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Review

# Eco-toxicity of nano-plastics and its implication on human metabolism: Current and future perspective

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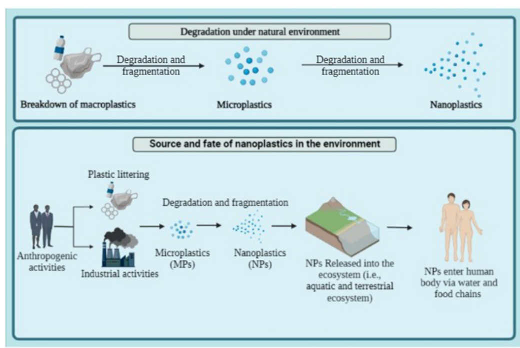
## HIGHLIGHTS

The major highlights of the paper are summed up below:

- The source and fate of nanoplastics and its distribution in the environment
- Eco-toxicity of nano-sized plastic particles and its deleterious impact on the living system.
- The toxic impact of nanoplastics on human health in terms of disturbance of metabolism.
- Nanoplastics mediated gut microbiome dysbiosis in humans resulting in metabolic disturbances.
- Current scenario and ongoing management strategies towards plastic pollution

## GRAPHICAL ABSTRACT

Fig. Degradation of plastics, source and fate of nanoplastics in the Environment.

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## ABSTRACT

In the current scenario, plastic pollution has become one of the serious environmental hazard problems due to its improper handling and insufficiency in degradation. Nanoplastics (NPs) are formed when plastic fragments are subjected to ultraviolet radiation, natural weathering, and biodegradation. This review paper focuses on the source of origin, bioaccumulation, potential nanoplastics toxicity impact towards environment and human system and management strategies towards plastic pollution. Moreover, this study demonstrates that nanoplastics interfere with metabolic pathways and cause organ dysfunction. A wide range of studies have documented the alteration of organism physiology and behavior, caused by NPs exposure. A major source of NPs exposure is via ingestion because these plastics are found in foods or food packaging, however, they can also enter the human body via inhalation but in a less well-defined form. In recent literature, the studies demonstrate the mechanisms for NP uptake, affecting factors that have been discussed followed by cytotoxic mechanisms of NPs. However, study on challenges regarding NPs toxicity for the risk assessment of human health is limited. It is important to perform and focus more on the possible impacts of NPs on human health to identify the key challenges and explore the potential impacts of their environmental accumulation and its toxicity impacts.

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**Contents**



## 1. Introduction

The plastic discovery, due to its strong chemical qualities, superior insulation, lightweight, and strength has ushered in a new era of convenience in both manufacturing and daily life (Gu et al., 2020a, 2020b). Plastics are widely employed in industry, building, medicine, research, agriculture, and other industries due to their unique properties. Despite advancements in plastic recycling and management policies, improper plastic disposal continues to be a global problem that results in uncontrolled environmental discharge (Barría et al., 2020). Plastics can be carried from terrestrial ecosystem to aquatic ecosystem due to their physical and chemical resilience, and hydrophobicity. Plastics are found in several types of ecosystems, including soil, groundwater, freshwater, marine water and in the atmosphere (Wang et al., 2021). Plastic fragments that are difficult to degrade due to their increased molecular weight and solid crystal structure have become one of the world's most serious and hazardous environmental issues (Yu et al., 2018). The enormous and unregulated application of plastics has resulted in eco-toxicity and environmental misbalance. As per the current plastic consumption rate in world, it is estimated that by year 2050, the plastic production will get elevated to 33 million, which will have larger impact on the environment (Lavers et al., 2022)

The most important aspect is that plastics degrade naturally at a very slow rate. Only between 6– and 26 % of these plastics gets recycled i.e., up to 94 % of them will likely be landfilled or enter nature via other channels (Alimi et al., 2018). There are research works that explain the toxicity of macro plastics. The macro plastic later upon weathering and fragmentation gets transformed into microplastics and nanoplastics which has become a major concern of eco-toxicity (Guo et al., 2020; Duan et al., 2021). Large fragments of plastic on physical, chemical, and biological degradation are broken down into microplastics (MPs) (1–5 mm) or nano plastics (NPs) (1 nm–1000 nm) (Jahnke et al., 2017).

The disintegration of larger plastic particles is caused by a variety of natural causes, including water's mechanical forces, ultraviolet (UV) radiation and biological metabolism i.e., when particles interact with both intracellular and extracellular living tissues, biological processes take place (Mattsson et al., 2018; Kwak and An, 2021). Since the demand for NPs is increasingly emerging and accumulating in all environmental compartments, there are limited research on the toxic response of NPs on humans. In recent decades, these particles have caused significant concern among the general population. As a result, the interaction of NPs with ecosystems and human populations, as well as the possible negative impacts on terrestrial, aquatic ecosystem and human health is needed to be studied extensively (Rubio et al., 2020; Sridharan et al., 2021).

There are two main routes of entry for NPs, namely inhalation, and ingestion. However, some data are also available regarding exposure via the skin. Using personal care products and cosmetics, or touching the face after contact with contaminated surfaces, can induce dermal exposure to nanoplastics indirectly. Due to their small size, these plastic particles may penetrate the skin barrier, such as through pores. One of the most prone areas for penetration of very small particles is the scalp's pores (Abbasi, 2021). Microfibers released from synthetic textiles are among many sources of these particles, which may result in inhalation in the outdoor or indoor environment (Prata, 2018). Several studies have found a link between inhaling these synthetic fibers and respiratory diseases (Facciolà et al., 2021). As NPs are inhaled, they reach the airways and are deposited based on particle characteristics, patient characteristics, and pulmonary anatomy; smaller particles (e.g., PE) reach deeper airways more readily. Small airways are reached by sedimentation and diffusion of particles between 1 and 5 m, while upper airways are deposited by impaction with rhino-pharyngeal walls. The deposition of nanoparticles follows Brownian motion (Carvalho et al., 2011; Bakand et al., 2012). A variety of mechanisms are responsible for the removal of MP particles after they are deposited, such as ciliary movement, phagocytosis from macrophages in the alveoli, and lymphatic migration causes the overproduction of reactive oxygen species (ROS), inflammatory cellular responses, oxidative stress, and cytotoxicity (Xu et al., 2019).

The rate of exposure by inhalation is comparatively lower than the rate of exposure by ingestion. Therefore, oral ingestion of NPs has received more attention since recent studies revealed these compounds were found in abundant quantities in different food and beverage sources, as well as in human feces (Liebmann et al., 2018). It has been documented that NPs can cause eco-toxicological effects on plants, phytoplankton, invertebrates, and other organisms in marine environments (Kumar et al., 2021). NPs can accumulate in large marine organisms by trophic transfer from prey to predator. It has been reported that NPs can transfer from algae to zooplankton and fish (Cole et al., 2013). These fishes are eaten up by higher animals or humans, resulting in the accumulation/ uptake of NPs into the body. There has been a wide variety of neutral or deleterious effects reported across several species. In humans, the oral route of exposure is considered to have significant effect in exerting NPs toxicity (Alaraby et al., 2022). The NPs generally inhibit the reproduction, growth, and development of organisms, contribute to oxidative stress, disrupt the gut microbiome, and change gene expression (Fig. 1) (Huuskonen et al., 2020; Kogel et al., 2020). However, the insufficient data on the effects of NPs necessitates the need to understand the nature of nanoplastics on terrestrial and freshwater ecosystems. In furtherance with this, it is important to study the characteristic factors responsible for the migration of NPs in various ecosystems and its adverse effects. These nanoplastics tend to become more hazardous and lethal upon interaction with the living system pertaining to their size, higher surface area to volume ratio which makes them more reactive (Sharma et al., 2022). Furthermore, these Nanoplastics also plays a role of

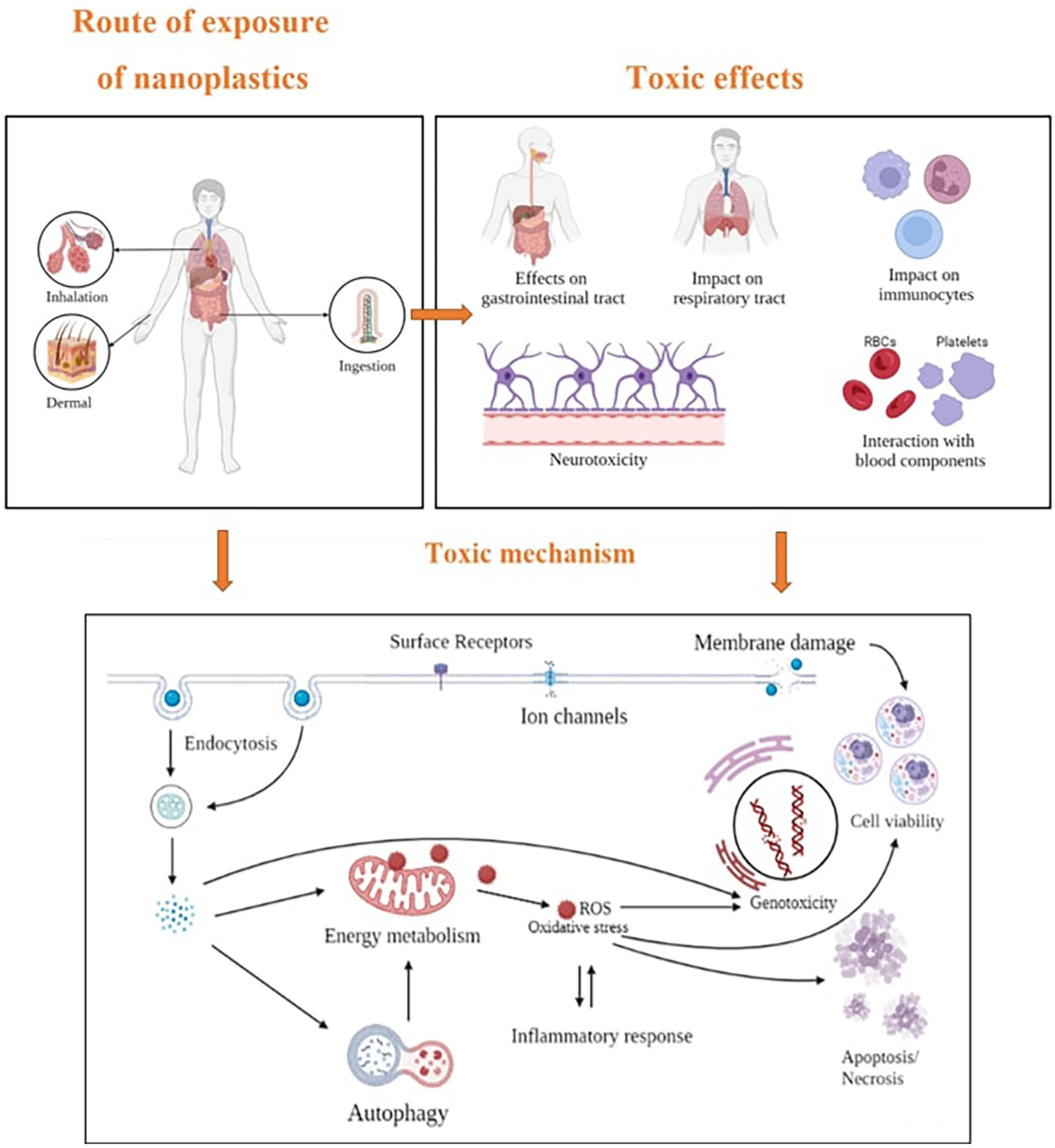


**Fig. 1.** Different routes of exposure of NPs in humans, general toxicity responses and its mechanism.

trojan horse, becoming a vector for many other potentially hazardous xenobiotics which result in upscaling of the lethal impact of nanoplastic pollution towards environment and other living system (Katsumiti et al., 2021).

Thus, this review emphasizes on the source and fate of nanoplastics and its distribution in the environment, eco-toxicity of nano-sized plastic particles and its deleterious impact on the living system, and its relation to gut microbiome dysbiosis and metabolic disturbances in humans, followed by management strategies towards plastic pollution. Therefore, this review provides a comprehensive insight on nanoplastics and its related toxicity that could pave a way towards effective control of plastic pollution and its negative effects on human health.

## 2. Use of different types plastic materials around the globe

### *2.1. Nano plastics and their by-products persistence in the environmental surrounding*

Nanoplastics are formed via weathering and physicochemical or biological degradation processes of macro plastic products which can exhibit colliding behavior. As defined by the nanoscale, NPs are particles with at least one dimension in the nanoscale (1–100 nm) (Gigault et al., 2018). Upon breaking down, a single microplastic particle -produces billions of NP particles, indicating the widespread nanoplastic pollution around the world (Hernandez et al., 2017). The nano-metric dimension of the plastic molecules enables an easier penetration towards biological membranes, transforming these particles into hazardous material (Yee et al., 2021). NPs may contain additives, monomers, or oligomers of the plastic's components, or dispersants that are either intentionally added or simply a byproduct of the manufacturing process which results in enhancement of the toxicity of these xenobiotics towards environment and human system (Sridharan et al., 2022). As a by-product of polystyrene, styrene monomers are released, adding to the toxicity of the material (Saido et al., 2014). In water, polystyrene nanoplastic by-products with small molecular weight were detected in large quantities, much higher than those being washed out from surfaces of nanoplastics exposed to air (Tian et al., 2019). The majority of NPs with potential for human exposure are composed of polyethylene, polyester, polyethylene terephthalate, polyetherimide, polystyrene, polypropylene, low-density polyethylene, high-density polyethylene, polyvinyl chloride, polyvinylidene chloride, polycarbonate, etc. (Lavers et al., 2022). Through the release of possibly cancer-causing substances, plastics were demonstrated to have negative impacts on cell viability and inflammatory gene expression in vitro (Rodrigues et al., 2019). Phthalates and bisphenol A are hazardous chemicals, linked to a number of health problems, including epigenetic modification, reproductive toxicity in both men and women, obesity and overweight, skeletal anomalies, allergy and asthma, and cancer (Benjamin et al., 2017).

There are three main sources of plastic particles in nano-sizes in the environment, which include Polymer nanoparticles produced for specific purposes, including cosmetics, 3D printer inks, or drug delivery, UV photo degradation, mechanical action, hydrolysis, and microorganisms can lead to plastic fragmentation, and Wastewater Treatment Plants (biosolids and effluent water) (Karapanagioti, 2017; Song et al., 2017; Mendoza et al., 2018). Additionally, nano plastics can be used to produce coatings, biomedical products, medical diagnostic devices, electronics, magnetism, and optics (Koelmans et al., 2015). The nano-plastics upon transformation from their parent molecule attain the altered physiochemical properties which affect their availability and biological activity in the environment (Mattsson et al., 2015).

Nanoplastics get categorized into primary or secondary groups depending on their origin and source (Bradney et al., 2019). As the name suggests, primary nano plastics are those that are introduced into the ecosystem in their original nano-sized with particular applications and consumer products, such as cosmetics, medicines, fibers and raw materials (Bessa et al., 2018). They are frequently released into the environment due to insufficient wastewater treatment plant (WWTP) infrastructure. Furthermore, the disposal of primary nanoplastic levels may increase as a result of the degradation of macro plastics, called secondary nanoplastics (Talvitie et al., 2015). Secondary nanoplastics get originated due to plastic litter, which is distributed in ecosystems as a result of human activities and industrial operations. Solid garbage disposal from land and individual ships at sea, as well as coastal landfill activities, are examples of human-generated sources. During transportation, sometimes due to accident or unintentional spillage of litter, secondary particles of plastic are accumulated in a natural ecosystem (Jahnke et al., 2017).

Nanoplastics used in products such as pharmaceutical and cosmetic industries can hinder the environment by utilizing the product directly or via wastewater through indirect activity (Sharma and Chatterjee, 2017). Most of these NPs are removed during wastewater treatment. However, not all particles are removed, some may get absorbed by the soil due to which plants may constitute a considerable source of nano plastics (Talvitie et al., 2017). Nano plastic particles also contribute as a source of medical and research applications. However, the cosmetic industry causes a greater amount of pollution by entering the environment through wastewater or use. Nano plastics, as manufactured products, typically arise from terrestrial sources. As a result of their accumulation in sewage and effluents, nano plastic particles may accumulate in aquatic ecosystems. According to estimates, 80 % of marine plastic comes from terrestrial sources such as landfills, NPs carried by water-bodies, bio-solids and compost, and improper handling and disposal of untreated wastes (Barría et al., 2020; Ganesh Kumar et al., 2020; Kumar et al., 2020). Also, ships/boats discharging litter and fishing nets are direct sources of marine litter (Ganesh Kumar et al., 2020). Domestic activities such as washing, laundry, cleaning, painting, etc. are the main source of NPs. As a result of clothes laundry, polyester, spandex fiber, acrylic and nylon are transported to sewage treatment plants (UNEP, 2018). A substantial number of NPs is released during the degradation and fragmentation of microbeads in shampoos and scrubs. It has been reported that even plastic teabags can release billions of nanoparticles (Hernandez et al., 2019). Other industrial sources include the direct production of NPs and feedstocks used for the manufacture of plastics (Yoshino et al., 2012; Phuc et al., 2014).

## 3. Exposure of Nano plastics towards environment and its toxic consequence

### 3.1. Eco-toxicity in aquatic ecosystem

Nano plastic eco-toxicity in the aquatic environment has been thoroughly researched and reviewed (Peng et al., 2020; Ganesh Kumar et al., 2020; Shen et al., 2019). Bacteria, algae, arthropods, echinoderms, bivalves, rotifers, and fishes are affected by the NP from various trophic levels (Brun et al., 2019). The NPs are bio-accumulated in the tissues which affects growth and reproduction, induces damage to the immune system, neurotoxicity, and causes metabolic disorders (Brandts et al., 2018; Pitt et al., 2018; Bergami et al., 2019; Yin et al., 2021; Sokmen et al., 2020). Moreover, freshwater ecosystems are capable of transporting and accumulating larger concentrations of NPs as well (Barría et al., 2020; Peng et al., 2020).

Recent research works provide a brief understanding of recent studies involving experiment on fishes which were fed with NPs. It has been reported that NPs show some toxicological/pathological effects on a variety of fishes (Table 1). Therefore, these are some of the evidences which depicts the acute and chronic toxicity related to nanoplastic exposure. In several investigations, larger polystyrene particles of roughly 100 μm or greater were found to have no significant effect on fishes (Ašmonaitė et al., 2018). Adult Crucian Carp and larvae may exhibit irregular feeding and mobility patterns as a result of NP accumulation (Mattsson et al., 2017). Internalization of NPs in fathead minnow has also been suggested (Greven et al., 2016), which could lead to detectable biomarker changes in blood cells (Banaee et al., 2019). NPs have been detected in the brains of fish in rare cases, causing alterations in brain appearances and behavior (Mattsson et al., 2017) or drastically inhibiting acetylcholinesterase (AChE) activity (Ding et al., 2018). NPs ingested by embryos and larvae have been observed to move to different tissues as they develop. According to the studies, NPs accumulate in larval guts or adult digestive tracts and the gills and liver in some cases (Wang et al., 2019; Qiao et al., 2019). According to studies, NP toxicity impacts the gut microbiota as well as biomarkers for the integrity of the epithelial barrier, inflammation, and oxidative stress. Toxicological

**Table 1**
Several toxicity investigations associated with NPs in aquatic organisms.

| Aquatic organisms | Types of NPs | Size | Toxic response | References |
|---|---|---|---|---|
| *Scenedesmus obliquus* | PS NP's | 70 nm | Toxicity to chloroplast, Reduction in chlorophyll content | Besseling et al., 2014 |
| Oysters | PS NP's | 50 nm | Decrease fertilization larval hatchability. | Tallec et al., 2018 |
| *Daphnia pulex* | PS NP's | 75 nm | Delayed egg laying, | Liu et al., 2019 |
| Sea Urchin *Paracentrotus lividus* | Carboxyl and amine NPs | 50 nm | Embryo toxicity and embryo lethality | Della Torre et al., 2014 |
| *Artemia franciscana* | Carboxyl and amine NPs | 40-50 nm | Disturbed feeding and motility | Bergami et al., 2016 |
| *Daphnia magna* | Carboxyl and amine NPs | 50 nm | Toxicity to chloroplast, disturbance of reproduction system | Besseling et al., 2014 |
| Crucian Carp (*Carassius carassius*) | PS NPs | 24 nm and 27 nm | Metabolic disturbances | Mattsson et al., 2015 |
| Zebrafish (*Danio rerio*) | PS NPs | 50 nm | Neurotoxicity and disturbed locomotion | Chen et al., 2017 |
| Zebrafish (*Danio rerio*) | PS NPs | 51 nm | Embryo toxicity and malformation of organs | Pitt et al., 2018 |
| Red tilapia (*Oreochromis niloticus*) | PS NPs | 100 nm | Toxicity to liver, brain and other enzymatic activities | Ding et al., 2018 |
| Zebrafish (*Danio rerio*) | NPs of size | 70 nm | Hepatotoxicity | Lu et al., 2016 |
| Zebrafish (*Danio rerio*) | NPs | 50 nm | Metabolic Disorders | Pitt et al., 2018 |
| Fathead minnow (*Pimephales promelas*) | PS NPs and polycarbonate NPs | 41 nm | Disturbance to blood cells and immune system | Greven et al., 2016 |
| Black rockfish (*Sebastes schlegelii*) | PS NPs | 15 um | Oxidative Stress, Cytotoxicity and locomotory disturbances | Yin et al., 2019 |

responses are often triggered by smaller plastic particles (i.e., 50 nm) and shows the highest significance in fishes (Yong et al., 2020). Therefore, these are some of the evidences which depicts the acute and chronic toxicity related to nanoplastic exposure.

According to recent studies, nanoplastics are made up of mostly polyvinylchloride, poly (ethylene teraphthalate), polystyrene, and polyethylene (Ter Halle et al., 2017). Since plastic nano-particles in the environment are typically formed via degradation of plastics rather than inside laboratories or commercial practices, it is very crucial to distinguish between other engineered nanoparticle pollution and Nanoplastics pollution (Gigault et al., 2021). The polymers in nanoplastics are hydrophobic in nature thus, they are ideal for capturing other hydrophobic pollutants while encountering. In contrast to other engineered nanoparticles, nanoplastics are heterogeneous. They are designed to have very specific sizes and shapes depending on the demand and purpose of their use. Nanoplastics are basically plastic polymers which are arbitrarily or accidentally and repeatedly degraded until they reach the nanoscale size. Furthermore, the disordered, polymeric nature of nanoplastics allows for shape and function flexibility that many traditional engineered nanoparticles lack (Rochman et al., 2019). Low concentrations (1 μg/ml) of naturally occurring NPs exposure triggers responses on genes related to endocytosis, mitochondrial metabolic disturbance, oxidative stress, DNA repair, and detoxification. Additionally, due to their colloidal nature and strong surface reactivity, they are more bioavailable to aquatic species (Venel et al., 2021; Arini et al., 2022).

### 3.2. Eco-toxicity in terrestrial ecosystem

Animals, humans, and other external forces like water flow and animal activity all transport NPs in the terrestrial environment. As known, soil differs from the natural context and soil which is researched in is a complex ecosystem with sophisticated pore patterns and a variety of living populations. NPs have accumulated on the soil surface as a result of modern agricultural techniques such greater use of agricultural membranes and sludge as well as modifications to irrigation practices. Furthermore, the plastic on the surface may migrate below or spread around due to the disruption of farming, harvesting, and other agricultural procedures. NPs travel downward through the soil's gaps as a result of the infiltration process, which occurs when water moves through the soil from top to bottom during irrigation or rainfall. Eventually, NPs ends up accumulating in the groundwater (Panno et al., 2019). One of the most prevalent organisms in the soil is the earthworm, which has a layer of viscous fluid on its surface. As earthworms move, plastics may be moved spatially as a result of NPs adhering to them (Rillig et al., 2017).

Additionally, NPs have an impact on the soil's microbiota and interfere with the actions of enzymes involved in the carbon, phosphorus, and nitrogen cycles. A study also revealed reduction in the activity of key biomes that control the cycling of nitrogen. It was found that, after being fed oatmeal containing polystyrene NPs, the soil oligochaete *Enchytraeus crypticus's* stomach contained significantly less *Xanthobacteraceae*, *Isosphaeraceae*, and *Rhizobiaceae* (Zhu et al., 2018). According to a paper, *Caenorhabditis elegans*, a nematode, is likewise harmed by polystyrene nanoparticles of 530 nm. The number of offspring decreased as the concentration of NPs reached 10 mg/kg. Adsorption by soil organic matter, oxidation of NPs mediated by organic acids, and interactions with soil minerals may all have an impact on the bioavailability and toxicity of NPs (Kim et al., 2020).

NPs not only provide a threat to pathogens but also have an impact on the plant growth. NPs may be absorbed, trapped, and translocate between tissues above ground. Smaller NPs can penetrate the nucleus and affect chromatin structure and function while larger NPs can deposit in the cytoplasm. Therefore, NPs have the potential to have genotoxic effects such the production of micronuclei and cytogenetic abnormalities (Giorgetti et al., 2020). Internalization of NPs in plants turns out to have a positive impact on their development. As compared to the control, root elongation in *Triticum aestivum* L. was increased by 89 % to 123 % significantly after polystyrene NPs exposure (Lian et al., 2020). Increase in plant biomass, nitrogen, and carbon was observed. Without any stress, seedlings developed more quickly after being exposed to NPs. This was most likely to cause increased amylase activity, hastening the production of solvable sugars from starch granules (Lian et al., 2020). Conversely, NPs have accumulated in wheat tissues, which have been found to affect higher trophic levels in the food chain. Because of this, it is necessary to investigate whether the paradoxical effects of NPs on plants are caused by soil variables or plant features.

Researchers have studied how plastic ingestion affects reproduction, gut microbiome profiles, behavior, and interactions between soil pollutants and plastic particles (Chae and An, 2020). There have been several studies performed on earthworms, since they are simple to handle in a lab setting and function as decomposers in soil ecosystems. Although NPs have been investigated for their impact on producers and consumers. Overall, NPs in soil have very little effect on terrestrial ecosystems (Qi et al., 2018; Song et al., 2019). To study oral exposure of plastics, their transport as well as the interaction between plastic particles and physiological variables like growth, physiological and behavioural change, locomotor activity, reproduction, and metabolism, researchers have used species of earthworms like *Eisenia fetida*, *Lumbricus terrestris*, and *Eisenia Andrei* (Rodriguez-Seijo et al., 2017; Rodríguez-Seijo et al., 2019; Yang et al., 2019). As a result of ingesting and transporting plastic particles in these studies, the organism's gut microbiomes were perturbed, and organic compounds were released into the environment (Groh et al., 2019).

## 4. Nano plastic toxicity in living-system

In most metabolisms, both degradative and synthesis reactions are catalyzed by enzymes and follow an ordered sequence. A metabolic pathway is a series of reactions that converts one compound into another (Blanco and Blanco, 2017). Whenever these pathways are disrupted by external or internal stimuli, it results in metabolic dysfunction. The pathways disturbance is associated with the liver, pancreas, kidney, and intestine. A dysregulated metabolism of the liver, pancreas, and intestine causes metabolic disorder.

### 4.1. Impact of nanoplastics in influencing disturbed metabolism

Recent studies have examined the impacts of NPs fragments on all of the components of the environment, including fresh water, marine water, terrestrial land and agroclimatic zone (Nelms et al., 2018; Ng et al., 2018; Alimba and Faggio, 2019; Song et al., 2019; Van Weert et al., 2019; Kogel et al., 2020; Meng et al., 2020). The oxidative stress caused by the plastics additives in aquaculture has been found to cause noticeable negative effects in nano-scale plastics (He et al., 2018; Miao et al., 2019). Although NPs rarely cause death to a living organism, they do slow down the physical development, decelerate cellular transformation, and lower the organ regeneration capacity. Therefore, the effects of NPs on the cells and tissues of mammals, particularly humans, remain problematic. Despite the fact that plastics are typically thought to possess negligible risk to people, a number of scientific results have sparked worries about their capacity to infiltrate tissues and the negative impacts of NPs because of their nano-size (Shen et al., 2019). NPs accumulates into human body via food from different food sources and water intake (Smith et al., 2018; Koelmans et al., 2019). Perhaps unsurprisingly, plastic containers and plastic teabags are common sources of NPs consumed by humans, also it can be accumulated via inhalation (Prata, 2018; Hernandez et al., 2019). Certain reports suggest that NPs has being detected in human stool samples, indicating that the ingested concentration being significantly higher (Schwabl et al., 2019).

Insulin resistance is central to metabolic syndrome (MS), causing metabolic dysregulation and eventual hyperglycemia and hyperlipidemia. A high blood sugar stimulates pancreatic beta-cells to produce more insulin, resulting in hyperinsulinemia. Overexpression of Renin Angiotensin Aldosterone System (RAAS), nephron sodium uptake through RAAS, while decreased or no activity are increased in hyperinsulinemia (Rask Larsen et al., 2018). As a result of dysregulated fat metabolism, free fatty acid (FFA) production increases, resulting in lipid deposition and obesity. Obesity creates inflammatory stress and dysregulation of adipocytokines. In addition to oxidative stress and prothrombotic states, increased FFA production causes thrombosis through other mechanisms. Endothelial dysfunction may be caused by oxidative and inflammatory stress, which may contribute to thrombosis. Further contributing factors to insulin resistance include oxidative stress, obesity, dysregulated adipocytokines, and pro-inflammatory cytokines (Hamjane et al., 2020).

The HIPPO pathway is a relatively novel mechanism that regulates whole-body metabolism. In the absence of the Hippo executer yes associated protein (YAP) in the endocrine pancreas, more upstream components of the Hippo pathway, such as Merlin, MST1, and YAP, are direct regulators of death in b-cells. When the pathway is disrupted, YAP and transcriptional coactivator with PDZ-binding motif (TAZ) translocate to nucleus and bind with TEAD transcription factors, inducing alteration in the gene expression involved in growth, proliferation, and survival. These represent 20-like protein kinases 1 and 2 (MST1/2) and large tumor suppressors 1 and 2 (LATS1/2) as core kinases (TAZ). There is a persistent activation loop between active caspase 3, the master apoptosis executer, under long-term metabolic or inflammatory stress. Under prolonged metabolic or inflammatory stress, cleaved MST1 (macrophage-stimulating protein) allows the potentiation of an apoptotic cascade, resulting in cell death and loss of insulin synthesis and secretion (Ardestani et al., 2018).

Alteration in other metabolic pathways such as glycogen metabolism, lipid metabolism, citric acid cycle, amino acid metabolism, pentose phosphate pathway etc. Are also responsible for mediating metabolic disorders in humans (Fig. 2). In a study, patients had enlarged liver and kidney due to excessive glycogen accumulation. This phenomenon is known as Glycogen Storage Disease Type I (GSD Ia). Glucose-6-phosphatase (G6Pase, encoded by G6PC), an ER-resident enzyme that is predominantly expressed in the liver and kidney and directly catalyzes the production of free glucose from G6P, is responsible for the development of GSD Ia (Chou et al., 2010). When a cell loses its ability to function, G6P builds up inside the cell, activating anabolic pathways that produce lactate, lipids, and glycogen. Patients continue to have abnormalities in hepatic metabolism, including increased glycogen synthesis and de novo lipogenesis as well as reduced lipid -oxidation and ketone generation. These abnormalities lead to steatohepatitis, hepatic adenomas, and hepatocellular carcinomas. Additionally, patients may experience hyperlipidaemia with elevated levels of VLDL and triglycerides in the blood and renal failure (Bandsma et al., 2008; Yiu et al., 2008). According to a study, lipid buildup in zebrafish after exposure to a pollutant result in liver damage (Zhou et al., 2019). The pollutant reduced the amount of fatty acid and lipid metabolism (fabp6 and fabp2) in larvae and liver, according to RNA-sequence data. After exposure, the mRNA levels of many enzymes involved in maintaining glucose homeostasis, including phosphoenolpyruvate carboxykinase (PCK) in the liver and glucokinase in larvae, all reduced. Results show that caused hepatocyte vacuolization 334 and neoplasm necrosis in adult livers, as well as liver deterioration in larval zebrafish (Jiang et al., 2020).

Researchers have previously reported that unmodified polystyrene nanoparticles with a diameter of 44 nm stimulate IL-6 and IL-8 gene expression in human gastric adenocarcinoma cells, suggesting that polystyrene may not necessarily induce pro-inflammatory responses because of its charge, but may instead be due to particle occurrence (Forte et al., 2016). In addition, another study was reported to show effects of polystyrene nanoparticles (30 nm) on the endocytosis in macrophages and HePG-2, HCT116 human cancer cells. Induced by the particles, large vesicle-like structures were formed, which blocked vesicle transport in the endocytic system as well as protein distribution, leading to bi-nucleated cells (Xia et al., 2016). Further evidence confirming the ability of polystyrene particles to produce ROS. According to their study, polystyrene particles with a size of 500 nm can stimulate ROS production in human liver cells (Liu et al., 2018). Besides polystyrene, an in vitro study reported that polyethylene particles showed obvious stimulation with respect to mice-derived macrophages, results in significant increased levels of IL-6, IL-1β, and TNF-α (Green et al., 1998). Based on these data, nanoscale plastic particles have the potential to activate cell responses, particularly immune response (Lehner et al., 2019).

However, numerous studies have documented pristine NPs' impacts on in vitro cultures of human cells. There are few studies on cellular uptake of NPs, with an inference of cellular toxicity negligible or absent, only at higher concentration it shows significance (Rafiee et al., 2018). Some of these studies have been performed in a range of human cell lines (Table 2). These table documents studies of cellular uptake, significance of cellular toxicity various concentrations of NPs. In human cell lines, it is depicted that toxicological responses such as cell viability was triggered by plastic particles (NPs) of size $^{<}$40 nm (Thubagere and Reinhard, 2010). And NPs of size 50 nm shows cell internalization and oxidative stress

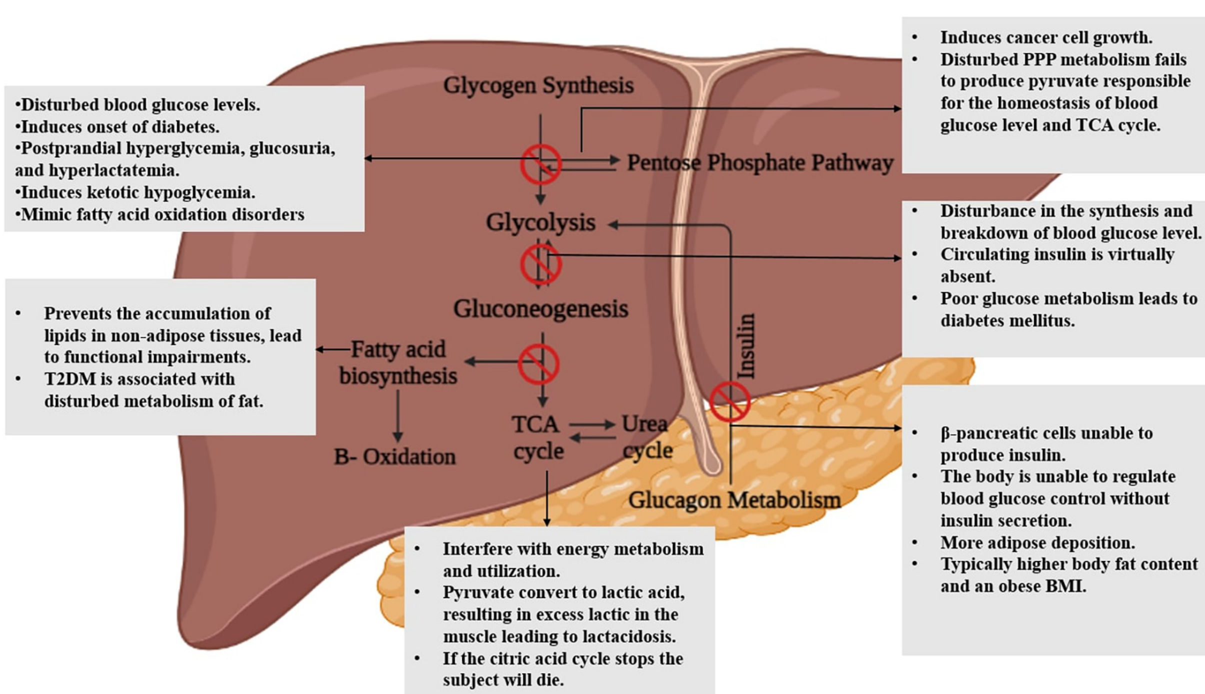


**Fig. 2.** Disturbance in the metabolic pathways inducing hepatic and pancreatic dysfunctioning.

**Table 2**
Several toxicity investigations associated with NPs in Human cell lines.

| Cells/cell lines | Types of NPs | Consequences | References |
|---|---|---|---|
| Caco-2 | Polyethylene terephthalate NPs. | Nano-PET has high propensity to cross the Caco-2 intestinal epithelial barrier model | Magrì et al., 2018 |
| Caco2 | Polystyrene NP's, | Particle translocation | Walczak et al., 2015 |
| Mammalian hepatocytes | Fluorescent Polystyrene-NPs | Internalized in mammalian hepatocytes | Johnston et al., 2010 |
| HepG2 cell line | PS-NPs interacted to PS-COOH PS-NH2 | Decrease cell Viability, Oxidative Stress | He et al., 2020 |
| HepG2 cell line | Unmodified polystyrene NP's | Altered cell line functioning | Zauner et al., 2001 |
| HepG2 cell line | Polystyrene NP's | Exhibited cell viability, genotoxicity, and transcriptomics, altered expression of cell proliferation and carcinogenic genes. | Kawata et al., 2009 |
| Panc-1 | Amino-functionalized PS NP's | Increased cellular uptake of particles under fluidic shear stress | Kang et al., 2016 |

(He et al., 2020). In an experiment, mammalian hepatocytes were exposed to PS-NPs for 30 min of incubation period, which resulted in cellular internalization and toxicity in hepatocytes (Powell et al., 2022). Another study documented the viability of HepG2 cells exposed to the PS-NPs, which decreased with the increase in concentrations. A significant reduction in cell viability was observed on exposure of HepG2 cells to high concentration of PS than low concentration. The toxicity of different concentrations of PS-NH2 and PS-COOH nanoplastics, 10, 50, 100 (μg/ml) that were 50 nm in size against HepG2 cell lines were studied. The exposure period of 24 h exhibited cytotoxicity at elevated concentration, which was demonstrated by significant increase in malondialdehyde, superoxide dismutase and glutathione level that correspond to lipid peroxidation and oxidative stress (He et al., 2020). NPs have a potential to enter the gastrointestinal tract (GIT) via ingestion process. It is not known whether nanoparticles are capable of crossing the human tissues directly. However, oral drugs containing polystyrene and PVC particles can cross the human gut tissues via endocytic tissues and are found to be present in lymph tissues and in the circulation, where the blood cells adhere to the NPs and facilitates the uptake of particles to other tissue, causing pro-inflammatory, cytotoxicity, oxidative stress, genotoxicity (Lehner et al., 2019). Concern about human exposure to NPs was first identified in the context of contamination of aquatic organisms (EFSA Panel on Contaminants in the Food Chain (CONTAM) 2016). A study reported that Mussel (*Mytiulus galloprovincialis*) kept in the water tank treated with PS-NPs (110 nm) of 0.05–50 mg/L concentration for 96 h, resulted in increased mRNA levels of *Hsp70*, oxidant status, antioxidant capacity, and lipid peroxidation in the digestive glands (Brandts et al., 2018). Another study reported that Juvenile large yellow croaker kept in the water tank treated with PS-NPs (100 nm) $10^4$ and $10^6$ particles/L for 14 days, resulted in decreased digestive enzymes activity (lipase, trypsin, and lysozyme) (Gu et al., 2020a, 2020b). NPs only after passing through fish's GITs or gills and dispersing throughout the body via the circulatory system directly affect humans (Chae et al., 2018; Su et al., 2019). According to another study, the bottle material influences nanoplastic, pigment, and additive distribution. When podocytes (i.e., human kidney cells) were exposed to NPs, it was seen that they have a heterogeneous surface, nucleus, and foot processes, in comparison with controls, indicating that plastic particles are potentially harmful to cell viability (Sarau et al., 2020).

Several studies were documented on hepatic tissues to study the effect of plastics. An experiment was conducted to determine the hepatic triglyceride, total cholesterol levels and hepatic pyruvate levels, to determine the lipid metabolism of liver using a BCA protein kit. In compared to the control group, the levels of hepatic TG and TCH reduced dramatically, but the levels of hepatic PYR increased significantly in the MPs-treated groups. The transcriptional gene expressions are also affected by the action of MPs on exposure. In comparison to the control groups, the MPs modulated the mRNA levels of carbohydrate regulatory element binding protein, pyruvated kinase, and citrate synthase, although glucose kinase was unaffected. These findings suggest the alteration in lipid metabolism on exposure to PS-MPs (Lu et al., 2018). Similar study was documented, where 24 mice were collected and treated with MPs for 1–2 weeks (divided into three groups: control groups, mice treated for one week, and mice treated for two weeks). The first week's findings revealed that mouse livers were damaged by oxidative stress, which resulted in an imbalance in the antioxidant system, the gut-liver axis was disrupted, and there was an increased insulin resistance. Besides the exposure period of 2 weeks, MPs has affected pathways of Glycine, Serine, and Threonine metabolism; Alanine, Aspartate, and Glutamate metabolism; Histidine metabolism; Glycero-phospholipid metabolism; and Glutathione metabolism, Phenylalanine, Tyrosine, and Tryptophan Biosynthesis. The metabolite profiles of substances connected to these pathways, including as cortisol, UDP-N-Acetyl-D-Glucosamine (UDP-GlcNAc), and choline, were affected by these results (Shi et al., 2022).

The mechanisms involved for insulin secretion and insulin resistance have been proposed based on significant changes in cortisol levels, acetylcholine concentrations, and GlcNAc concentrations. The adrenal glands create cortisol, one of the steroid hormones. Cortisol receptors are present in majority of the body cells. In vivo, it has been demonstrated that high plasma cortisol levels limit non-hepatic glucose utilization, elevate plasma insulin, and boost hepatic gluconeogenesis. Additionally, cortisol and cholinergic signaling pathways, including as glycerophospholipid metabolism and insulin production, are strongly linked. Acetylcholine, which travels to the pancreas via the bloodstream, can be produced by the liver from cortisol. Acetylcholine acts on anti-muscarinic acetylcholine receptors M3 in the pancreas (M3R). As a result, the large drop in cortisol may affect insulin secretion, resulting in insulin secretion dysregulation and insulin resistance (Shi et al., 2022). These metabolites also interfere with the metabolism of Glycine, Serine, and Threonine, insulin, and glycerol phospholipids in the gut microbiota. These metabolites may undergo microbial conversion during digestion to trimethylamine (TMA), which is subsequently oxidized in the liver by the Flavin-containing mono-oxygenase enzyme. Increased plasma TMAO levels have been linked in epidemiological studies to an increased risk of thrombosis and type 2 Diabetes Mellitus (T2DM). As a result, there may be an increase in the obesity-mediated insulin resistance pathway as well as an increase in insulin secretion (Brial et al., 2018; Walter et al., 2020). Another study demonstrated zebrafish larvae were exposed to PSNPs for 2 days. When exposed, PSNPs accumulates in neuromasts and the larval jaw movement is already developed, so it is easier to consume particulate matter from the surrounding environment (Brun et al., 2018). According to the findings, PSNPs were mostly found in the exocrine pancreas, gallbladder, and gastrointestinal system. The cortisol levels in larvae were measured after two days of exposure. The larvae had considerably higher cortisol levels than controls following exposure to PSNP. Both insulin expression and total body glucose levels were decreased. This most likely led to an increase in cortisol levels which then triggers the expression of the genes g6pca and pck1, which are involved in glycogenolysis and gluconeogenesis (Brun et al., 2019). Stress-induced high cortisol levels are associated to lower eating in larval zebrafish at a later stage of development, which exacerbates low glucose levels and creates a negative feedback cycle (De Marco et al., 2014). In conclusion, excessive cortisol exposure during the early stages of life can result in adulthood-related consequences such as irreversible epigenetic change of the glucocorticoid receptor, high basal cortisol levels, impaired tailfin regeneration, and immunoregulation (Wilkinson and Goodyer, 2011; Hartig et al., 2016).

### 4.2. Toxic impact of NPs on gut microbiome dysbiosis

There are 10 to 100 trillion microorganisms in the adult gut microbiota, which is ten times as many as our total somatic and germ cells combined.

Also, the genomes of gut microbiota (microbiome) have 100- to 150-fold more genes than our own genomes (Backhed et al., 2005; Qin et al., 2010). As humans have evolved, their gut microbiota has profound effects on how they react to various situations (Hur and Lee, 2015). Genes present in a person's intestinal microbial community (microbiome) represent a genetic collection with more than one order of magnitude more genes than in the human genome. Microbes in the gut help develop host immunity, digest food, regulate gut endocrine function and neurological signaling, modify drug action and metabolism, eliminate toxins, and produce numerous compounds that influence host health (Fan and Pedersen, 2021).

There are some mounting evidences that MPs/NPs are entering the human gut on a regular basis via food and drinking water, manufacturing wastes, or pollutants from plastic packaging (Dawson et al., 2018; Mason et al., 2018; Pivokonsky et al., 2018; Hernandez et al., 2019; Compare et al., 2012). Nanoplastics have the ability to penetrate the bloodstream due to their small size they can be easily carried with the blood cells. After ingestion, the intestinal epithelium is the first barrier to be exposed to NPs. For the first time in 2018, a study from United European Gastroenterology (UEG) discovered MPs in human feces, raising concerns about the potential harm of MPs to humans (Schwabl et al., 2019). This indicates that taking MPs/NPs orally exposes these exogenous contaminants to the gastrointestinal tract (GI) tract directly. The intestinal barrier is necessary for intestinal homeostasis and metabolism to occur (König et al., 2016). Various metabolic disorders are linked to damage in gut barrier integrity (Qiao et al., 2021). *Firmicutes* and *Bacteroidetes* make up the majority of the human gut microbiota, while *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Verrucomicrobia*, and *Cyanobacteria* accounts a tiny percentage (Abenavoli et al., 2019). Due to its sensitivity, the gut microbiome has emerged as a novel toxicological target for some environmental pollutants, such as plastic pollution, and it has the potential to function as a medium to indirectly affect the health of the host. Plastic particles and other pollutants enters the gut region through intestinal epithelium barrier and disturbs the gut microbiota. It interacts with the microbes present in the gut. It results in disruption of the cell wall and releasing intracellular materials, thickening the cell wall and releasing cytoplasm, releasing ions via ion channels, and damaging DNA, therefore, results in the internalization of plastic particles into the bacteria (Fig. 3) (Singh and Dubey, 2018). The body's metabolic processes are controlled by the microbiome. Furthermore, numerous studies have linked changes in microbiota composition with the metabolic disorders such type II Diabetes, obesity, lipid disorders, and other metabolic dysfunctions (Pascale et al., 2018).

The gut microbiota in the feces and cecal contents of mice that were impacted by MP were studied in an experiment, and the results revealed an abnormal gut microbiota composition of feces and cecal contents at the phyla and genus levels. It was observed that polystyrene MP reduced the population of *Firmicutes* considerably. *Oscillospira*, for example, is related to thinness and healthy life, and it may also aid in the formation of secondary bile acids (Konikoff and Gophna, 2016). *Ruminococcus* may play a role in morbid obesity. As a result, findings revealed that MPs may cause gut microbial dysbiosis in mice. Similarly, when zebrafish were exposed to polystyrene MPs containing water at semi-static settings for 14 days in an experiment, after 14 days, the abundance of *Firmicutes* in the groups had increased dramatically. The abundance of *γ-Proteobacteria*, on the other hand, fell dramatically in the gut. In addition, the polystyrene MPs-treated group showed a considerable reduction in *β-Proteobacteria*. According to prior research, it was stated that increased *Firmicutes* in the cecum improves nutrient absorption and is associated with the development of obesity (Ley et al., 2005).

## 5. Management of nanoplastics in the environment

The persistence of nanoplastics in the environment is gaining attention these days, as the distribution of nanoplastics occurs through the aquatic ecosystem and is transported further via terrestrial mobility. Because of significant knowledge gaps, assessing the risk of NPs remains difficult. However, the first step is to gather reliable data on NPs exposure in marine, freshwater, and terrestrial environments (Wagner and Reemtsma, 2019). Therefore, addressing NP pollution requires to apply novel approaches towards remediation technologies, formulation, and public awareness. Despite the fact that little effort has been made in NP remediation, current studies have proposed several possible directions (Wang et al., 2021).

Approaches such as bioremediation, microbial degradation of larger plastic particles, membrane separation with a reactor, and photo-catalysis along with the traditional procedures such as filtration, coagulation, centrifugation, flocculation (Devi et al., 2022; Zhou et al., 2022) is conducted with several biotic as well as abiotic factors, such as assimilation, mineralization, enzymatic mechanisms, substrates and co-substrates concentration, temperature, pH, oxidative stress, etc. (Kumar and Hashmi, 2021).

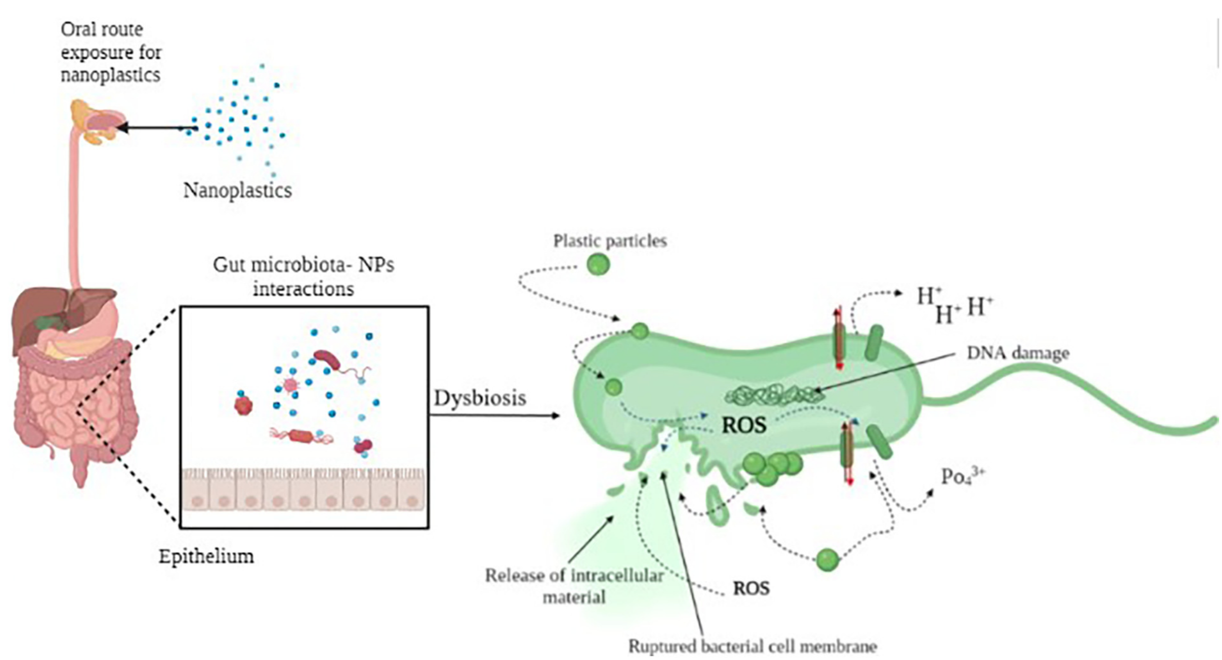


**Fig. 3.** Toxic impact of NPs on gut microbiome.

For example, one of the remediation technologies such as biodegradation involves three stages, including:

1. Depolarizing the plastic particles converts them into monomers and oligomers. This process is achieved by extracellular enzymes (González-Pleiter et al., 2019).
2. Assimilation of these monomers and oligomers occur when they enter the host i.e., the microorganism's cell and become a part of their biomass (Iram et al., 2019).
3. Mineralization includes the oxidization of the assimilated matter, and thus producing CO2 and H2O (Pathak, 2017).

Thus, nanoplastics pollution can be addressed by source reduction by minimizing plastics incorporation in the economy, and appropriate waste management (Sarkar et al., 2022). Appropriate development of waste water treatment system, waste valorization, economically sound waste management techniques and viable alternatives are all required to reduce NPs in the environment.

## 6. Future perspective of nanoplastics toxicity

This paper gathers a comprehensive review on the origin and distribution of nanoplastics, general toxicity and eco-toxicity, and toxic consequences of nanoplastics on Human health. Since many decades, plastic wastes have become a concern for the environment. Many studies examined the toxic effects of nanoplastics on ecosystems (i.e., aquatic and terrestrial). Several studies states the effects of additives, by-products and functional groups of plastic particles, making these particles more detrimental. Many questions still remains unresolved. It is therefore important to consider the stability of plastic particles when mixed with different contaminants in future studies because this can affect the way the particles interact with organisms. In addition, it would be important to study the concentration at which these NPs-contaminants adsorb and desorbed inside the organism, leading to higher or lower levels of elimination of these contaminants into the environment. Due to the transformation of these plastic particles and conversion of contaminants, this can alter the overall toxicity of a mixture and affect its metabolism, which should be considered (Lin et al., 2019; Spurgeon et al., 2020).

## 7. Conclusion

According to the findings mentioned, the plastic pollution has become a major concern and challenge for the human society. This scenario of plastic pollution showing much more deleterious effect towards environment and human system owes to transformation of macroplastics to micron and nano sized plastics molecules. Nanoplastics appears in the environment in form of primary and secondary sources, possessing potentially upscaled ecotoxicity due to its characteristic feature of size, shape, surface area to volume ratio making it much more reactive and hazardous. The deleterious effect of nanoplastics towards living system ranges from micron level to the human's system where these nano sized plastics interfere and result in cytotoxicity and other metabolic disturbances. Since, the toxicity of NPs for humans is still unknown, a number of concerns need to be resolved, including the exposure of NPs to human populations and the environment. Studies based on different types and shapes of NPs, time- and concentration-dependent manner are exposed to human bodies, and the necessity for the advancement of more sophisticated high-throughput analytical techniques to find these plastic particles in the environment. In addition to overcome these obstacles, efforts must be made to reduce plastic production and usage, as well as to increase recycling and environmentally safe disposal of plastics.

## CRediT authorship contribution statement

**Shoumi Haldar:** Manuscript Writing.
**Yuvashree Muralidaran:** Manuscript Writing and Formal Analysis.
**Diana Míguez:** Formal Analysis.
**Sikandar I Mulla:** Formal Analysis.
**Prabhakar Mishra:** Conceptualization.

## Data availability

This is a review paper

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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