electrical, and temperature-withstanding properties (Campanale *et al*., 2020). Potential and harmful microplastic invades the ocean and affects the Zooplanktons and its oocytes causing integrational transmission which eventually enters the human body through the food chain (Choi *et al*., 2020). Experiments have shown that microplastics can breach the physiological barrier and have potential adverse effects even on the immune system (Chiu *et al*., 2015). Due to its physiochemical properties, the plastic nanoparticles can disseminate easily into the environmental soil causing toxicity of the agricultural land and even affecting the quality of crops (Choi *et al*., 2021).

PLASTIC AND ITS STABILITY

Plastics are chemically inert elements; they are synthetic organic polymers made of a vast number of monomers like ethylene, styrene, and propylene by the process of polymerization and polycondensation. Being a high molecular weight polymer; its biodegradation depends on its intricate physical and chemical properties. The exposure and its infiltration capacity into the biological system are based on its particle size. The impedance of plastic against biodegradation is based on its resistance against microorganisms and enzymes; it takes centuries to undergo degradation. The plastic can disintegrate into numerous micro and nanoparticles; many are through non-biodegradation like physical, thermal, photodegradation, thermos-oxidation, etc. Some of the environmental bacteria and microorganisms with the help of extracellular enzymatic activity can support the natural biodegradation to some extent (Yee *et al*., 2021; Geyer *et al*., 2017). To overcome the problem of degradation a novel concept of bi-plastic was found, and a new variety of plastic with high biodegradability was invented by using renewable resources and biomass. Bioplastics are made of naturally available resources like plants, animals, microorganisms, (Tokiwa *et al*., 2009) etc. Based on favourable climatic conditions biodegradable plastic can undergo decomposition within 6-8 weeks by transforming into CO_2 and H_2O. An alternative to plastic would be an ideal solution to tame its accelerating adverse impact on the environment. Hence it is high time to find an appropriate and feasible alternative to tame and address its negative impact on human health and the ecosystem at the earliest (Moshood *et al*., 2021). At present globally 80% of the plastic is not recycled; hence large quantities will enter the waste stream. Plastic waste management strategies like incineration and pyrolysis have some limitations from the environmental standpoint because of toxic fume liberation into environment. Until we find the best feasible and sustainable alternative it is difficult to reduce its wide domestic and industrial applications. Hence eco-friendly and sustainable, effective, and feasible strategies to recycle or dispose the plastic waste materials are still under trial (Thomas *et al*., 2023).

DISCUSSION

The sanctity of biotic and abiotic resources plays an important role in the quality of life and effective survival of various species in the ecosystem. These two important factors rely on each other; their equilibrium is essential for survival. Several pollutants are generated through human activity on earth; plastic is one of the most dependent items. Hence a proportionate abundant plastic waste will be generated simultaneously; it has the quality of durability and it is long-lasting. The ubiquity of microplastic and nano plastic, and their physiochemical properties cause detrimental effects through contamination; its ingestion into the body can cause toxicity even during the gestation period. It is a substantial concern concerning the risk-free growth of babies and uneventful labor and taming the threats of congenital defects. MP can easily transmit to organs and systems like the gastrointestinal tract, liver, lungs, etc. MP was detected in many biological samples including blood, breast milk, amniotic fluid, meconium (Medley *et al*., 2023), etc. Microplastics are universal in the worldwide climate; as a regular rising poison, their potential well-being risks have been generally disturbing. People are possibly presented to microplastics through oral admission, inward breath, and skin contact. They summed up the poisonous impacts of microplastics in trial models like cells, organoids, and creatures. These impacts comprise oxidative pressure, DNA damage, organ brokenness, metabolic turmoil, invulnerable reaction, neurotoxicity, as well as regenerative and formative poisonousness (Li *et al*., 2023). **S**tudy involving the analysis of blood samples of human participants was taken for the investigation. Their exposure to the plastic was found evident with the presence of polymeric plastic contamination in the blood sample. They identified these plastic particles through spectroscopy analysis of samples. Hence, human biomonitoring plays an important role in understanding the extent of infiltration of toxins. Probably this is one of the important factors under consideration of health risk assessment and to consider possible measures for prevention. The fate of bio-ingested plastic polymers and their natural biological expulsion depends on the capacity of the body to identify, detoxify, and scavenge them successfully. These microplastic contaminants are likely to adhere to the lipid particles, protein particles, and endothelial lining of vessels, or they may get localized with various immune cells. The number of microplastics in biological specimens may indicate the sum of their total exposure and their invasion through different sources like air, water, food (Leslie *et al*., 2022), etc. Anthropogenic MP waste is vaguely dispersed on the earth. The size of MP about 100 nm is the most feasible to enter the biological system of

animals. Evaluation of environmental air standards has shown an immensely high concentration of microplastic pollutant suspension in the indoor air; it is 1.5 times more than the outside air which is dominated by synthetic fibres like Polymers. Polyester, Polyethylene, Styrofoam, fibres, Polypropylene, Polystyrene, etc. These are some of the widely distributed MP elements found in the air, water, and earth. The toxicity induced by these MP depends on their degradation quotient based on their physiochemical properties. Consumption of whole or complete aquatic organisms in the form of seafood including bivalves, plankton, fish, etc. obviously resulted in the direct main source of ingestion of microplastic pollutants by predators like humans, which facilitates an entry into the high-level food chain. They have found that the disseminated concentration of microplastics as different types of soil contaminants threaten vast varieties of flora and fauna. The primary plastics are uniform in shape and size, unlike secondary plastics. Primary plastic pollutants are found to be more hazardous than secondary plastics. Based on their physiochemical properties and based on the duration and severity of microplastic exposure or contact by an individual. The primary plastic can enter the biological stream and can breach the biological barrier of various organ system functions including the endocrine system causing malfunctions. Hence, they are considered as strong disrupters of the biological system which can cause various types of cancers in an individual (Lee *et al*., 2023).

Effects on Cell

Biological markers can be utilized to assess the impact of microplastic interaction and its impact on biological systems; three important markers include, assessment of enzymatic activity, gene expression studies, and histopathological markers (Patra *et al*., 2023). The exposure and impact of microplastic ingestion may be due to constant metabolic insult and it may be a way long subtle biological phenomenon. It may later be invaded into the organs like the liver and kidney which are the potential sites of toxin deposition. As a result, hampered cell-savaging activity may result in hepatotoxicity and nephrotoxicity, which may lead to increased oxidative stress, inflammatory response, altered cell metabolism, increased disease susceptibility, and complications followed by organ failure (Goodman *et al*., 2022). A study, showing even at lower concentrations 0.1 µm Polystyrene Microplastics (PS-MPs) can enter the hepatocytes and cause damage such that nuclear DNA, as well as mitochondrial DNA, are released into the cytoplasm, where the DNA sensing adaptor STING (Stimulator of Interferon Gene) is activated, it is suppressing a Series of reactions [cGAS/STING pathway i.e., cyclic guanosine monophosphate-adenosine monophosphate synthase-STING pathway paving the way for the entry of NFkB into the nucleus where it promotes gene expression of inflammatory cytokines [IL-6 (Interleukin-6), IL-1β (Interleukin 1 beta), TNFα (Tumour Necrosis Factor-alpha)] and fibronectin, causing fibrotic changes in the liver as a result of long-term insult. The fibrosis was alleviated by introducing a STING inhibitor (Shen R *et al*., 2022). MPs exert stress on the endoplasmic reticulum of liver cells (relieving alleviated the PS-induced oxidative stress), which causes autophagy in hepatocytes. This is accompanied by increased ROS production, decreased mitochondrial membrane potential, and activation of PERK (Protein kinase RNA-like ER kinase) signalling pathway (Pan L *et al*., 2021). A study showed that Oxidized Microplastics and Nanoplastics (oxMPs, oxNPs) were more harmful than virgin Microplastics and Virgin Nano Plastics (vMPs, vNPs). Human professional phagocytes (i.e., monocyte cells THP-1 and macrophage-like mTHP-1 cells) phagocytoses ~50% NPs and ~60% MPs and there was increased ROS production despite phagocytes possessing anti-oxidant properties; where DNA damage was also observed. *In vitro* studies using oxMPs and oxNPs need to be carried out to understand the effects of MPs and NPs more realistically (Visalli A., 2023). Experimental vivo studies with exposure of MP in lower animals have shown suppressed innate immune response associated with accumulation of MP in hepatocyte ECM causing impairment in its function (Huang *et al*., 2023).

Impact on human's trough aquatics

The omnipresent microplastics and their marine ecotoxicity are significant public worries. Microplastics are ingested incidentally by the marine fauna or are taken up in a roundabout way through the established pecking order. These particles can collect in cells and tissues and influence the ordinary natural elements of organic entities, including their protection components. There is restricted data accessible about the reaction of invulnerable cells to microplastics; the level of take-up by the cells, the reaction of various organs, or the effect of ecological convergences of microplastics are matters that stay hazy (Abihssira-García *et al*., 2020). Toxicological studies have highlighted the effects of MPs on marine organisms and mammals. Most disposable plastic products degrade slowly in the environment, breaking down into Microplastics (MPs) and Nano Plastics (NPs), which pose significant ocean environmental risks causing severe toxicity in large number of aquatic animals. The ingestion of MPs, and their interactions with the human body, particularly about immune responses and immunotoxicity, where the MP can be absorbed by cells, disrupting intracellular signalling pathways, altering immune balance, and ultimately damaging tissues and organs. The primary toxicological mechanism of MP exposure involves the generation of reactive oxygen species, which can trigger the production of Danger-Associated Molecular Patterns (DAMPs) and disrupt Toll-Like Receptors (TLRs), leading to cytokine production and inflammatory responses in immune cells. MPs can interact with cell membranes or intracellular proteins, forming a protein corona and binding to external pollutants, chemicals, and pathogens, amplifying their toxic and adverse effects. Comprehensive research into the immunotoxicity effect

of MPs on biological system, and their chemical composition, shapes, sizes, combined exposures, and concentrations, are essential considerations. Therefore, further investigation is urgently needed to clarify the immunological risks posed by human exposure to various types of MPs entering the human biological system through see food source (Yang *et al*., 2022). Water pollution with large-scale and small-scale plastic litter is an area of growing concern. Macro-plastic litter is a well-known threat to aquatic wildlife; however, the effects of micro-sized and nano-sized plastic particles on the health of organisms are not well understood. Small-scale plastic particles can easily be ingested by various aquatic organisms and potentially interfere with their immune system. The experiments with freshwater fish species as a model organism for polystyrene and Polycarbonate Nanoplastic Particles (PSNPs and PCNPs, respectively) in plasma were performed, and the effects of PSNPs and PCNPs on the innate immune system of fathead minnow were investigated. *In vitro*, the effects of PSNPs and PCNPs on neutrophil function were determined using a battery of neutrophil function assays showed a significant increase in degranulation of primary granules and neutrophil extracellular trap release compared to a nontreated control, whereas oxidative burst was less affected. This experimental observation outlines the stress response of the cellular component of fish's innate immune system to polystyrene and polycarbonate nanoparticles/aggregates and indicates their potential to interfere with disease resistance in fish populations (Greven *et al*., 2016).

Effects on Skin

Skin is the most exposed protective barrier of the body exterior; it renders protection against various physical and chemical irritants. Dermal uptake of the plastic nanoparticles will be much quicker if the skin is exposed due to damage (Leslie *et al*., 2022). Microplastics (MPs) and Nano Plastics (NPs) have become a growing concern in dermatology because of their far-reaching presence in surface-level plans and the climate. These little engineered polymer particles brief a fundamental investigation of their likely effect on dermatological homeostasis. Proof proposes that MPs and NPs may for sure prompt cutaneous changes, incite fiery reactions, and upset the homeostasis of the skin's physiological capabilities in the long run. While an exact comprehension of the ramifications of MPs and NPs on dermatological wellbeing stays a continuous logical undertaking. Exposure of minuscule plastic particles in cosmetic applications is a growing serious concern from the point of dermatology. Cosmetic formulations are a rich source of various types of synthetic plastic polymers. Constant and long-term contact with topical cosmetic applicants on the skin may gradually breach the cutaneous barrier. Which in turn provokes skin irritation followed by subtle inflammatory reactions. Certain chemical enhancers are prime modifiers of the skin barrier function which facilitate nanoplastic particles to invade the barriers of the skin by altering the properties of the protecting lipid layer of the epidermis. Later nanoparticles can also make an entry into the deeper strata of skin through skin perforations, sweat perforators, and hair follicles; which later results in inflammatory reactions to enhance the protective activity through several immunocompetent cells present in various layers of skin (Aristizabal *et al*., 2024). The experiments have shown that the constant dermal contact with microplastic particles not only induces the benign toxicological effect but in the long-run, may result in altered cell cycle events followed by life-threatening malignant changes. The advancement of cutaneous squamous cell carcinoma is firmly connected to ecological variables. Microplastics, and other contaminations, are being seriously studied for their potential well-being impacts. Nonetheless, the impact of microplastics on skin disease is not yet known, and it is a significant logical inquiry that should be tended to (Wang *et al*., 2023).

Effect on Gestation Period

Untamed growing ecotoxicity by MP/NP is crucial threat; they behave as vectors which can commute large varieties of toxic and chemical particles into various natural resources. Studies underscoring its adverse biological effect through altered cell enzymatic activity, and mitochondrial activity, gene expression in number of tissues in the body initiating subtle deterioration in organ system function. Such adverse effects especially on the placental barriers may cause severe threat for the mother as well as the growing foetus (Patra *et al*., 2023). The preconception period and prenatal period are considered critical from the point of pregnancy, the gestation period by preventing undue exposure or ingestion of micro-toxins. Based on the severity, strength, and duration of exposure to the microplastic pollutants may result in hampered fetal growth, causing fetal anomalies, preterm birth, low birth weight, chromosomal defects, stillbirth (Rani and Dhok, 2022), etc. The placenta is not only a transporting membrane; it acts as an immune barrier to protect the fetus against intruding antigens or foreign particles. MPs are considered foreign bodies which can trigger the immune reaction within the host; where the expression of the immune marker in a cell is an indication of immune response. Experimentally pregnant mice were exposed by ingestion of 250 µg PS-MP given intraperitoneally during the first week of the gestation period. Later these animals were scarified during the second week of the gestation period. The percentage of immune cells quantified on flow cytometry where CD45+ cells i.e. hemopoietic cell marker, and Natural Killer (NK) cells for innate immunity were found to be decreased. The level of IL is increased and TNα reduced in intervention groups. MP intervention groups were found to be associated with the reduction in size of uterine arterioles, with elevated resorption of the embryo. These observations indicate triggered immune response and its determinantal effect on experimental MP intervention. Probably this may result in increased risk due to compromising maternal and fetal immune protection response leading to adverse

pregnancy outcomes (Hu *et al.*, 2021). Chemokine receptors are transducers having the capacity to trigger cellular responses on binding chemical molecules. They play an important role in the transplacental transport of chemicals which is an essential phenomenon facilitating the exchange of important immune competent cells between the mother and the baby. MP makes an entry into the placenta through the paracellular or cell-mediated pathways, which ultimately internalize the MP through absorption or translocation. Due to the interference of circulating MP or NP, it may alter the diffusion quotient of essential gases like O_2 and cell regulatory pathways which may ultimately result in undue hypertension followed by eclampsia risk in the mother, or its consequence may result in underweight or undernourishment in neonates (Smith *et al.*, 2018). A small cohort study involving 6 samples of human placenta were studied for MP contaminates. Through Raman Spectro microscopy manmade human plastics were found in both the maternal side and the chiromniotic side of the placenta. Depending on the surface charge, particle size, surface chemistry, and interacting substance/molecule on MP. Once MP are going to invade the human body, they are likely to be seen in various biological samples and organs like the placenta. The probable mechanism by which the MPs can enter the tissues through penetration, where the endocytosis-driven mechanism by M cells in the gut will help in the transportation across the epithelium into the subepithelial layer; later MP molecules will be directed towards the lymphatic channels which later enter the bloodstream (Ragusa *et al.*, 2021). Some of the studies have underlined the toxic effects of microplastic on pregnant animals and their placenta along with its adverse effects on the cell and cell organelles. Exposure to MP toxicity was expressed by undue dilatation of ER (endoplasmic reticulum) or causing protein misfolding in the mitochondrial membrane. Strength of toxicity and duration of exposure showing undue enhanced oxidative stress response in a cell. A study was conducted to find the deposition of microplastic in the tissues, where the placenta was the primary consideration. The TEM (transmission electron microscopy) microscopy of the placenta has shown microplastic contaminates in different compartments of villi. They were seen inside the Syncytiotrophoblast, which shows its role in the transport of nanomicroplastic contaminants. MP was also found in the endothelium of the fetal capillary. These microplastic contaminates in the placenta are coined as "Plasticenta" (Ragusa *et al.*, 2022). Untamed growing ecotoxicity by MP/NP is a grievous threat; they behave as vectors that can commute large varieties of toxic and chemical particles into various natural resources. Studies underscored its adverse biological effect through altered cell enzymatic and mitochondrial activity, and gene expression in several tissues in the body initiating subtle deterioration in organ system function. Such adverse effects especially on the placental barriers may cause severe threats to the mother as well as the growing fetus (Patra *et al.*, 2023).

Effect on Respiratory System

Ultrafine plastic particles can easily get into the respiratory passages and be absorbed much more easily. Early childhood exposure to such plastic toxins or allergens can induce respiratory symptoms like bronchitis, asthma, etc. which may manifest in the due course of the time (Gould *et al.*, 2020). Respiratory passage is inevitably the most exposed passage system of the body to the environment. It is always under threat due to several varieties of pollutants and dust particles suspended in the air. Though the body has an excellent cellular mechanism to trap, identify, and scavenge harmful pollutants, some of the potential introducers may breach the respiratory membrane barrier by disrupting the membrane causing increased permeability and decreased efficacy of the respiratory filtration membrane which makes the person prone to several respiratory disorders (Dong *et al.*, 2020). In a study on human alveolar epithelial (A549) cells, PS-NPs (Polystyrene-Nano Plastics) promoteReactive Oxygen Species (ROS) and NADPH Oxidase 4 (NOX4) an ROS generator located in the mitochondria and endoplasmic reticulum causes mitochondrial dysfunction with altered membrane potential causing reduced cellular energy metabolism escalating ER stress. It was further revealed that PS-NPs with smaller sizes with positive surface charges had stronger adverse effects. They can induce epithelial cell transformation into mesenchymal phenotype (Halimu *et al.*, 2022). Metabolomic study showed that human Lung Cell (L02) viability increases slightly after exposure to low concentrations of NPs (Nanoplastics) possibly as a mechanism to combat adverse conditions, but the same capacity was decreased after exposure to high concentrations of NPs. It was also found experimentally that the NPs entered the cells and there was an increased mROS (mitochondrial Reactive Oxygen Species), altered MMP (Mitochondrial Membrane Potential), and decreased mitochondrial ATP production. Consequently, it downregulated purine metabolism, increased Xanthine Oxidase which is an enzyme involved in purine nucleotide breakdown activity, decreased mitochondrial coupling efficiency, and affected the metabolism of nicotinic acid and nicotinamide, thus in turn affecting the energy currency production through the electron transport chain, and cellular respiration. A similar study on human liver cells, BEAS-2B revealed that biosynthesis of the amino acid Arginine, which takes place in liver cells (partly in mitochondria and partly in the cytoplasm), metabolism of acidic amino acids (Glutamic acid and Aspartic acid) is also affected because of NP exposure (Lin *et al.*, 2022). Reactive Oxygen Species (ROS) formed due to MP (Microplastics) exposure causes oxidative stress, mitochondrial membrane damage, DNA damage, protein oxidation, and lipid peroxidation, it triggers several cascades signalling pathways including the p53 signalling pathway, Mitogen-Activated Protein Kinases (MAPKs) the c-Jun N-terminal Kinases (JNK), p38 kinase, Transforming Growth Factor-beta (TGF-β) pathways, etc. ROS may lead to organ damage ex: toxicity in respiratory, cardiovascular, nervous, renal,

reproductive, and immune systems and in the liver (Das, 2023). Basic experiments to study the environmental risk showed that the micropollutant chemical contamination by carbamazepine, diazinon, diuron, etc. Among these chemicals are not undergoing degradation and some may undergo degradation, some have shown their toxic effects on aquatic animals like zebrafish embryos, and algae (Shao *et al*., 2019), etc. Murine's experimental studies by oral administration of PSNP (Polystyrene Nano-Plastic) on mice showed neurocognitive dysfunctions. Its biological effects of large dose of PSNP on the neuronal stem cell culture and on mice animal models showed structural adverse changes on the brain. These experiments showed neurotransmitter deficiency, altered neuronal plasticity along with cognitive function impairment. The outcome is a possible indicator of a fetoplacental breach where micro-nano plastics cause the malformation of the brain in the progeny (Jeong B *et al*., 2022). An experimental study on Zebra fish model may be instrumental in understanding neurodevelopment. A study showed that exposure to Polystyrene Microplastics (PSMPs) in zebrafish (*Danio rerio*) embryos showed behavioural change-these zebrafish showed hyperactivity during later stages of their life. There was an increased gene expression due to enhanced oxidative stress on the nervous system. In addition to these observations, the zebra fish that were challenged with PSMPs for a second time showed hypomethylation of DNA (Im *et al*., 2022). Fish is a natural source of protein, which is vastly consumed by the human. Many aquatic animals get into the human body through the consumption of varieties of seafood causing health hazards in humans. Most of the discarded nondegradable contaminants that enter the river will ultimately reach the ocean causing water pollution of the ecosystem. Mismanagement of microplastic through anthropogenic activity causes severe ecotoxic threats through inevitable, purposeful unscientific channelization of disposables, especially materials like plastic. MP is mistaken as prey by the fish and can cause undue toxication of the gills, gut, etc. Internal toxicity build-up can cause an increased chance of oxidative stress, genotoxicity, immunotoxicity, neurotoxicity, etc. MP causes toxicity in humans through the process of endocytosis and perception phenomenon. Many experiments have shown that MP is easily transmissible through the circulatory channels; nano plastics sizes <240 mm can breach the placental barrier through perfusion and can affect the developing fetus. Similarly, polystyrene particles too have similar capabilities to breach and contaminate the placental circulation or it may affect breeding capabilities in aquatic animals (Bhuyan, 2022).

Effect on Gastrointestinal Tract

Due to poor biodegradability and inadequate reusing, the gigantic creation and utilization of plastics have prompted far and wide natural tainting. These particles collect across environments - even in the most far-off territories. The nano-and microplastic openness upsets the stomach microbiota and basic digestive capabilities (Hirt and Body-Malapel). Different forms of microplastic contaminants will take different routes to enter the human body. These plastic elements are found in many items that come in direct contact with individuals; items which are including cosmetics, milk bottles, food packaging and wrapping materials, cups used for drinking beverages, toothpaste, hair gel, food containers, etc., possessing plastics in various forms. These plastic materials will react when they come in contact with the temperature, causing nanoparticle release from its surface, which happens during cooking, food processing, and plastic wrappers covering used to serve hot, fresh, and quick delivery of food items; later it gets mixed with the food materials and subsequently will enter the GI tract on ingestion (Kadac-Czapska *et al*., 2022). The microbiota is a dynamic, multispecies community consisting of bacteria, fungi, archaea, and protozoa, contributing a vast array of cells and genes that outnumber those of the host organism. Among the various non-sterile body cavities, the human gut hosts the most intricate microbiota, which has a profound influence on host homeostasis and immune balance, making it crucial for overall health (Lazar *et al*., 2018).

Among the various effects induced by MP pollutants, their invasion into the gastrointestinal tract and their interference with tissue metabolism is a sole concern from the point of effective digestion and assimilation. The gut microbiome is essential for several biochemical processes including the synthesis of Vitamin K. Its imbalance may result in a harmful toxic gut environment, which may clinically manifest in the form of vague gastrointestinal complaints (Jin Y *et al*., 2019). Sub-lethal impact of plastic ingestion is a matter of prime concern. It was found that plastics >20 microns can penetrate the organs, but plastics <10 microns can cross the cell membrane. The experimental outcome from the animal model indicates damage in the stomach mucosal architecture including the disruption of gastric glands. Such effects on humans are likely to induce gastritis and deacidification. The plastic-induced lesion in the stomach analysed histopathology by using a special stain where the collagen fibres are considered an important tissue marker to assess scar tissue formation; It has indicated the damage in the mucosa and submucosal layer in the stomach wall evidence of fibrosis; this effect often referred as "Plasticosis." Which can be referred to as the best illustration showing the "Anthropocene effect." Later in the long run it may worsen the condition by creating a prone environment that increases the chance for opportunistic parasitic infections or impaired secretion of gastric juice and intrinsic factors, which is followed by improper absorption of essential micro and nano-nutrients. Hence sublethal impact of plastic needs to be explored further from the point of inducing comorbidities (Charlton-Howard *et al*., 2023). Gut microbiota can be affected by the chronic exposure of the body to microplastic pollutants. MP exposure shows metabolic dysregulation of carbohydrate absorption in the gut by affecting its digestion, absorption, and assimilation due to dysbiosis of

gut microbiota. Studies have also found some genes that are responsible for the enzymes causing plastic degradation genes like the FeaB gene encodes Phenylacetaldehyde dehydrogenase involved in styrene degradation. FeaB is considered as most abundant plastic-degrading gene found in the human gut microbe (Nugrahapraja H *et al*., 2022). The microbiota plays a crucial role in shaping the host immune system's development, function, and regulation. In turn, the immune system has evolved to support this symbiotic relationship, ensuring the balance between host and microbes. When functioning properly, this collaboration enables the immune system to defend against pathogens while maintaining tolerance to harmless antigens. However, in high-income countries, factors such as excessive antibiotic use, dietary changes, and the removal of traditional symbiotic partners (e.g., nematodes) may have led to a microbiota that lacks the necessary resilience and diversity to support balanced immune responses. This disruption is thought to contribute to the rise of autoimmune and inflammatory diseases in regions where the microbiota-immune system relationship has been most altered (Belkaid and Hand, 2014).

Effects on the Nervous System

Many *in vitro* and *in vivo* studies have shown that MNP (Micro/Nano-Plastics) can breach the BBB and cause severe impact on neuronal niche causing adverse effects on neurophysiological properties. Polystyrene is a commonly used material for the transport of MNP. The surface of MNP is crucial which drives its interaction in the existing environment. The protein corona formation will influence the wettability of the surface, electrostatic charge, and steric hindrance which ultimately influence the toxicity gradient which is seen in experiments. The transport of MP can happen through the process of endocytosis, where the MPs are internalized without the formation of phagosomes where the activity of macrophages, neutrophils, and dendritic cells may play a trivial role, hence initiating immune reactions. The corona protein specificity on the outer surface is a crucial matter of concern with the BBB (Blood-Brain Barrier) breaching (Kopatz *et al*., 2023). BBB is a shield that protects the brain tissue against the entry of toxic circulating substances into the concerned organ. The brain endothelial capillary will play an important role in imparting protection by acting as a physical and metabolic barrier. Alterations in the components of these barriers may affect the transport and may result in the pathogenesis of several diseases. Understanding the efficacy of this membrane is important from the point of prevention of several diseases affecting the CNS or from the pharmacotherapeutic standpoint (Persidsky Y *et al*., 2006). The experimental interventional studies show the dissemination of micro and nano-plastic particles into the neurons on plastic polymer ingestion; it is potentially causing neurotoxicity due to increased levels of oxidative stress followed by neuroinflammatory changes. These changes are associated with tapering concentrations of neurochemicals and neurotransmitters resulting in feeble nerve impulse conduction effects which may manifest in the form of behavioural changes (Prüst *et al*., 2020). Several other basic study outcomes shown various types of adverse effects of plastic polymers. It was found that the PN-NP (Polystyrene Nanoparticles) can enter the neurons readily; greater cellular uptake and strong neurotoxic effects show the altered function of neuronal stem cells associated with developmental brain anomalies. Some study also underscores the ingestion of nano-particles on the gut immune system showing more intense macrophage activation with immune reaction when compared to ingestion of microparticles (Kaushik *et al*., 2024). Plastic particle toxicity is an urgent concern for the point of the environment and the individual's health. Microplastic ingestion can result toxic environment for the neurons, its ineffective scavenging leads to way long accumulation in the cells due to its constant exposure leading to chronic and potential adverse effects on health. Its toxicity may result in improper neuronal function due to increased oxidative stress followed by an inhibitory effect on Ach receptors, followed by altered neurotransmitter quantity, cell malfunction, cell damage, or apoptosis. Such consequences may make one to prone for neurodegenerative changes that may manifest as altered behaviour or higher cognitive brain functions (Prüst *et al*., 2020). Experimental intervention through the ingestion of MPs to the animals indicated the reduced free radicle-savaging activity by weak antioxidant enzyme effects. These changes were found to be associated with the formation and accumulation β amyloid proteins in the hippocampal neurons which manifests as impaired cognitive abilities. Indeed, certain neurons in the cerebral cortex play a vital role in establishing the recent memory-forming abilities that may be affected due to the consumption of microplastic molecules knowingly or unknowingly (Sincihu *et al*., 2023).

Effect on Endocrine System

Several plastic additives like bisphenol and phthalates are also showing disruptive effects on health and are often referred to as Thyroid-Disrupting Chemicals (TDC) (Andra and Makri, 2012). Endocrine disruption mediated diseases could be due to pleiotropic effect of various chemicals coming in contact through commonly used plastic materials (Maradonna et al., 2022). MP acts as a molecular sponge based on the hydrophilic and hydrophobic character of MP-NP (microplastic and nanoplastic) molecules that can interact with the coexisting molecules in the water media. Such potential endocrine-disrupting nanoplastic molecules are widely disseminated into the water/fluid media, which mimic natural hormones and can cause adverse impacts on various endocrine organ functions (Cortés-Arriagada *et al*., 2023). *In vivo*, experimental exposure to MP-NP showed altered thyroid and parathyroid hormone production and transcriptome expression of PAX8, CREB, and MAFB genes associated with declining thyroglobulin formation and reduced synthesis of Thyroid Stimulating Hormone (TSH) Parathyroid Hormone

(PTH). These effects could be due to interfering nanoparticles probably causing a protective physiological barrier breach followed by altered metabolic homeostasis (Zhang *et al*., 2024)

Effects on Reproductive System

By considering the environmental plastic pollutants, the biological processes like gametogenesis, formation of quality gametes, successful achievement of fertilization, and its sustainability, and completion of an uneventful gestation period followed by birth is an important matter of today's concern. Intricate physical and chemical properties of various forms of microplastic subtle impact our biological system interfering with the food chain; showing adverse effects on various systems of the body. Among them, the impact on the reproductive system is a matter of keen concern from the point of fertility in an individual. However, the exact mechanism that caused the adverse impact leading to subfertility or infertility still remains inconclusive. However, many observational and experimental study findings support the negative effect of MP on fertility in an individual (Wang *et al*., 2024). study on male mice revealed that PS-MPs ingestion reduced sperm motility, accelerate sperm deformity, decrease the activity of sperm-metabolism-related enzymes (Succinate dehydrogenase and Lactate dehydrogenase), drop in serum testosterone levels by activating the p38 MAPK signalling pathway and by inducing oxidative stress through the production of reactive oxygen species. ROS Scavengers are antioxidant molecules that eliminate the ROS. In this case, N-Acetylcysteine (NAC) was used. Treatment with p38 inhibitors and ROS scavengers decreased the damage and improved testosterone secretion (Xie *et al*., 2020).

An experimental study on male mice showed that Polystyrene Microplastics (PS-MPs) not only decrease sperm count and motility but also cause damage to testicular tissues, alter semen biomarkers, suppress *StAR* and*P4*50scc genes which are involved in testosterone biosynthesis, and decrease the serum testosterone concentrations. Vacuole formation and shedding of germ cells into seminiferous tubules were some of the significant histopathological observations. Immunoglobulin-binding protein, inositol-requiring protein 1α, X-box-binding protein 1 splicing [XBP1s], Jun kinase [*JNK*], CCAAT/Enhancer-Binding Protein (C/EBP) homologous protein [*CHOP*], etc. Factors related to Endoplasmic Reticulum Stress (ERS) were elevated (ERS inhibitors alleviated the damage and enhanced testosterone levels, indicating that reproductive toxicity could be because of activation of ERS pathway); apoptotic modulator (e.g., Caspase-12, -9, and -3) were inhibited indicating that reproductive toxicity could be because of activation of apoptosis pathway, as found out by molecular studies (Wen *et al*., 2023). In male mice, the hormone testosterone is biosynthesized in Leydig cells from the cholesterol. Under the influence of LH, (Luteinizing Hormone), cholesterol present in the cytoplasm enters mitochondria with the help of Steroidogenic Acute Regulatory Protein (StAR). In the mitochondria, cholesterol is converted into pregnenolone with the help of P450scc. Pregnenolone is then sequentially converted into testosterone in the endoplasmic reticulum with the help of P450c17, 3β-HSD, and 17β-HSD. A study on male mice revealed that MPs, on chronic exposure, enter the Leydig cells in the testis promote the AP-2 gene, and suppress the Sp1 gene, thereby reducing the transcription of LHR (Luteinizing Hormone Receptor). So, entry of LH into Leydig cell decreases, leading to a sequential decrease in Adenylyl Cyclase (AC), Cyclic Adenosine Monophosphate (cAMP), cAMP-dependent Protein Kinase A (PKA), Steroidogenic Acute Regulatory Protein (StAR) (thus suppressing the entry of cholesterol from the cytoplasm to mitochondria) and steroid synthase [P450scc (thus suppressing conversion of cholesterol into pregnenolone in the mitochondria), P450c17, 3β-HSD, 17β-HSD (thus supressing sequential conversion of pregnenolone into testosterone in the Endoplasmic Reticulum)], ultimately reducing testosterone biosynthesis (Jin *et al*., 2022).

Epigenetic Influence

Environment and behaviours will have a profound influence on the biological system. It has a subtle influence at the cellular level without affecting the DNA. Epigenetic phenomenon is a relatively recent revolutionary concept that changed the way we look at the body and understand the disease. Epigenetic views underscore the basis of disease acuteness and its resistance which varies phenomenally in different individuals. Epigenetic terrain is considered one of the most important and subtle mechanisms that drive gene expressions by leaps and bounds. It was tallied with acute and chronic exposure to various pollutants and lifestyles linked with altered changes in various levels of gene expressions without affecting actual DNA sequence; but altered various methylation status and its impact on health risk and disease susceptibility is much under the focus. It is one of the important considerations from the point of planning countermeasures against disease prevention and therapeutic standpoint (Limón *et al*., 2024).

Basic experiments shown that increased oxidative stress followed by increased inflammatory markers like interleukin and TGF-β which may lead to increased genotoxic effects which was studied through micronuclei assay. It is found that dissemination of microplastic particles may induce biological epigenetic modifications where there is no change in the DNA but there is some change in the way they express which could be influenced by slight histone modifications. Such effects are based on the factors like individual's lifestyle, diet, exposure to pollutants (Poma *et al*., 2023), etc. Plastic lineage animals were examined for their germ cell qualities; investigations are showing epigenetic phenomenon where histone molecules of DNA were found with methylation changes which is suggestive of epigenetic modifications in the experimental animal model. These alterations in germ cells tend to show transgenerational inheritance of modified gene expression of germ cells due to epigenomic changes which may

lead to detrimental effects on the growth and development of the embryo in the subsequent generations. Adverse epigenomic changes can influence various organs and systems like the liver, nervous system, reproductive, etc. These findings indicate that ancestral exposure to plastics influences the transgenerational effect on their offspring (Thorson *et al*., 2021).

CONCLUSION

Plastic usage is ubiquitous; it is indispensably blended with our civilized modern lifestyle. Only 9% of the plastic is recycled and most of the waste plastic is vaguely and unconditionally disposed by most of the population. Its huge accumulation is due to its improper and ineffective unscientific disposal methods. The exposure impact of microplastic and nanoplastic elements may differ based on their capacity for infiltration into the biological system. There are exciting and overwhelming outcomes acknowledged by various scientific research works underscoring the multiple forms of hazardous effects of MP-NP on the human body. Considering the current scenario of plastic addiction, failure to minimize its usage inevitably causes long-term adverse and progressive catastrophe impacts on our health and environment. In a developing country like India, until the invention of the best suitable alternative to replace plastic materials, especially for domestic purposes, a most civilized societal understanding, rational plastic usage and proper collection and disposal guidelines with strict and punishable statutory policies are the need of the hour.

ABBREVIATIONS

MP: Microplastic; **NMP:** Nano Microplastic; **DNA:** Deoxyribonucleic Acid; **STING:** Stimulator of Interferon Gene; **NF-kB:** Nuclear Factor Kappa Beta; **IL:** Interleukin; **TNF-α:** Tumour Necrosis Factor Alpha; **ROS:** Reactive Oxygen Species; **PERK:** Protein Kinase RNA-like ER Kinase; **ox MP:** Oxidised Microplastic; **ox NP:** Oxidised Nanoplastic; **VMP:** Virgin Microplastic; **VNP:** Virgin Nanoplastic; **ECM:** Extracellular Matrix; **DAMP:** Danger Associated Molecular Potentials; **TLRs:** Toll-Like Receptors; **PSNP:** Polystyrene Nanoparticles; **PCNP:** Polycarbonate Nanoparticles; **NK:** Natural Killer; **ER:** Endoplasmic Reticulum; **TEM:** Transmission Electron Microscopy; **mROS:** Mitochondrial Reactive Oxygen Species; **ATP:** Adenosine Triphosphate; **MMP:** Mitochondrial Membrane Potential; **MAPK:** Mitogen-Activated Protein Kinase; **TGF-β:** Transforming Growth Factor-Beta; **JNK:** Jun-N-terminal Kinase; **GI:** Gastrointestinal Tract; **MNP:** Micro Nanoparticles; **BBB:** Blood-Brain Barrier; **CNS:** Central Nervous System; **TDC:** Thyroid-Damaging Chemicals; **TSH:** Thyroid-Stimulating Hormone; **PTH:** Parathyroid Hormone; **NAC:** N-Acetylcysteine; **ERS:** Endoplasmic Reticulum Stress; **LH:** Luteinizing Hormone; **LHR:** Luteinizing Hormone Receptor; **cAMP:** Cyclic Adenosine Monophosphate; **PKA:** Protein Kinase A; **StAR:** Steroidogenic Acute Regulatory Protein.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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