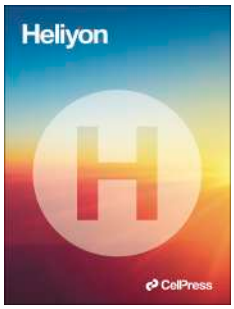

PROBIOTICS AN EMERGING THERAPEUTIC APPROACH TOWARDS GUT- BRAIN-AXIS ORIENTED CHRONIC HEALTH ISSUES INDUCED BY MICROPLASTICS: A COMPREHENSIVE REVIEW

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PROBIOTICS AN EMERGING THERAPEUTIC APPROACH TOWARDS GUT- BRAIN-AXIS ORIENTED CHRONIC HEALTH ISSUES INDUCED BY MICROPLASTICS: A COMPREHENSIVE REVIEW

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Running Head: PROBIOTICS AND MICROPLASTIC (MP) INDUCED GUT DYSBIOSIS

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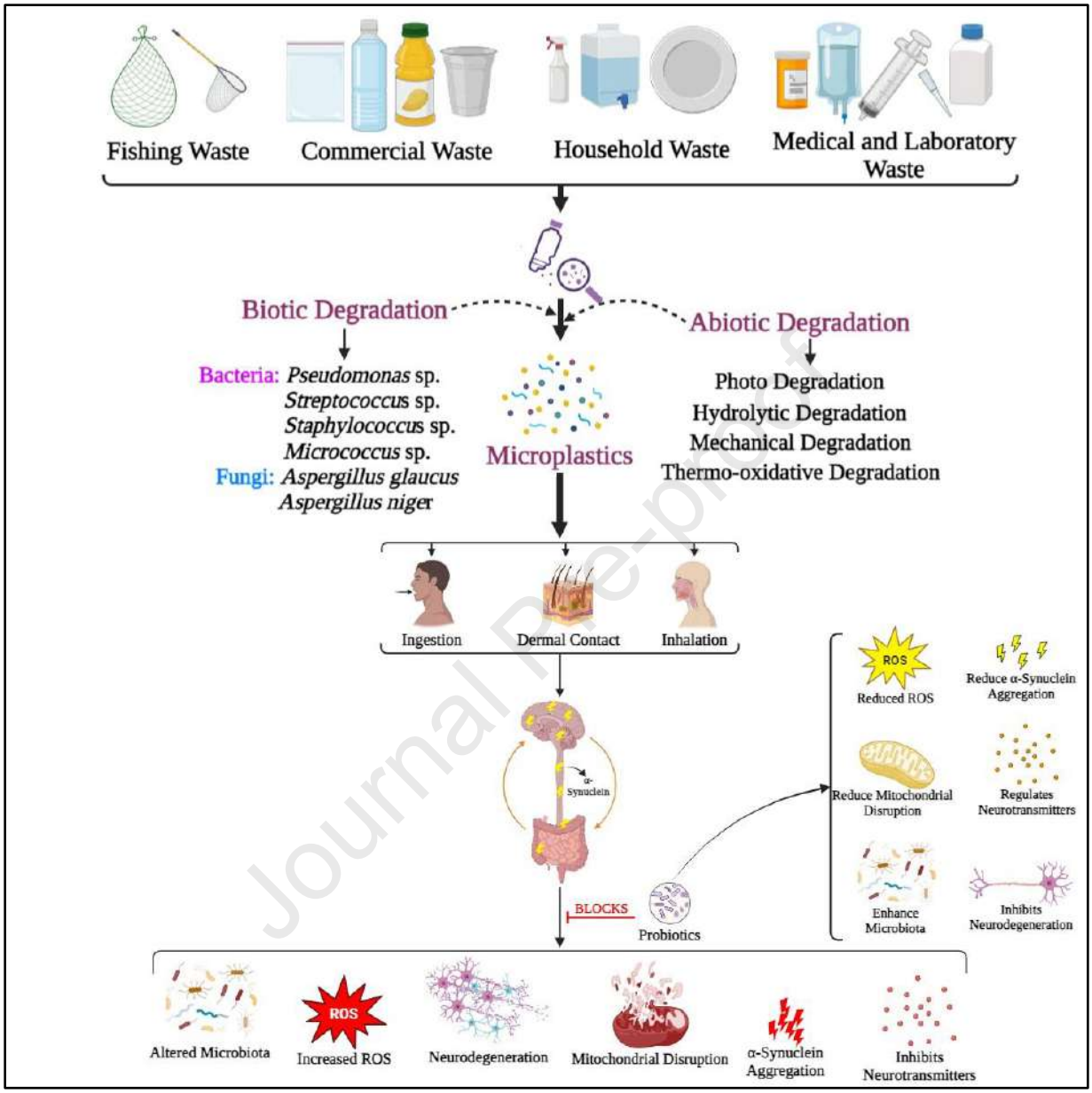
Highlights

- Food ingested MP trigger direct damage to the GI tract causing intestinal dysbiosis, inflammation, ROS, neurodegeneration, and organelle damage
- The hydrophobicity and large surface areas of MP allow toxic pollutants to attach to their surfaces and the entry routes determine the place of accumulation and severity
- Probiotics regulate the gut-brain, gut-liver, gut-lung, gut-skin, hypothalamic-pituitary-adrenal, hypothalamic-pituitary-thyroid, and hypothalamic-pituitary-gonadal axis to control dysbiosis.

Keywords:

Microplastics (MPs), Gut Dysbiosis, Intestinal Barrier, ROS, Neurotransmitter, Neurodegeneration, Gut-Brain-Axis, Probiotics.

31 **GRAPHICAL ABSTRACT**



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ABSTRACT

Applications for plastic polymers can be found all around the world, often discarded without any prior care, exacerbating the environmental issue. When large waste materials are released into the environment, they undergo physical, biological, and photo-degradation processes that break them down into smaller polymer fragments known as microplastics (MPs). The time it takes for residual plastic to degrade depends on the type of polymer and environmental factors, with some taking as long as 600 years or more. Due to their small size, microplastics can contaminate food and enter the human body through food chains and webs, causing gastrointestinal (GI) tract pain that can range from local to systemic. Microplastics can also acquire hydrophobic organic pollutants and heavy metals on their surface, due to their large surface area and surface hydrophobicity. The levels of contamination on the microplastic surface are significantly higher than in the natural environment. The gut-brain axis (GB axis), through which organisms interact with their environment, regulate nutritional digestion and absorption, intestinal motility and secretion, complex polysaccharide breakdown, and maintain intestinal integrity, can be altered by microplastics acting alone or in combination with pollutants. Probiotics have shown significant therapeutic potential in managing various illnesses mediated by the gut-brain axis. They connect hormonal and biochemical pathways to promote gut and brain health, making them a promising therapy option for a variety of GB axis-mediated illnesses. Additionally, taking probiotics with or without food can reduce the production of pro-inflammatory cytokines, reactive oxygen species (ROS), neuro-inflammation, neurodegeneration, protein folding, and both motor and non-motor symptoms in individuals with Parkinson's disease. This study provides new insight into microplastic-induced gut dysbiosis, its associated health risks, and the benefits of using both traditional and next-generation probiotics to maintain gut homeostasis.

INTRODUCTION

Microplastics (MPs) are a growing societal issue due to their widespread distribution and accumulation throughout ecosystems[1,2]. MPs are ubiquitous and persistent in a variety of settings due to the large and ongoing production, usage, and disposal of plastic materials in contemporary civilization[1,3,4]. The low density and high durability of polymers have led to a steady increase in plastic production since the 1950's [5,6]. Current society is experiencing a rapid increase in the worldwide population, along with rapid industrialization[7–9], leading to various social, financial and ecological concerns such as increased energy demand, environmental damage, and climate change[10–12]. Improper waste disposal and the slow degradation of plastic have made these polymers abundant resulting in extensive environmental pollution issues [13]. Once in the environment, plastics begin to degrade and break into smaller pieces through various processes of abiotic and biotic degradations **(Fig.1)** [14–18]. The size of primary or secondary MPs ranges from 0.1 µm to 5 mm[9,19]. The majority of traditional techniques for recycling MPs involve reintroducing plastic scrap primarily into the processing unit's heating cycle. This is followed by converting waste into new plastic products by blending it with virgin polymer, which can significantly lower production costs [20]. Plastic wastes may occasionally undergo chemical or thermochemical alteration to be recycled in the industrial loop. There are three different ways that MPs can degrade: physically, chemically, and biologically. Chemical recycling methods like pyrolysis are very common in the industrial world [20–22]. A variety of enzymes are involved in the biological degradation process [23,24]. The fundamental procedure involves breaking down polymers into smaller particles, which are then broken down into oligomers, dimers, and monomers. Microbes assist in the mineralization processes that follow this degradation. Microorganisms absorb monomers through specific cell transport systems, allowing them to enter catabolic pathways as a source of carbon. Carbon dioxide and water are the end products of aerobic metabolism in cells, leading to the mineralization of plastic. It is commonly known that microalgae attach themselves to plastic surfaces in wastewater streams. This attachment initiates the decomposition of plastic by generating the exopolysaccharide and ligninolytic enzymes. These polymers generally function as a carbon source, boosting the amount of proteins and carbohydrates in cells and accelerating growth [25]. Additionally, it was found that pro-oxidative chemicals or pretreatment are not necessary for *Oscillatoria subbrevis* and *Phormidium lucidum* to cling to and degrade low-density polyethylene surfaces [26].

Furthermore, an extensive variety of intracellular and extracellular enzymes originating from fungi possess the ability to catalyze an extensive array of reactions and degrade petroleum-based polymers. The metabolism of aliphatic, alicyclic, and aromatic compounds is aided by the oxidation and conjugation events associated with the cytochrome P450 family enzyme systems, epoxidases, and transferases [27]. According to Shin et al. (2018) they perform a wide range of reactions, such as epoxidation, sulfoxidation, desulfuration, dehalogenation, and deamination [28]. For the breakdown of MPs, bacterial consortiums as well as pure cultures can be used. Comparatively, biological methods were more effective, but their effectiveness is limited to certain types of MPs. The presence of organic substances in the environment influences the activity of microorganisms involved in MP degradation[29].The biggest drawback, however, is the incredibly slow rate of disintegration. Therefore, new inventive methods to enhance the degrading bacterial isolates and optimize the environment are required to speed up the degradation process.

MPs can adsorb a variety of pollutants, such as PAHs, PCBs, heavy metals, pathogens, and more, due to their small structure, improved hydrophilicity, surface roughness, the existence of a negative charge on their surface, and the availability of functional groups [30].Subsequently ,hydrophobic, electrostatic, and non-covalent interactions between contaminants and MPs are intensified [31–33]. The human body can come in contact with MPs through ingestion of MP-contaminated food, inhalation of MPs present in the air, and dermal contact with these particles, found in commercial products, textiles, or in dust, leading to health issues [34]. Aquatic organisms, such as zooplankton [35], sea grass[36], algae [37], copepods[35], mussels [38], crustaceans [39], Echinodermata species [40] and fishes [41] are among those that can easily consume MPs. The consumption can have various detrimental effects, including obstructing the alimentary canal [42], disrupting the endocrine system [35], and ultimately inhibiting body growth and causing death[43]. Phthalates, a chemical found in plastic and ingested through food, can alter estrogen activity, leading to reproductive, developmental, and structural damage to host organs [44]. Another food-ingested polymer, polybrominated diphenyl ether, can interfere with reproductive health, hormone signaling, and neuronal development, resulting in neurotoxicity, carcinogenicity, behavioral abnormalities in humans, reducedIQ in children, and autism spectrum disorders upon exposure [45]. MPs can act as vectors for transferring hydrophobic organic compounds from water due to their large surface area and hydrophobic nature. This leads to pollutants accumulating more rapidly in aquatic organisms, making them more harmful to humans when consumed. MPs have been found in various fish species consumed by humans, including parrot fish (Scaridae), marine and freshwater killfish (*Aplocheilus*sp.), tuna (*Scombridae*), cutlass fish (*Trichiurus* sp.), swordfish (*Xiphias gladius*), and croaker fish. MPs have been detected in human saliva [46], placenta [47,48], lungs [49,50], stool [51,52], and breast milk [53].

The gastrointestinal (GI) tract is the primary site of action for the significant health effects of food-intake plastic particles, directly harming the body on both a local and systemic level **(Fig.1)**. The host is negatively impacted by the increased gut bacterial load and diversity, which alters the host's immunological and metabolic pathways, leading to inflammation and gut discomfort [54]. It has been reported that gut organisms are involved in metabolizing proteins and complex carbohydrates, which help protect the host’s immune system. They facilitate cross-talk between gut epithelial cells and immune cells [55]. Additionally, communication via the vagus nerve, the metabolism of tryptophan and short-chain fatty acids (SCFA), and the growth of neurons all contribute to regulating the central nervous system. In the GI tract, gut organism-mediated fat digestion, fat absorption, and complex carbohydrate degradation are essential for maintaining human health. Although the digestion of plastic particles and their effect on resident microbial colonization of the gut can be studied using *in vitro* and *in vivo* models, the overall impact of plastic particles on gut microbes is still unclear. Ethical restrictions, study costs, and the complexities of multi-step human digestion are real barriers to understanding the effect of plastic particles on gut dysbiosis. Through a static model, endpoint analysis of digestion and step-specific kinetic studies can be monitored [56,57]. However, dynamic simulators can monitor the effects of contaminated food, heavy metals, and pharmacological compounds in a computerized GI model and the area of large intestine nanomaterial-induced gut organisms' metabolic bioconversion [58]. Thus, the lack of physiological information on plastic particle-induced gut dysbiosis represents a

research gap that needs to be addressed. In this manuscript, the main objectives are to investigate the harmful effects of MPs on the gut as they act as pollutants. Although several degradation processes are available, the existence of MPs in the environment creates a lot of problems. MPs can enter the body through food, disrupting gut health and the gut-brain axis. Whether acting alone or in combination with other pollutants on their surfaces, MPs can compromise the intestinal barrier, alter the microbial population in the gut, and trigger various cascades that result in the production of ROS, causing organ damage and neurotoxicity. We present a potential mechanism initiated by MPs upon entry, discuss the consequences, and propose a control mechanism using different probiotics based on their modes of action.

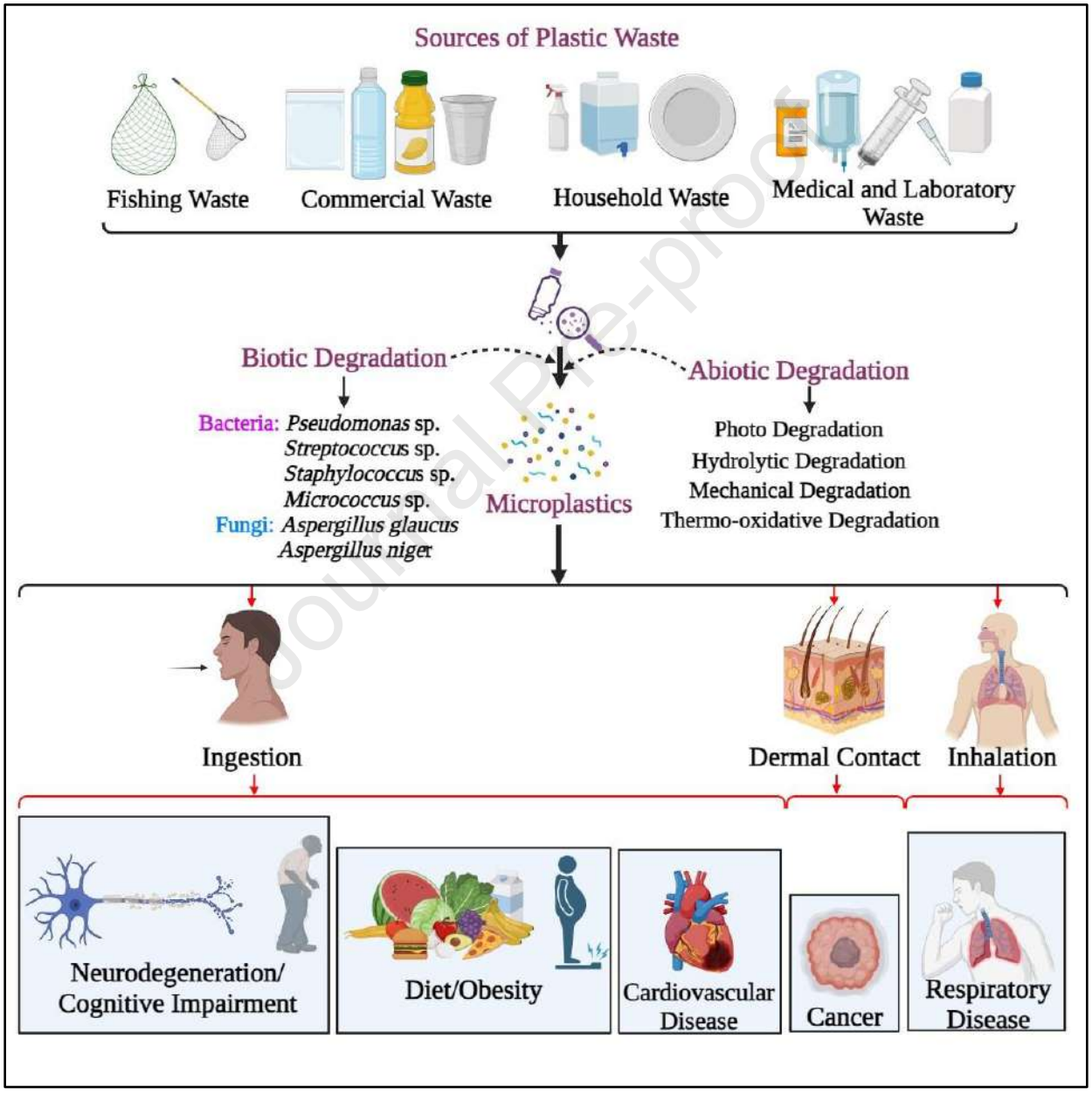

Fig.1. Schematic Representation of Microplastics (MP) Generation and Their Portals of Entry to Establish Severe Health Issues in Human

CELLULAR AND MOLECULAR EVENTS TRIGGERED BY MP

The gut-brain axis (GB axis) is a complex network process that not only helps the organism interact with its environment but also aids in nutrient digestion and absorption, intestinal motility and secretion, complex polysaccharide decomposition, and intestinal integrity maintenance. Thus, it connects the central nervous system (CNS) and the GI tract [59]. This demonstrates that the brain, the main organ responsible for many physiological processes, and the GI are closely related [60]. However, exposure to different antibiotics and pathogens can alter the composition of the gut microbiota and lead to dysbiosis, which can adversely affect the host's health [61]. The autonomic nervous system (ANS), the vagus nerve, and the X cranial nerve form the core of the GB axis. Afferent fibres send information from the inner organs to the brain, connecting the CNS to the enteric nervous system (ENS). The vagus nerve detects signals from various stimuli, while the efferent vagal nerve response depends on the gut environment, host immune system, and metabolism [62,63]. Additionally, the hypothalamic-pituitary-adrenal axis (HPA axis) can connect the CNS with the gastrointestinal tract [63]. During times of stress, the hypothalamus releases corticotrophin-releasing hormone, which stimulates the pituitary gland to produce adrenocorticotropic hormone (ACTH). Thisleads to the synthesis of cortisol (or corticosterone in rats), by the adrenal glands, which also regulate various gastrointestinal functions. Toxic additives found on MP surfaces can penetrate lipid bilayers and blood-brain barriers, disrupting the normal function of hypothalamic axes like the hypothalamic-pituitary-adrenal axis (HPA), the hypothalamic-pituitary-thyroid axis (HPT), and the hypothalamic-pituitary-gonadal axis by interfering with hormone receptors [64].

It is already established that organisms from higher trophic levels ingest MPs either by consuming them directly, mistaking them for prey, or through lower trophic organismsthat have already ingested MPs due to their limited ability to differentiate between plastic and food [65]. Previous studies focused on MP formation and its potential health risks, but recent studies have highlighted the entry points of MP and their effects on the human body [66–68]. The accumulationof MPs can lead to long-term adverse effects in the host body, ultimately increasing morbidity and mortality rates [65,69,70]. According to Celi *et al*. (2017) [71], the symbiotic balance between the intestinal tract and local microbes without any dysfunction determines the gut health in animals **(Fig.2)**. However, aquatic animals have a more dynamic gut microbial existence compared to terrestrial vertebrates, and they are highly sensitive to dietary changes [72,73]. Environmental factors [74], such as diet, antibiotic exposure, environmental toxins, and acute enteric pathogens can affect host-microbial homeostasis, microbial diversity, and load, leading to gut dysbiosis [65,66,67]. The genetic makeup of the host is one intrinsic factor, but extrinsic factors also play a role. In the gastrointestinal tract, gut microbial compositions vary for herbivorous, carnivorous, omnivorous, and filter-feeding fishes. Issues related to gut health due to microbiota are believed to stem from the interactions between consumed MPs and gut organisms in the colon [78]. Intestinal microorganisms can respond to environmental factors that trigger host metabolic and immunological changes through a complex and dynamic system **(Table 1)**[79,80]. Therefore, the contribution of gut organisms is crucial for maintaining a healthy gut and should not be ignored [72,81].

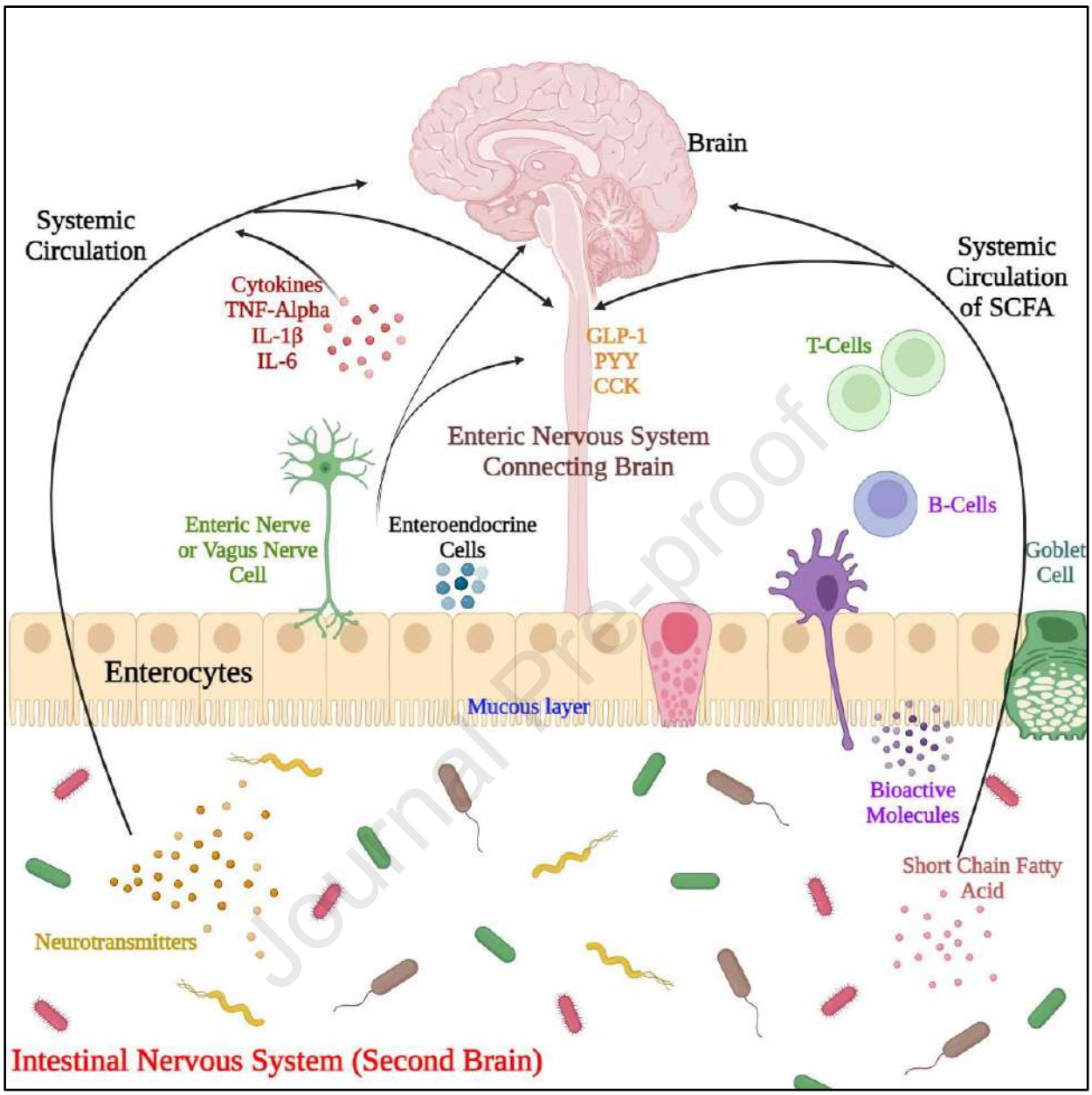

Fig.2.Schematic Representation of Gut–BrainAxis.

The cell membrane serves as a barrier to prevent the free movement of molecules from the cell interior to the outside and vice versa. This helps to maintain homeostasis by keeping a stable intracellular environment, allowing different biochemical reactions to proceed in an organized manner. Cells can absorb MP through passive infiltration, endocytosis, phospholipid hydrolysis, or membrane transport mechanisms [82]. Except for endocytosis, all other mechanisms can either directly damage the cell membrane or indirectly enhance ROS production, leading to damage. Experimental evidence has shown that PE MP, due to its sharp edge or unique shapes, can rupture erythrocyte membranes and cause severe hemolysis [83]. Moreover, a significant amount of MP adsorbed on the lipid bilayer can reduce the size of the cell membrane, increase membrane tension, decrease membrane density, alter fluidity, and compromise membrane integrity [84,85]. Brief exposure to MP can also lead to a sudden rise in intracellular ROS levels resulting in membrane damage and lipid peroxidation [86]. PS-MPs can trigger excessive ROS-activated Ca^{2+} influx in human hepatocytes through store-operated Ca^{2+} channels (SOCs). In L02 hepatocytes,

calcium overload halts the cell cycle in the S phase and initiates apoptosis **(Fig.3)** [87].This overview highlights the molecular initiating events and key molecular events (KEs) caused by micro- and nanoplastics. These include the generation of free radicals, activation of oxidative stress metabolism, lipid peroxidation, DNA damage, and initiation of downstream signaling pathways that precede cascades of branching molecular changes potentially leading to irreversible oxidative damage and exacerbation of inflammatory processes.

- **Consequences due to the altered Gut barrier:**

a. Physical barrier:

Exposure to MPs disrupts the intestinal barrier. In *Artemia parthenogenetica* larvae, 10 μm PS-MPs induced deformation of intestinal epithelial cells [88]. As the concentration of exposed MP increases, the intestinal cells of earthworms become enlarged and irregular in shape, and the size of the nucleus is altered [89]. To maintain cell integrity, tight junction proteins must be functional. These proteins include the intercellular junction complex protein, composed of occludin, claudins, and the ZO family proteins [90]. Only then can the intestinal barrier work properly. Tight junction proteins, such as Zo-1 and Claudin-1, have slightly lower transcription levels in the colon and ileum of mice after 6 weeks of exposure to 5 μm MPs at a concentration of 1000 g/L [91].

b. Chemical barrier:

The mucus layer, which acts as a barrier preventing contact between antigens in the intestinal cavity and host cells, is known as the chemical barrier. The mucus is primarily produced by goblet cells and consists of mucin, digestive enzymes, antimicrobial peptides, immunoglobulins like IgA, enzymes, and proteins such as lactoferrin [92,93]. Additionally, these cells release other mucus-like substances such as FCGBP, ZG16, CLCA1, AGR2, and TFF3 [94,95]. Abnormal mucin expression is directly linked to various diseases. For example, Muc2 deficiency in ulcerative colitis, impairs the defense mechanism. Conversely, a 14-day exposure to MPs increases intestinal mucus in marine medaka fish [96,97]. In juvenile guppies, larger MP size enhances secretion from goblet cells [98]. However, in goldfish larvae, PS-MPs disrupt the structure of the intestinal mucosa and submucosal structure [99]. Exposure to polystyrene beads, polystyrene chips, or polypropylene fibres significantly reduces the amount of mucus in the intestines of zebrafish. Furthermore, PE-MPs and PS-MPs in zebrafish guts cause epithelial shedding, increased mucus secretion, and a decrease in goblet cells [100]. In mice, mucin secretion decreases at the mRNA level for genes like Muc1, Muc2, Muc3, Klf4, Meplin-β, and Retnlb [101]. Key biochemical molecules with antibacterial properties in the mucus layer are bile acids and adenylate [102,103]. Bile acids impact the gut microbiota composition and interact with it[104]. Exposure to MPs decreases the concentration of serum bile acid [101].

c. Microbiological barrier:

Symbiotic microorganisms utilize two mechanisms to create a microbiological barrier in the gut [93]. They compete for nutrients, release antibacterial substances, and occupy attachment sites to enhance resistance against infections, ultimately improving gut health [94]. Additionally, these microorganisms can aid in nutrient digestion and absorption, providing energy to the epithelial cells [95]. The colonic cells rely on short-chain fatty acids, gut metabolites, for their growth, development, and metabolism [96]. Recent studies have demonstrated that MPs can impact gut microbial diversity and composition **(Table 2)**. For example, in *F. candida*, PE-MPs completely change the diversity of the gut microbiota [14]. PS-MPs in juvenile guppies, promote the growth of *Proteobacteria* while inhibiting *Actinobacteria* [97]. Exposure to large PS-NPsincreases the populations of *Firmicutes* and *Bacteroidetes*while decreasing *Proteobacteria* [98]. In zebrafish larvae, PS-MPs significantly decrease Bacteroidetes [99]. PE-MPs can also alter the load of *Firmicutes*, *Bacteroides*, *Proteobacteria*, and *Verrucobacterium*. *Aeromonas*, *Shewanella*, *Microbacterium*, *Nevskia*, and *Methyloversatilis* increase with MP exposure, while, *Pseudomonas*, *Ralstonia*, and *Stenotrophomonas* decrease [100]. Another study found that PS-MP exposure in zebrafish alters microbial diversity by increasing *Fusobacteria* and *Planctomycetes* and decreasing

Proteobacteria[105]. In mice, PS-MPs reduce*Bacteroides* and *Firmicutes*while elevating*Melaina* bacteria. Additionally,MP exposure increases*Staphylococcus sp.* and decreases*Parabacteroides sp*[106].

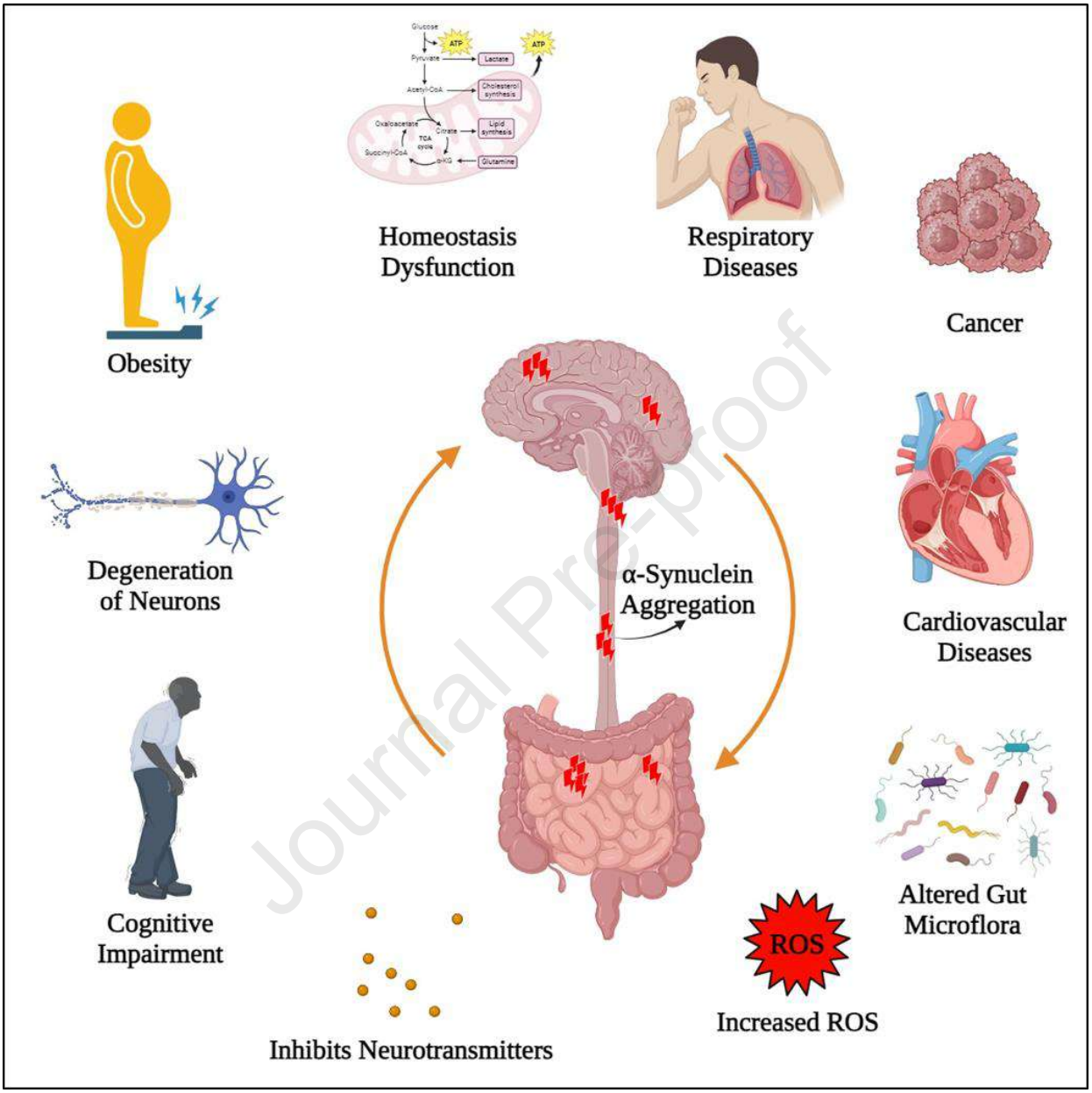

Fig.3. Schematic Representation of MP-Induced Dysbiosis. Gut Brain Axis which controls the entire homeostasis of the body, upon alteration,disrupts the normal functions, resulting in Chronic Disorders.

d. Immune Barrier:

Under the intestinal epithelium, various immune cells, such as T cells, B cells, dendritic cells, and macrophages, can trigger immune responses by presenting antigens, generating antibodies, and secreting chemokines and cytokines [107]. These secreted substances create the immune barrier of the intestine. For instance, secretory IgA

primarily exists on the surface of the intestinal mucosa to provide an immunological barrier. In adult zebrafish, exposure to PS-MP significantly impacts phagocyte and lymphocyte levels[108]. The total number of M1 macrophages decreases, while the T cell population increases. Conversely, PS-MPs can decrease the number of regulatory T cells in the spleen, leading to a significant reduction in the Th17 cell population in CD^{4+} cells [106].

- **Altered Homeostasis due to abnormal Endocrine Pathways:**

The toxic substances present on the MP surface initiate endocrine and developmental abnormalities as they act as endocrine disruptor chemicals (EDCs). They can alter hormonal expression **(Table 3)** by interfering with receptors and altering hormone synthesis, secretion, transport, and mode of action [109]. The adrenal cortex secretes glucocorticoids, which play a critical role in maintaining homeostasis, making it the most sensitive organ to EDC exposure [110]. By disrupting the HPA axis, EDCs induce various stress responses such as changes in behavior, anxiety, metabolic disorders, neurological disorders, altered immune functions, post-traumatic stress disorder (PTSD), etc. [111,112]. The presence of DEHP drastically reduces aldosterone levels, which suppress angiotensin II expression in the adult adrenal gland[110].

PBDEs, BPA, phthalates, and organotin are present on the MP surface and act as thyroid-disrupting chemicals (TDCs) [113]. The thyroid gland becomes hyperactive upon phthalate exposure, leading to developmental abnormalities. During childhood exposure, the weight of the thyroid gland is reduced [114,115]. Mice exposed to BPA show induced inflammatory actions in the hypothalamus by activating either astrocytes or toll-like receptors (TLR4) [116]. Both cadmium and arsenic-containing MPs reduce LH secretion and induce xeno-estrogenic effects on the inner part of the pituitary gland [117]. Arsenic-containing MPs increase mRNA expressions of genes responsible for oxidative responses, which facilitate neurological disorders, oxidative stress, and apoptosis [115]. Similarly, MPs in combination with Pb and cadmium influence LH and FSH levels in proestrus rats, while Pb exposure alone causes a reduction in pituitary membrane fluidity [118].

When analyzing the effect of MP on male reproductive organs, MPs containing phthalate esters (PAEs) can accumulate in the testes, altering testicular weight, physiology, sperm count, and sperm vitality[119]. Additionally, MPs can lead to morphological changes in sperm, such as the loss of the sperm acrosome and the development of small-headed (cephalic), headless (acephalic), and tailless sperm, among other abnormalities[120,121]. Oxidative stress plays a significant role in male infertility, speeding up cell division and mitochondrial oxygen consumption in testicular tissues[115]. Changes in acid phosphatase (ACP), superoxide dismutase (SOD), and malondialdehyde (MDA) levels in the testes can disrupt spermatogenesis [119]. In the ovaries, granulosa cells, essential for normal ovarian development, maturation, and folliculogenesis [122] are affected by the accumulation of MPs. This accumulation can decrease the level of Anti-Mullerian hormone (AMH) in rat ovaries and granulose cells, leading to abnormal folliculogenesis, suppression of follicle growth, reduced estradiol synthesis, and an irregular estrous cycle [115,123].

- **ROS-induced stress generation and DNA damage:**

MPs can induce ROS due to their size variation, dose variation, surface properties, and exposure times [124,125]. MP-induced extracellular ROS generation is associated with polymer aging and depends on environmental conditions [126,127]. Photooxidation or UV radiation can initiate the formation of free radicals on aged MP surfaces by either subtracting a hydrogen atom or adding it to an unsaturated carbon chain. These radicals then react with atmospheric oxygen to produce alkyl radicals with peroxy radicals as an intermediary component [124,128]. In mammalian cells, MPs are engulfed by phagocytic cells through endocytosis or pinocytosis,triggering the immunological defense mechanism [129]. To clear the ingested MP, NADPH-oxidase and/or other enzymes produce superoxide and hydrogen peroxide, leading to elevated ROS levels [126]. In signal transduction, both O_2 and H_2O_2 serve as key mediators to induce oxidative stress cascades. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidases (GPx) play important roles in the complex ROS scavenging system used by innate

immune cells like neutrophils. This system converts superoxide anion radical (O_2^-) and hydrogen peroxide (H_2O_2) into their final metabolites, water (H_2O) and oxygen (O_2),to maintain homeostasis[128]. According to the literature, ROS induces Mitogen-Activated Protein Kinase (MAPK) signaling cascade activation, which can trigger autophagy, inhibit ERK signaling, and activate p38MAPK components. This activation can be down-regulated by the immediate enhancement of nuclear factor erythroid 2-related factor 2 (Nrf2) activities [130]. Several cascades induced by MPs were summarized in **(Fig.4).**

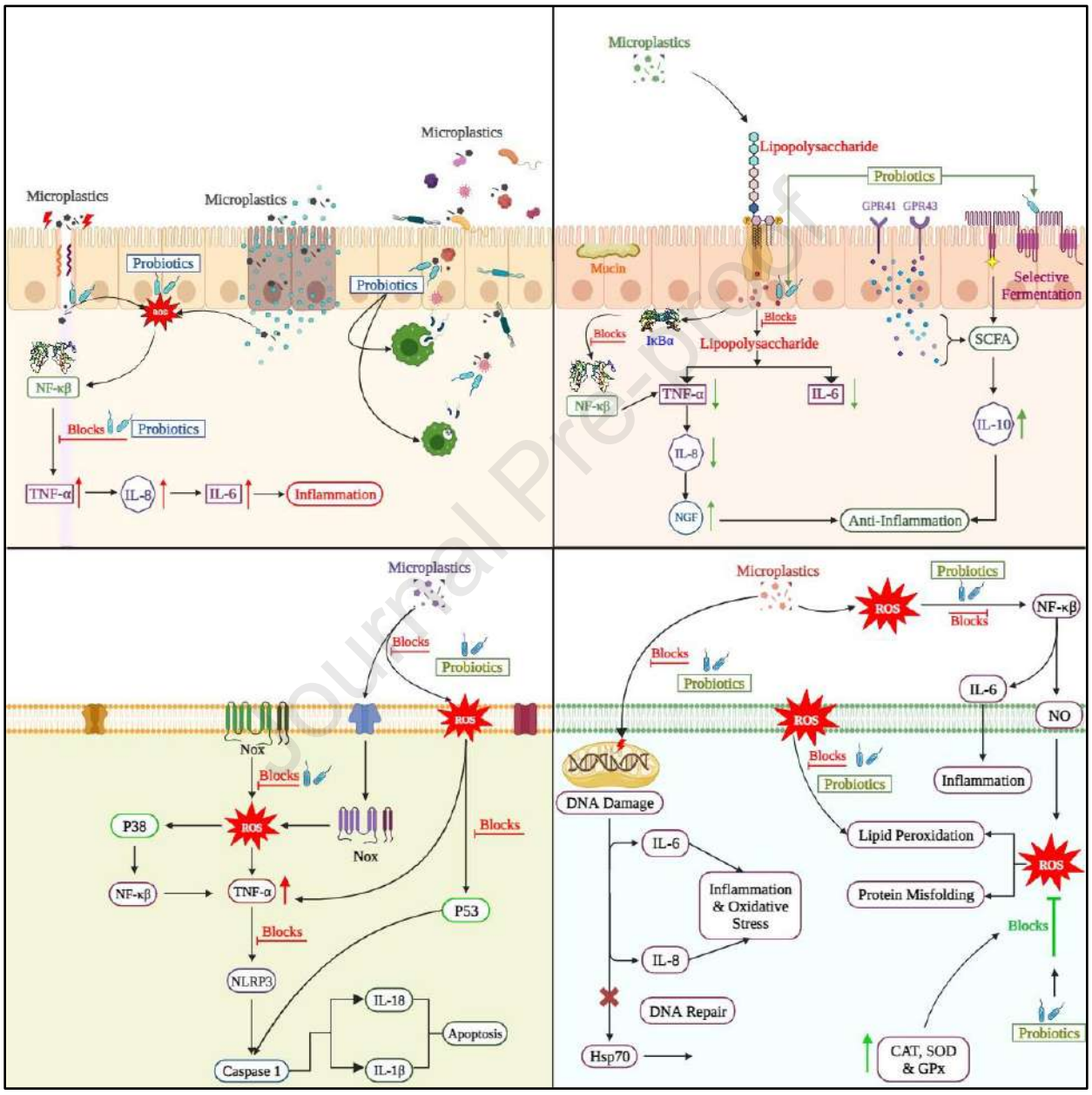

Fig.4. Schematic representation of MP-induced biochemical pathways which disrupt the homeostasis and reestablishment of it with probiotics. A: Blocking of NFκβ pathway by Probiotics; B: SCFA mediated anti-inflammation; C: Blocking of Nox-dependent pathway by Probiotics; D: Controlling ROS by CAT, SOD, GPxand reduced DNA Damage

In the marine copepod *P. nana* and the Mitten Crab *E. sinensis*, the MAPK downstream pathways were initiated by exposure to MPs [128]. There was a positive correlation between MP-induced ROS, elevated ERK and p38 kinase phosphorylation in *P. nana* [124]. Additionally, higher expression of the Nrf-2 transcription factor upon MP exposure suggested that MPs trigger respiratory bursts via ERK and p38 MAPK pathways in an Nrf-2-dependent mechanism [124]. Excessive ROS can severely damage the cell membrane by inducing the peroxidation of membrane lipids (LPO) and other lipid structures present in the cell [128]. The LPO rate was enhanced in the brain and muscle tissues of *Dicentra rchuslabrax* after exposure to MPs [131]. However, in the hemocytes of the marine mussel *Mytilus* sp., MP exposure elevated ROS, but no significant change was recorded for LPO [132]. After MP exposure, LPO and8-Oxo-Guanine damage was also observed in DNA. A 20 μm PS MP can induce DNA strand breaks in the hemocytes of *S. plana*, which is very similar to PEMP exposure [133]. Though the definite mechanism of DNA damage induced by MP is partially known, several studies suggest that MP triggers oxidative stress followed by damaging DNA[124].

- **Neurotoxicity:**

Exposure to MP can also induce neurotoxicity, which is associated with neurodegenerative diseases. MP-mediated ROS induction, activation of microglia in the brain, inhibition of acetylcholinesterase (AChE), and elevation of circulating pro-inflammatory cytokines can trigger *in vivo* neurotoxicity in aquatic animal and mammalian models [134]. AChE breaks down acetylcholine (ACh) into choline and acetic acid, with ACh acting as a neurotransmitter to control the function of motor neurons [128]. AChE inhibition leads to the accumulation of ACh in the synaptic cleft, causing issues with muscular movement [128]. Exposure to MP induces AChE inhibition in the brain of *Phrynomantismicrops*[135]. However, in *S. plana*, exposure to both PE and PS microspheres induces anti-cholinesterase activities [128]. MP (5-20 μm) causes inflammation after inducing a neurotoxic impact in animal models[136]. Experimental results using *C. elegans* demonstrated that because nematodes lack the blood-brain barrier (BBB), their neurotoxicity is significantly more severe [137]. The present study in SH-SY5Y cells showed that hydrogen peroxide (H_2O_2) and AChE metabolism are directly related, to ROS-dependent abnormalities in the cholinergic system in brain cells. The levels of AChE decrease as H_2O_2 alters the enzyme and its isoform's structure allosterically [138]. Moreover, it has already been established that in MP-induced neurotoxicity. MP serves as a significant carrier of heavy metals. The biofilm on its surface accelerates the accumulation of metal ions[30]. However, whether metal is present or absent within the cell determines metal dysbiosis. In many neurodegenerative diseases, an imbalance of metal homeostasis initiates a cascade that ultimately leads to neural network dysfunction. Neural dysfunction results in oxidative stress, aggregation of misfolded proteins, mitochondrial damage, malfunction, autophagy, and energy depletion [139].

- **Inflammation**

When various toxicants, pathogens, MPs/NPs, and xenobiotics are exposed, the body responds by triggering inflammation, whichis a localized defense mechanism. It can be a very destructive process with multiple levels of complexity [140,141]. MPs can trigger the inflammatory response at the molecular level by activating pro-inflammatory cytokines, signaling molecules secreted mainly by immune cells (leukocytes) [142]. Though the exact mechanism is not very clear, pro-inflammatory responses can be related to oxidative stress and lysosome membrane disintegration [128]. MP-induced inflammation, at its second and third levels, can initiate cellular responses and tissue damage. Inflammatory tissue damage was detected in various *in vivo* models of MP exposure [136]. Immune effector cells such as phagocytic cells encounter them frequently as they provide the first line of defense against foreign particles. *In vitro*, cell line models have already shown that MPs can not only regulate cytokine release but also alter the expression of inflammatory gene responses. Gene expression of pro-inflammatory cytokines IL6, IL8, and IL1β is up-regulated after PS-MP exposure in human gastric adenocarcinoma cells, which induces cell death [143]. In the THP-1 monocytic cell line, a size-dependent cytokine release study revealed that IL6 production increases with an enhancement of particle size; however, for IL8 secretion, the opposite trend was obtained [128]. In

addition, exposure to 0.5 μm PS-MPs enhanced both the mRNA levels and protein expression of IL1α, IL1β, and IFN in the zebrafish gut [140]. Following a seven-day exposure period, zebrafish gills, liver, and gut began to accumulate PS MPs (5 μm), which triggered the normal inflammatory damage processes of vacuolation, leukocyte/neutrophil infiltration, necrosis, and lipidosis in the liver[128]. Liver histopathology findings support the finding, with elevated levels of SOD and CAT activities inducing oxidative stress followed by an inflammatory response [136].

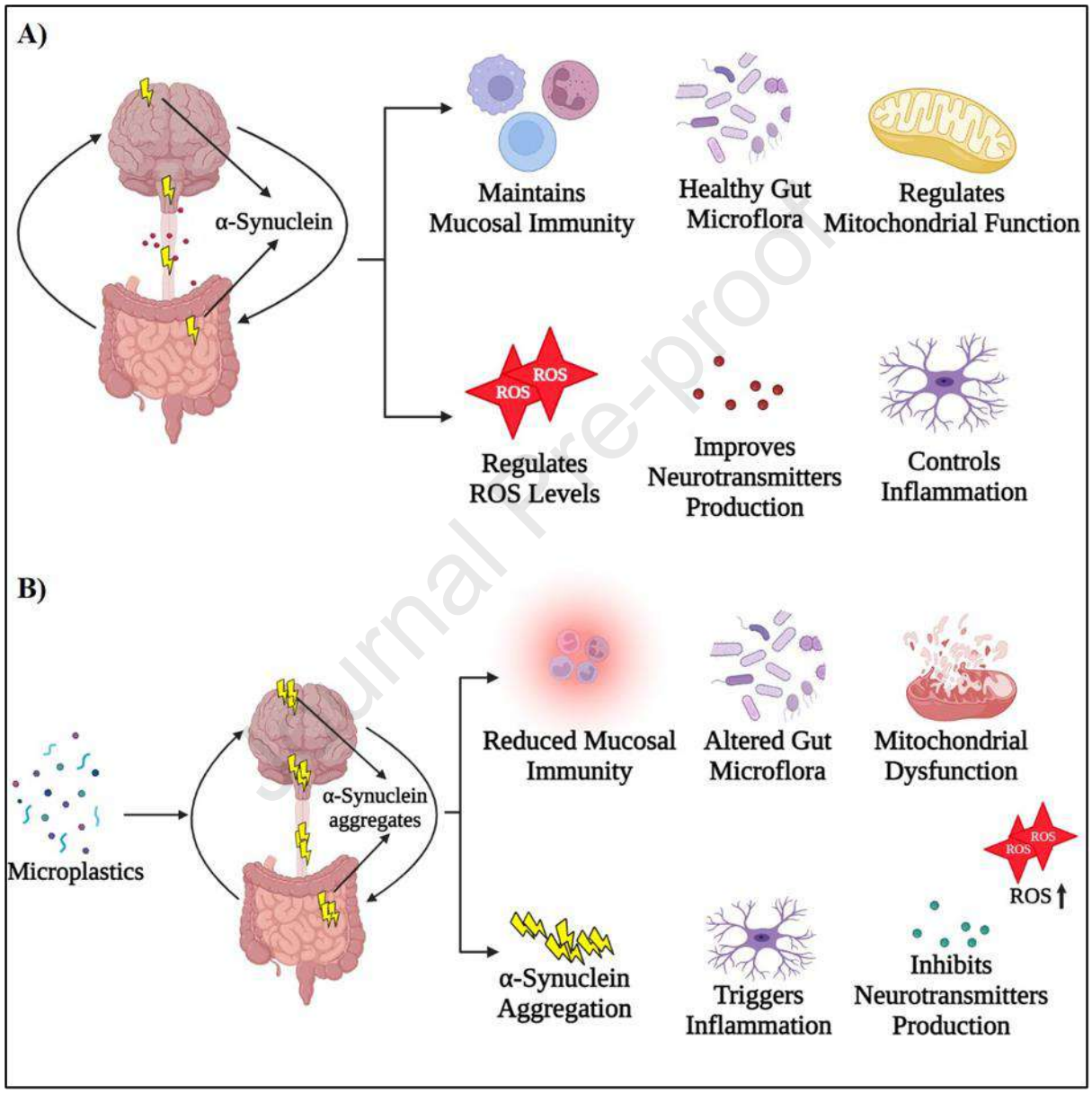

Fig.5. Disruption of Homeostasis. A. Normal condition in which Gut-Brain Axis regulates physiological, biochemical and neuronal pathways, B. MP-induced PD brain in which altered Gut-Brain Axis triggers several altered mechanisms to hinder physiological, biochemical and neuronal pathways

- **Dysfunction of Bowel:**

Exposure to MP can cause gut dysbiosis, leading to discomfort in the bowel. When exposed to MP, low vagal activity reduces bowel contractions, motility, and can cause constipation. Conversely, high vagal activity can enhance bowel contractions, potentially leading to diarrhea[144]. Similar to Irritable Bowel Syndrome (IBS), the sympathovagal balance is disrupted in MP-exposed gut [145]. Previous studies have shown that female IBS patients with increased parasympathetic may experience constipation due to lower vagal activity, which is directly linked to severe abdominal pain [146]. The stress axis and the autonomic nervous system are closely linked with elevated levels of corticotrophin-releasing factor (CRF) expression increasing sympathetic tone during constipation [147]. The parasympathetic nervous system stimulates smooth muscle contractions and secretory actions in the GI tract, while the sympathetic nervous system inhibits these processes. The parasympathetic afferent pathway sends information about gastric accommodation and gastric-colic reflex to corticolimbic structures [148]. This information is also transmitted to areas of the brain such as the hippocampus, amygdala, prefrontal cortex, and hypothalamus for processing [149]. Through sympathetic afferent pathways, signals reach the thalamus and then the sensory cortex and pain matrix via the spinal cord [150].

- **Disruption of Cell Organelle:**

Mitochondria are organelles responsible for generating intracellular ROS by using one-electron carriers such as cytochromes, iron-sulfur proteins, and various oxidases. Instability in the mitochondrial membrane potential is the main reason for excessive ROS generation[128]. In mice and *rotifer B. koreanus*, exposure to PS-MPs has been recorded to cause mitochondrial membrane dysfunction, which requires further validation [124]. It is already known that excessive oxidative stress in the cytosol can stimulate Na/K trans-membrane channel opening in mitochondria. This elevated membrane channel ionic flux disrupts the mitochondrial membrane potential and releases free radicals through the ROS-induced ROS-release"(RIRR) mechanism [128]. In human pulmonary cells, MPs induce apoptosis by increasing intracellular ROS levels and altering the mitochondrial membrane potential, directly affecting cell viability [151]. Alteration of the membrane potential and impairment of cellular energy metabolism are mediated by a NADPH oxidase 4 (NOX4)-dependent mechanism that causes mitochondrial dysfunction in the respiratory epithelium **(Fig.4)**. Furthermore, a recent study revealed that the release of mt-DNA into the cytoplasm indicates MP-induced mitochondrial damage and dysfunction followed by mitochondrial breakdown [152]. In Caco-2 cells, MPs induce alterations in mitochondrial depolarization and inhibit ATP-binding cassette transporter activity leading to changes in ATP synthesis and increased toxicity[140]. Additionally, MP-induced mitochondrial ROS accelerates the expression of various proteins targeting BCL2-associated cell death, endoplasmic reticulum stress, inflammation, and autophagy, ultimately leading to kidney damage and protein leakage[13]. Moreover, MPs can induce lipid accumulation in macrophages under acute oxidative stress conditions, initiating macrophage foam cell formation, a characteristic feature of atherosclerosis pathology[153,154]. MP-induced mitochondrial membrane damage depends on particle size [124].

Another cellular organelle, the lysosome, contains a variety of hydrolytic enzymes that can digest foreign substances or phagocytose the target cell. Lysosomes are severely affected by MP/NP exposure as membrane stability is altered. Upon exposure to MPs, lysosomal hydrolase activity was reduced, which can alter the lysosomal pH value and impair autophagy [155]. Presently, lysosomal membrane stability is being used as a biomarker to evaluate the effect of MPs [156]. In blue mussels (*Mytilus galloprovincialis*), the function of the lysosome was completely disrupted after exposure to MPs [128]. Furthermore, experimental evidence also indicates a correlation between MP-induced ROS generation, oxidative stress, and disruption of lysosomal function as MPs are detected in the lysosome [157]. Though the exact mechanisms of lysosome disruption by MPs are not fully understood, MPs can induce lysosomal dysfunction either directly or indirectly. In direct damage, MPs can enter the cell via endocytosis or permeation and initiate lysosomal disruption during their digestion [128]. Experimental evidence revealed that PS MPs altered the lysosome's ability to maintain an acidic pH and inhibit autophagy. As a result, lipid droplets (LDs) accumulated in PS MP-infected macrophage lysosomes, triggering cellular foam formation [158]. In the indirect mechanism, MPs trigger the production of excessive ROS and disrupt the lysosome, as the lysosomal

membranes are highly susceptible to ROS [159]. Cathepsins are released into the cytoplasm by enlarged lysosomes, and these enzymes ultimately cause damage to the mitochondria and subsequent apoptosis [160]. The toxicity of ROS scavengers, such as N-acetylcysteine, lessen macrophages when they interact with the MP surface, indicating the harmful effects of ROS on lysosomes and macrophages[161].Additionally, experimental evidence indicated that the plastic surface of disposable laboratory equipment, such as centrifuge tubes, enhances amyloid fibrillation by interacting with prions and amyloids. Windheim et al., (2022) conducted an experiment using centrifuge tubes made of polycarbonate, polystyrene, acrylonitrile copolymer, and polypropylene. They found that tubes made of polystyrene showed higher levels of amyloid absorption **(Fig.5A-B)**[162].

PROBIOTIC A NEW APPROACH TO CONTROL MP-INDUCED GUT DYSBIOSIS

Microbiota, whichplays a crucial role in maintaining the body's immunity, can be utilized in the treatment of metabolic disorders and mental illnesses. Exposure to MP significantly changes the composition of the gut, leading to the development of complications and chronic disorders. Probiotics, a group of beneficial microorganisms, play a critical role in regulating microbiota [163]. In PD, probiotics help improve GI function by reducing gut permeability, bacterial translocation, and neuro-inflammation in the ENS [164]. Probiotics show great promise in treating various disorders, including neurodegenerative diseases, by connecting hormonal and biochemical pathways to enhance gut and brain health **(Fig.6)** [165]**.** Consuming probiotics either alone or in food enhances antioxidant activity or reduces oxidative damage in cells. *Lactobacillus reuteri* can speed up gastric emptying and decrease regurgitation in infants. It is well-established that neuroinflammation is closely linked to neurodegeneration, behavioral deficits, and other neurological tissues[166,167]. Toll-like receptors (TLR) and NOD-like receptors (NLR) cells identify microbe-associated molecular patterns (MAMPs) from bacteria triggering signaling cascades that result in the expression of pro- or anti-inflammatory cytokines **(Fig.4)**. Probiotics have the potential to be used in the treatment of neuroinflammation and neuronal diseases. Reports suggest that probiotic beverages may help alleviate both the motor and non-motor symptoms of PD. Furthermore, consuming *L. salivarius* LS01 and *L. acidophilus* significantly reduces proinflammatory cytokines while increasing anti-inflammatory cytokines. By reducing levels of pro-inflammatory cytokines, probiotics can enhance intestinal barrier integrity in patients with inflammatory bowel disease. This is achieved by decreasing the differentiation of $CD4^+$ T cell into Th_2 cells and inhibiting nuclear factor kappa B both of which are crucial in controlling inflammation [145].

Probiotic strains such as *Lactobacilli* and *Bifidobacteria* can synthesize antioxidants, vitamins, and bioactive compounds, reduce free radicals, and have beneficial effects on disorders associated with oxidative stress, including PD [164]. In PD patients, LA02 downregulates ROS in the early stages of the disease. Consumption of yogurt and probiotics such as *Bifidobacterium* sp. and *Lactobacillus* sp. can improve bowel contractions, motility, and intestinal balance [168]. They can enhance barrier function by promoting mucus secretion from goblet cells. The probiotic *L. plantarum* BMCM12 can secrete extracellular proteins, that weaken pathogen attachment and protect the intestinal barrier [169]. Probiotic formulations also enhance CNS activity by modulating inflammation and interacting positively with the gut microorganisms. Due to increased intestinal permeability to endotoxins, PD patients have high levels of pro-inflammatory cytokines (lipopolysaccharides) in their gut. The presence of amyloids can also harm gut health by increasing pro-inflammatory cytokines [170]. Probiotics safeguard the brain by preventing stress-induced synaptic dysfunction between neurons. In rats, two weeks of probiotic treatment significantly reduces the levels of ACTH and corticosterone, indicating its suppressive effects on the HPA axis. Probiotics have the potential to prevent or reverse physiologic damage caused by HPA-mediated chronic stress [171]. In rats injected with Aβ in the lateral ventricle, treatment with *Lactobacillus acidophilus, Bifidobacterium longum,* and *Bifidobacterium bifidum* in combination improves impaired spatial cognition and restores synaptic plasticity [172].

The manufacture of non-specific antimicrobials for numerous illnesses, transmissible antibiotic resistance genes, variable host-specific probiotic capacity, and toxic metabolites are some of the drawbacks of conventional probiotics. Over time, unique behaviors have been observed in conventional probiotic bacteria due to genetic

alteration, opening up new possibilities. It is now possible to create therapeutic systems that surpass the capabilities of wild-type microorganisms through the integration of novel gene editing methods with distinctive design strategies. Bioengineered probiotic LAB is one of the next generation of whole-cell-mediated biotherapies being developed to treat human ailments [173].Probiotics are now more often seen as microbial "physicians," rather than just as a means of delivering medication. Engineered bio-therapeutics have several advantages over microbiota-directed techniques such as FMT [174]. The primary advantage of genetic engineering is its capacity to provide functions that endogenous microbiota cannot naturally exhibit [175]. Engineered probiotics have the potential to supply the host's mucosal immune system with enzymes, vaccines, antibiotics, and cytokines [173]. This could provide a more efficient drug delivery technique than abiotic treatments. Additionally, probiotics can be altered to incorporate biotic sensors, which serve as non-invasive diagnostic instruments [176].Probiotics have mostly been utilized to deliver proteinaceous medications that are easily synthesized or modified by commensal bacteria[177]. Therefore, the biosynthetic capacities of common probiotics need to be continuously extended to boost the flexibility of probiotic-based treatments[178]. Furthermore, artificial probiotics with the ability to respond to stimuli and alter their activity in response to conditions that are specifically customized to them are required[173].

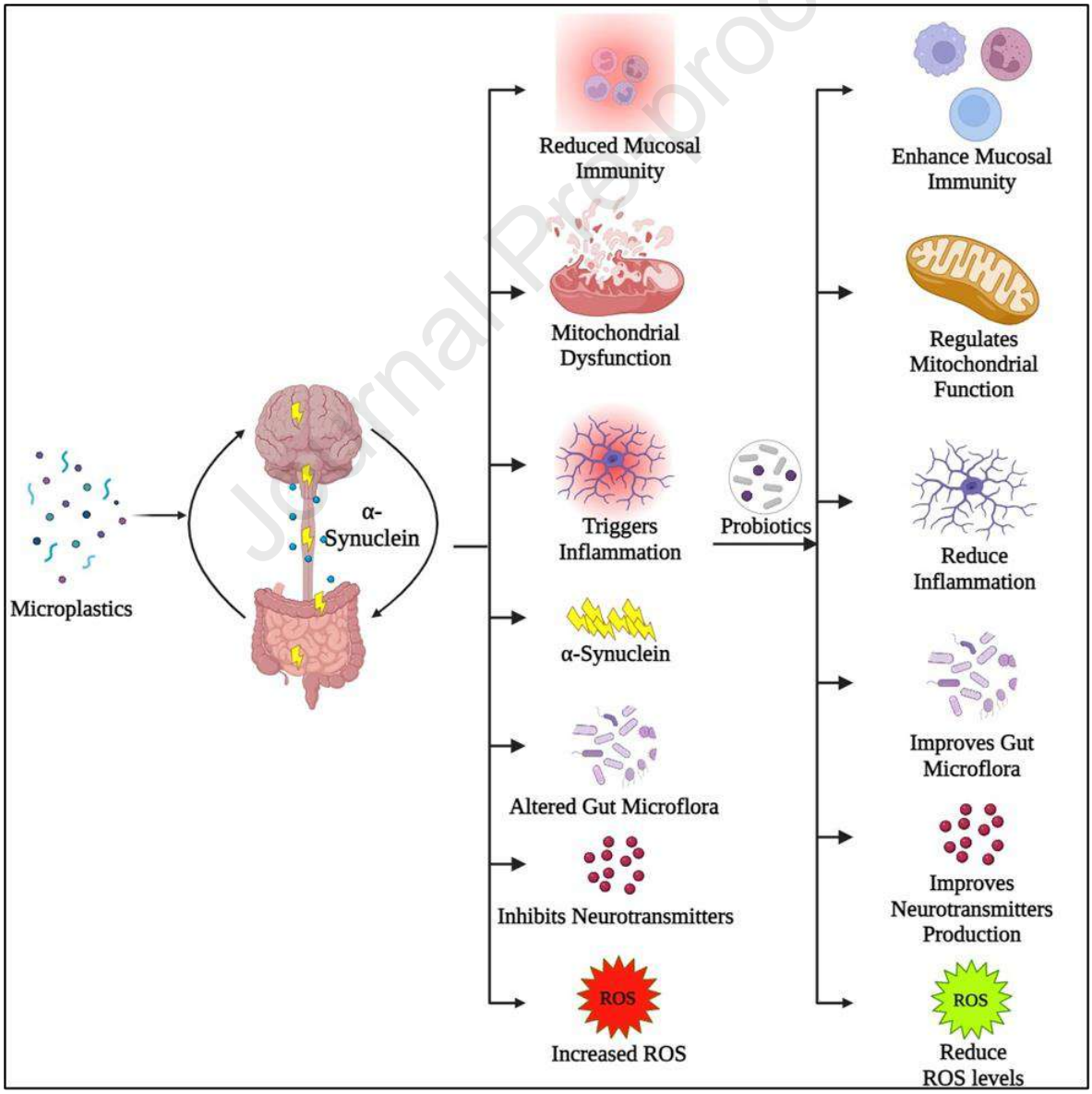

Fig.6. Probiotics the New Therapeutic Approach to Control Gut Dysbiosis Induced by MPs

The main challenge in developing probiotics is determining the optimal platform[178]. Safety and host survival are difficult trade-offs [177]. Since some engineered *Lactobacillus* species are not native to the human microbiota, they are quickly flushed out by better-adapted microorganisms, which reduces their therapeutic effects [179]. Probiotic engineering tools should be extended to encompass resident microbiota to further the engineering of host-microbiota interactions. Another significant issue in the production of probiotics is the generation of effective integration and expression of foreign DNA. Essential functions may be hampered by off-site alterations brought on by exogenous DNA inclusion. Off-site modifications may also result in the production of a hazardous metabolite [176]. Thus, extra caution should be used when altering the genome of genetically modified probiotics to avoid compromising the organism's inherent advantageous traits or resulting in the production of dangerous substances in organisms that have traditionally been Generally Regarded as Safe (GRAS).

COMMERCIAL ASPECT OF PROBIOTICS

Personalized medicine is an innovative approach that identifies the unique metabolism associated with each patient's complex condition, considering individual variations in genetics, environment, and behavior[180]. This new approach can predict how an individual will respond to different foods and medications by regular assessing their microbial load, offering the opportunity to create new disease-specific treatment options. With these factors, in mind, the development of designer probiotics and next-generation probiotics could be a safe and effective strategy in the era of personalized medicine, helping to improve targeted diseases through modifications of the gut flora. Over the past few decades, the gut microbiota has emerged as a valuable indicator for prognosis, health, and drug efficacy [181]. Research in microbiology has shown that both GI and non-GI diseases are linked to imbalances in the gut microbiota. Since each disease presents uniquely and patients may respond differently to the same treatment due to variations in disease location, treatment methods, and diagnostic tools, it is crucial to embrace the concept of personalized therapy tailored to each patient’s characteristics. Next-generation probiotics have become a promising customized treatment method due to their capability to alter the gut microbiota and potentially improve the targeted condition. There are two common approaches to creating next-generation probiotics. The first involves identifying a strain associated with a specific health phenotype and confirming its ability to replicate that phenotype using appropriate experiments. The second approach entails identifying a potent substance capable of reversing the disease pattern and incorporating it into a well-researched probiotic strain that can act as a delivery system. Various bacterial strains have been discovered and studied as natural growth promoters (NGPs) for treating pathogenesis, obesity, cancer, inflammatory bowel disease (IBD), and other disorders. The recent development of CRISPR/Cas9 genome editing tool has enhanced the platform for more precise genome editing, allowing for the addition of new features or the activation or deactivation of genes to promote host colonization and enhance human health.

The following characteristics of potential probiotic strains could mitigate or even reverse the effects of heavy metal toxicity: 1) Strong antioxidant properties; 2) immunoregulatory properties to help them adapt to changes in the intestinal environment induced byheavy metals;3) good intestinal adhesion or colonization ability to play beneficial roles in the gut; and4) high tolerance to acid and bile, allowing them to remain active in the GI tract. These characteristics enable them to bind, tolerate, or detoxify heavy metals with remarkable effectiveness. *L. plantarum* TW1-1 was usedto neutralize Cr toxicity; *L. plantarum* CCFM8610 and *Bacillus cereus* were used to neutralizeCd toxicity; *L. plantarum* CCFM8661 and*L. reuteri* P16 were used to neutralize Pb toxicity; and *L. brevis* 23017 was used to counteract Hg toxicity[182–184]. By promoting intestinal peristalsis and sequestering heavy metals in the intestines, these strains can reduce the absorption of heavy metals in the gut and reverse changes in the gut microbiota caused by heavy metals. This, in turn, aids in the removal of heavy metals from the stool [185].Enzymes secreted by microorganisms have previously been shown to be capable of breaking MP polymer chains [186]. ATP-binding cassette transporters, which facilitate the hydrolysis process, mediate the uptake and outflow of tiny fragments across the cell membrane in both prokaryotic and eukaryotic cells. Enzymatic processes such as hydroxylation, hydrolysis, and oxidation convert the MPs into monomers [187]. High molecular weight MPs

are broken down by extracellular enzymes before being incorporated into microbial cells [188]. The degraded MPs are then catabolically directed within the microorganisms to produce energy for intracellular polymerization and integration into cellular structures [189]. Using function- and sequence-based metagenomic approaches powered by metagenomic (MG) methodologies, a search is conducted for bacteria that degrade MPs. The function-based strategy involves screening for different enzymes at random, while the sequence-based technique predicts multiple efficient genes in producing MP-degrading enzymes [188]. Selecting a probiotic strain that counteracts severe metal toxicities and using genome editing to modify genes that encode plastic breakdown could potentially resolve the issue. However, further experimental investigation using various biological models is necessary to support this theory.

Among them, trials are ongoing with *L. rhamnosus* and *Lactobacillus helveticus* against acute gastroenteritis. Although these probiotic strains were found to be stable, the duration and severity of diarrhea and vomiting remained unchanged between the control and treatment groups. On the contrary *Bacillus clausii* significantly reduced the duration of diarrhea and hospital stay compared to controls. Additionally, 400 infants were randomly assigned to a control formula or a test formula containing prebiotic bovine milk oligosaccharides and the probiotic *Bifidobacterium lactis* to assess acute gastroenteritis. The promising results of the probiotic strains make the trial very crucial[190]. Similarly, a significant reduction in diarrheal and respiratory infections over a 6-month follow-up period was recorded with *L. reuteri DSM 17938*[191]. This strain was foundto be effective against infant colic. In addition, *L. plantarum,L. casei*, *Lactobacillus gasseri*, *B. longum,B. bifidum* as well as *Lactobacillus delbrueckii* and *Streptococcus thermophilus* were also tested against IBS, *Helicobacter pylori* infection, *Clostridium difficile* infection, traveler's diarrhea etc.,[190]. In a clinical trial it was observed that *L. rhamnosus* GG (LGG) was effective against infant asthma by reducing the concentration of exhaled nitric oxide. This strain was also equally effective in reducing the occurrence of allergic symptoms and accelerating the acquisition of cow's milk protein tolerance [190]. However, *Lactobacillus reuteri*, *Lactobacillus rhamnosus* HN001, *Lactobacillus paracasei* subsp. *paracasei* F19, *Bifidobacterium bifidum*, *B. lactis*, and *Lactococcus lactis* did not show any significant reduction in asthma symptoms [192]. The risk of atopic dermatitis in children up to the age of two can be reduced if the pregnant mother is receiving a combination of *Lactobacillus rhamnosus*, *Bifidobacterium breve*, and *Propionibacterium freudenreichii*. Australian researchers conducted a study that used probiotic and peanut oral immunotherapy (PPOIT)[193]. The therapy lasted for 18 months, and *L. rhamnosus* CGMCC1.3724 was used as a probiotic with significant improvement in symptoms[194].

Certain strains of *Lactobacillus* including *Lactobacillus plantarum* ECGC 13110402, *Lactobacillus fermentum* ME-3, *Bifidobacterium lactis* HN019, *Streptococcus thermophilus*, *Lactobacillus acidophilus* L1, *Bifidobacterium longum* BL1, and *Lactobacillus plantarum* 299v have shown promise in treating hypercholesterolemia in clinical trials [193]. Bacteriocins controlled the condition by acting as inhibitors of the angiotensin-converting enzyme (ACE)[195]. Clinical trials have shown that supplements containing *Lactobacillus casei* W56, *Lactococcus lactis* W19, *Lactobacillus acidophilus* W22, *Bifidobacterium lactis* W52, *Lactobacillus paracasei* W20, *Lactobacillus plantarum* B62, *Lactobacillus plantarum* W23, and *Lactobacillus salivarius* W24 decreased intestinal inflammation in AD patients. Mixtures of *Lactobacillus acidophilus* (2×10^9 CFU/g), *Lactobacillus reuteri* (2×10^9 CFU/g), *Bifidobacterium bifidum* (2×10^9 CFU/g), and *Lactobacillus fermentum* (2×10^9 CFU/g) were administered to Parkinson's patients for 12 weeks.In addition to controlling the gut-brain axis, probiotics can efficiently degrade and/or adsorb environmental chemicals such as endocrine disruptors (EDs). Lyophilized cells of LAB could remove BPA through an adsorption mechanism [196]. Similar findings have been observed in the yeast *Pichia pastoris* [197,198]. Researchers have studied the environmental BPA detoxification and degradation capacities of *Lactobacillus* spp., *Bifidobacterium* spp., and *Streptococcus thermophilus*[199]. Furthermore, the concentration of SCFA significantly increased in the microbiota of probiotic-treated mice [200]. Dairy *Lactobacilli* can bind to and break down pesticides[201] and BPA [202], suggesting the potential for a financially viable bioremediation technique using microbial cells to address the effects of increased ED exposure [203]. Probiotics can also block pathogen attachment by producing mucin from goblet cells[204].

Probiotics appear to be safe based on the majority of research, with no true contraindications. However, in light of a few incidents, certain individuals should proceed with caution. Patients with small gut syndrome, compromised immune systems, or advanced age should consider any potential adverse effects before starting [205].Given that probiotics are widely consumed, probiotic-associated illnesses are uncommon[206]. Although reporting has not been consistent or comprehensive, reported adverse events in probiotic clinical trials are usually not product-related [207]. Almost all reports of infections by common probiotic genera or species are restricted to patients with impaired immune systems. Nevertheless, it has seldom been established that the bacteria extracted from the illness are the same strain as the probiotic organism that was given [208]. To investigate potential negative effects, Hempel et al. analyzed 622 human probiotic intervention studies. Out of these, 387 studies documented the presence or absence of specific adverse outcomes, such as fungemia and bacteremia, which could have been caused by probiotic exposure [209,210]. Overall, the relative risk (RR) for gastrointestinal infections or other adverse events in probiotics-exposed patients was not significantly higher than that of controls in randomized controlled trials [209]. Despite the abundance of research, the current literature does not provide definitive answers on the safety of probiotic interventions, the scientists note in their conclusion. For example, the efficacy of probiotics in Irritable Bowel Diseases (IBDs) has been assessed in numerous studies and meta-analyses. However, while some authors have reported data on probiotic-related adverse effects [211], there is a lack of information regarding meta-analyses.

Similar to Ford *et al*. (2018) systematic review and meta-analysis of 36 trials involving 4,183 patients on the effectiveness of probiotics, prebiotics, synbiotics, and antibiotics in treating irritable bowel syndrome (IBS),it was found that probiotic-treated patients experienced adverse events more frequently than those treated with a placebo, although the RR was not significantly higher. The authors also observed significant variation between research studies [212]. The duration of probiotic therapy is likely to impact the results. Formulations with a low bacterial concentration may have no effect or may work counter to expectations while only formulations with a high bacterial load may have a favorable effect. For instance, children who received daily doses of *Lactobacilli* equal to or greater than 10^{10} CFU experienced a significant reduction in the duration of their diarrhea. Additionally, some individuals taking probiotics may experience a temporary increase in edema and gas production, as well as constipation, which typically resolves within a few weeks [201,202]. Several lactic bacteria produce bioactive compounds such as histamine, tyramine, and phenylethylamine, which can lead to headaches and other symptoms[215]. Bennet (2016) noted that gastrointestinal symptoms were the most common side effect in a review discussing the quantitative risk-benefit analysis of probiotic use in IBS and IBD[216]. However, it can be challenging to differentiate between gastrointestinal symptoms caused by the natural progression of IBD and those induced by probiotic exposure[198,205]. Liu *et al*. (2016) demonstrated the negative effects of probiotic administration in a tilapia model, simulating immune-compromised conditions in humans[218]. Abrupt suspension of probiotics led to gut dysbiosis in the fish model making them susceptible to *Aeromonas hydrophila* infection. They clearly stated that the risks identified in their study were relevant for immune-compromised patients or neonates, as gut dysbiosis and opportunistic pathogen infection could lead to serious problems. Claudiano *et al*. (2020) presented experimental evidence of *Aeromonas hydrophila* infection causing hemolysis, neurological disturbances, and high mortality in *Piaractus mesopotamicus*[219]. Yue *et al*. (2022) also reported on heavy metal-induced gut dysbiosis followed by *Aeromonas* infection which initiated brain injury in common carp[206]. Hemin, a degraded byproduct of hemoglobin, can activate microglia and play a critical role in Intracerebral Hemorrhage (ICH)-associated inflammatory brain damage[220]. Dodd *et al*. (2022) demonstrated a correlation between brain injury and neurodegeneration[221].

CHALLENGES AND FUTURE ASPECTS

Human exposure to MPs has been estimated to range from tens of thousands to millions per year, equating to several milligrams per day. The presence of biofilm on MP surfaces exacerbates the harmful effects of these smaller units. Bacterial adherence is facilitated by the high degree of pores and functional groups present in small-

sized, degraded MPs, which have a more defined surface area. Contaminant circulation and adsorption-desorption on MPs are crucial factors that influence the lethality, bioaccessibility, relocation, and residual concentration of pollutants [222]. This biofilm can capture nearby metals, forming metal aggregates, that make them unavailable for essential cellular homeostasis, ultimately leading to metal-induced neurotoxicity [30]. The essential metals are necessary for the brain parenchyma to perform its normal biological functions. Metals such as sodium, potassium, magnesium, calcium, copper, manganese, iron, zinc, molybdenum, nickel, etc., play an important role in regulating the physiological pathways such as electron transport chain, oxygen transport, protein folding, synthesis of neurotransmitters, redox reactions, cell adhesion, metabolism, and defense. Each brain compartment has a unique metals concentration. These metals are essential in the diet to maintain homeostasis but can be toxic in excess. In neurons of invertebrates, nanoplastics appear to upregulate neurotransmitter precursors and downregulate acetylcholine and gamma-aminobutyric acid (GABA) reuptake transporters, both mechanisms of which are indications of neurotoxicity[223,224]. In vertebrates, the accumulation of micro and nanoplastics led to toxicity in the liver and intestines, inducing dysfunction, metabolic changes, inflammation, gene alteration, and increased oxidative stress [225]. They also disrupt the degranulation of neutrophils [226,227].Studies also reported that MPs were deposited in lipid-rich brain tissue, resulting in behavioral alteration. Exposure to PS-MPs caused alterations in gut microbiota composition and showed higher toxicity in mice with dietary restriction, which leads to gut barrier dysfunction due to elevation in pathogenic bacteria, increased intestinal permeability, and decreased mucus secretion and water intake [228]. A decrease in microbial diversity and an increase in proinflammatory species characterize dysbiosis. This imbalance in microbiota triggers inflammation and produces genotoxins such as carcinogenic metabolites [229]. Not only that chronic fatigue, digestive problems, trouble urination, acid reflux or heartburn are the complications found in association with gut dysbiosis.

Several studies proved that in PD, gut microbiota alteration, reduced short-chain fatty acids, intestinal permeability disruption and intestinal inflammation [230], shows the interconnection between the enteric and central nervous systems. Levodopa, a precursor of dopamine, is an effective drug for PD [231]. Long-term consumption of levodopa can lead to dyskinesia, motor fluctuations, and hallucinations and it is less effective as a therapeutic for mental changes, postural instability, gait difficulty, and dysphagia [232,233]. Levodopa treatments can also lead to mild adverse effects like nausea, dizziness, headache, and drowsiness [231]. Thus, the intervention of new formulation is the basic requirement to overcome neuronal issues. Formulated probiotics like *Bifidobacterium animalis*, *Ruminococcaceae*, *Lachnospira*, *Lactobacillus fermentum* and *Klebsiella oxytoca* significantly improved the degradation of tryptophan, gamma-aminobutyric acid, short-chain fatty acids, dopamine levels and serum acetic acid [234]. The gastrointestinal tract serves to maximize the rate of nutrient gain to maintain the integral nutrient balance [235]. The chemical properties of plastics such as net electrical charge are altered due to environmental interaction, affecting the interactions with organic molecules [236]. The constituent and function of the intestine microbes can be altered by probiotics, prebiotics, and synbiotics [237]. Due to their capability to regulate the composition of intestinal flora, they can reduce inflammation and oxidative stress, and enhance the crucial active metabolites [238]. MPs can trigger inflammation and excessive production of ROS, which can disrupt essential cellular activities [239]. Probiotics can reduce polyethylene MPs-induced oxidative stress and also restore antioxidant enzyme activities, which include superoxide dismutase, catalase, glutathione S-transferase, and glutathione peroxidase [240]. Furthermore, probiotics are the preferred choice in modern times for establishing gut homeostasis due to their high potential and minimal side effects.

Earlier studies have been conducted on the formation of MPs, removal strategies, and their exposure to terrestrial, aquatic, and marine habitats. However, research on the toxicities of MPs in mammals and the human brain, leading to neurodegeneration, is limited. As a result, there is a gap in understanding the risk of MPs exposure to humans due to the lack of validated methodologies, approved reference materials, and consistency in analytical processes. The potentially harmful effects of various types of MPs on mammal and human health remain unknown due to the significant variation in particle size, shape, and chemical composition of plastics. Additionally, there is a lack of animal models that accurately reflect the effects of MPs on humans. More research should be conducted

using models of other animal species, such as rabbits, birds, pigs, and monkeys.Probiotics have shown promising results in treating gut dysbiosis and other GI disorders, but there are a few drawbacks to consider. Some of these obstacles include using obligate anaerobes as probiotics to overcome gut transit survival difficulties, identifying and isolating novel prebiotic sources, and producing synbiotics at an affordable cost. Low rigidity and ineffective marketing are post-production issues for probiotics because they are not recognized as medical products in many countries [59]. Personalized medicine is an innovative approach that considers individual differences in genetics, environment, and behavior to determine the unique metabolism associated with each patient's complex condition. Metabolic issues and mental disorders can be addressed using microbiota, which is crucial in maintaining the body's immunity. Probiotic supplementations also enhance CNS function by reducing inflammation and promoting a beneficial relation with the gut microorganisms. Probiotics can protect the brain by preventing the breakdown of synaptic corrections between neurons caused by stress. Nowadays, probiotics are seen as microbial "physicians" as opposed to merely a means of delivering medication. In developing probiotics, we have discovered that the main challenge lies in selecting the most effective platform [178]. A challenging trade-off is finding a balance between the survival and safety of the host[177]. The therapeutic effects of certain engineered *Lactobacillus* species are reduced because they are quickly eliminated by more well-adapted microbes, as they are not native to the human microbiota.

Considering all the potential effects of MP exposure on humans, which can lead to gut dysbiosis followed by neurodegeneration, it is urgently necessary to conduct extensive studies with human and mammal animal models to determine the impact of probiotics supplementation in establishing homeostasis. Comprehensive scientific research results will be used to raise awareness among everyone, including the public, lawmakers, the education sector, and industry. Furthermore, to control the excessive use of plastic items, strong administrative rules and policies must be implemented. Without implementing these measures, the overall health of ecosystems and living organisms will inevitably deteriorate in the future. Therefore, more research on this specific issue is needed to protect the safety of aquatic and terrestrial life and to understand the mechanism of its cytotoxicity. We believe that both the government and industry must make significant efforts to protect people from MP exposure. These efforts should include keeping plastic out of food, conducting thorough wet cleanings every few days, carefully selecting building materials and personal care products and considering probiotics supplementation as a therapeutic approach for reestablishing homeostasis. Additionally, governments should fund studies to identify and measure the dangers of MPs. We advocate for interdisciplinary collaboration among scientists to enhance our understanding of the effects of early life MPs and chemical exposure. The Earth is currently grappling with a pervasive and insidious issue of plastic pollution and without a clear long-term solution in sight, it is crucial to thoroughly define and explore the hazards, particularly concerning human health.

CONCLUSION

At present, the main reason humans are exposed to MPs is the increasing consumption of plastic. MPs have the ability to absorb, release, and act as reservoirs for various toxic chemicals and heavy metals, allowing these toxins to enter the human body and cause serious health issues. As the concentration of MPs increases in the body, they begin to modulate several biochemical and physiological pathways by altering the gut-brain axis. This can lead to inflammatory lesions, tissue degradation, ROS, metal imbalance, changes in gut phenotype, gut barrier function, endocrine secretion, and neurodegeneration. While there is limited information on the stages of plastic in the human diet, it is evident that regardless of degradation, MPs contaminate the environment, enter the body through contaminated foods, and disrupt intestinal homeostasis. Recent studies have shown that nano- and microplastics have various effects on the intestines, including disrupting intestinal homeostasis, altering gut permeability, and affecting levels of cytokine secretion. Since the human diet plays a significant role in disrupting gut microbes and causing disorders, probiotics are a suitable and compassionate therapeutic target to manage gut dysbiosis and protect bi-directional axes such as the gut-brain axis, gut-liver axis, gut-lung axis, and gut-skin axis. The altered gut induced by MP consumption also leads to oxidative stress, inflammation, and reproductive issues. Probiotics can effectively

control ROS, inflammation, and reproductive problems. In conclusion, probiotics play a crucial role in managing MP-induced gut dysbiosis. With the assistance of gene editing techniques, both conventional and next-generation probiotics may address many health-related concerns in the future. Given the increasing use of synthetic materials, further research is necessary to fully understand the harm that microplastics poseto human health and the environment, as well as to facilitate their complete eradication through cutting-edge gene editing technologies.

SEARCH STRATEGY

A systematic literature search was conducted to identify the harmful effects of MPs on the gut pollutants. All relevant studies focusing on plastic disposal, the conversion of plastic to microplastic, metal accumulation on their surface, their entry into the body, initiation of metal-induced gut dysbiosis, and neurodegeneration were included. The search strategy utilized electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. Various combinations of keywords related to plastic pollution, plastic to microplastic conversion, metal accumulation, metal entry, MP entry, health issues due to metal administration and MP exposure, signaling cascades, inflammation, cellular and neuronal stress, gut dysbiosis, neurodegeneration, probiotics as therapeutics, probiotics as personalized medicine, probiotics side effects, and Parkinson's disease were used as search terms. Additionally, reference lists of relevant articles and reviews were manually searched to identify additional studies. This study included original research articles, review articles, and meta-analyses published in English without restrictions on the publication date. Experimental studies, clinical trials, and observational studies investigating the therapeutic roles of probiotics for metal toxicity, neuronal disease and altered gut microorganisms were also considered. Exclusion criteria comprised studies not directly related to the topic, duplicate publications, conference abstracts, editorials, and commentaries. The selection process involved screening initial search results based on relevance, followed by a full-text assessment for eligibility. Data from selected studies were systematically extracted, including study design, metal accumulation on MP surface, signaling cascades due to metal imbalance, probiotics control on the gut-brain, gut-liver, gut-lung, gut-skin, hypothalamic-pituitary-adrenal, hypothalamic-pituitary-thyroid, and hypothalamic-pituitary-gonadal axis, experimental or clinical outcomes with conventional and nonconventional isolates, probiotics implications for controlling neurodegeneration, and molecular tools to improve probiotics efficiency. Synthesized data were thematically organized to provide a comprehensive overview of the harmful effects of MPs, their mode of interactions, stress induction, altered gut, neurodegeneration, and therapeutic application of probiotics, contributing to a deeper understanding of the complex regulatory networks involved in metal-induced gut dysbiosis.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

Question	Response
Data Availability	No

Sharing research data helps other researchers evaluate your findings, build on your work and to increase trust in your article. We encourage all our authors to make as much of their data publicly available as reasonably possible. Please note that your response to the following questions regarding the public data availability and the reasons for potentially not making data available will be available alongside your article upon publication. Has data associated with your study been deposited into a publicly available repository?	
Please select why. Please note that this statement will be available alongside your article upon publication. as follow-up to " **Data Availability** Sharing research data helps other researchers evaluate your findings, build on your work and to increase trust in your article. We encourage all our authors to make as much of their data publicly available as reasonably possible. Please note that your response to the following questions regarding the public data availability and the reasons for potentially not making data available will be available alongside your article upon publication. Has data associated with your study been deposited into a publicly available repository? "	Data will be made available on request

SUPPLEMENTARY DATA

There is no separate file for supplementary data

COMPETING INTERESTS

The authors declare that they have no competing interests

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AUTHORS' CONTRIBUTIONS

IP is responsible for conceptualization, validation, writing and editing and SU is responsible for writing, drawing and editing. Both the authors were critically revised the manuscript concerning intellectual content and approved the final manuscript

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FIGURE LEGEND

Fig.1.Schematic Representation of Microplastics (MP) Generation and Their Portals of Entry to Establish Severe Health Issues in Human

Fig.2.Schematic Representation of Gut–Brain Axis.

Fig.3. Schematic Representation of MP Induced Dysbiosis. Gut Brain Axis which controls the entire homeostasis of the body upon alteration disrupt the normal functions resulting in Chronic Disorders.

Fig.4.Schematic representation of MP induced biochemical pathways which disrupt the homeostasis and reestablishment of it with probiotics. A: Blocking of NFκβ pathway by Probiotics; B: SCFA mediated anti inflammation; C: Blocking of Nox dependent pathway by Probiotics; D: Controlling ROS by CAT, SOD, GPx and reduced DNA Damage

Fig.5.Disruption of Homeostasis. A. Normal condition in which Gut Brain Axis regulates physiological, biochemical and neuronal pathways, B. MP induced PD brain in which altered Gut Brain Axis triggers several altered mechanisms to hinder physiological, biochemical and neuronal pathways

Fig.6.Probiotics the New Therapeutic Approach to Control Gut Dysbiosis Induced by MPs

TABLELEGEND

Table 1: VARIOUS PROBIOTICS AND THEIR PROBABLE MODE OF ACTIONS TO NEUTRALIZE MP TOXICITIES

Table 2: MP INDUCED GUT MICROBIAL COMPOSITION VARIATION IN DIFFERENT SPECIES OF ANIMALS

Table 3: EFFECT OF MP ON VARIOUS MAMMALIAN GLANDS

Table 1
VARIOUS PROBIOTICS AND THEIR PROBABLE MODE OF ACTIONS TO NEUTRALIZE MP TOXICITIES

SL. NO	PROBIOTICS	MODEL	MPS	PROBLEMS	MODE OF ACTION	REFERENCES
1	AquaStar® (commercialprobiotics)	Nile tilapia (*Oreochromis niloticus*)	Polystyrene (PS)-MPs	a) Hepatic oxidative stress b) Activation of Mitogen-Activated Protein Kinase (MAPK) signaling c) Autophagy d) Inhibition of ERK signaling e) Activation of p38MAPK components	Nuclear factor erythroid 2-related factor 2 (Nrf2) down regulate p38MAPK	[240]
2	Commercial-probiotic pellets [200 mL/kg, 1×10^8 colony-forming unit (CFU)/mL]	Tilapia	Polystyrene (PS)-MPs	a) Altered levels of estradiol b) Testosterone	(Nrf2) down regulate p38MAPK attenuation of nuclear transcription factor κB (NF-κB) preventing apoptosis	[241,242]
3	*Lactobacillus plantarum* encapsulated with alginate/ chitosan NP	*Oncorhynchus mykiss*	MP coated with Pb	a) Lead toxicity mitigation, growth, b) hematological development c) modification in the intestinal enzyme activity	Bile salt hydrolase mediated deconjugation of bile acids lowering the activity of β-glucuronidase to suppress the intestinal damage	[243]

4	*Bacteroidetes* and *Proteobacteria*	*Micropterus salmoides*	PS-NPs single and DEHP-PSNP combined exposures on	a) The growth b) ROS c) Histopathology d) Intestinal microbiota composition	compete for receptors and binding sites with pathogen and restore intestinal barrier	[244]
SL. NO	**PROBIOTICS**	**MODEL**	**MPS**	**PROBLEMS**	**MODE OF ACTION**	**REFERENCES**
5	*Lactobacillus, Bifidobacterium longum*, and *Enterococcus* Combined formulation forFMT	Mice	Polystyrene microplastics (PS- MP)	Male reproductive toxicity	Anti-inflammatory Cytokine production TLR2/TLR4/MyD88 Signalling	[242,245]
6	*Bacillus*	Mice	MP surface coated with HM (Pb, Cd, Hg, As, Al, Cu, Mn, Cr)	Heavy metal toxicities	Insoluble metal complex by siderophores Insoluble metal precipitation	[246]
7	*Lactobacillus sp*	Mice, Rat	MP surface coated with HM Pb, Cd, Mn Pb, Cd, Al,Cu	Heavy metal toxicities	Reduce its availability and release it through feces a) By trapping through transporter protein b) By EPS binding protein	[113,247]
8	*Bacteriodes*	Zebrafish	MP surface coated with HM Hg As, Bi	Heavy metal toxicities	Reduction of metal toxicities by metal a) Methylation b) Demethylation c) Thiolation d) Reduction e) Oxidation	[100,185,247]

9	*L. rhamnosus* ATCC 7469	Zebrafish Caco-2 cell line	PE-MPs and PS-MPs MP coated with E. coli strain (serotype O149: K91, K88ac)	a) Altered barrier b) Altered gut colonization c) Inflammation	a) Upregulation of mRNA level for the Muc1, Muc2, Muc3, Klf4, Meplin-β, and Retnlb genes b) Toll-like receptor (TLR)-4 and nucleotide binding oligomerization-domain–containing protein (NOD) 2 (NOD2) mediated enhanced Akt phosphorylation and expression of tight junction protein	[100,242]
SL. NO	**PROBIOTICS**	**MODEL**	**MPS**	**PROBLEMS**	**MODE OF ACTION**	**REFERENCES**
10	*L. acidophilus R0011* *L. rhamnosus R0052*	*P. nana* and Mitten Crab *E. sinensis*	PE MP	MP-induced ROS and activate ERK and p38 MAPR	Nrf2 down regulate p38MAPK	[124]
11	*L. plantarum 299v* *Bifidobacteria*sp	Human and Mice	MP carrying pathogen	C. difficile–associated diarrhea E. coli O157:H7 infection	SCFA G protein–coupled receptor (GPR) 41 and GPR43 ATP-binding-cassette–type carbohydrate transporter mediated protection like decreased lipolysis and inflammation and increased adipogenesis and leptin release	[248,249]

SL. NO	PROBIOTICS	MODEL	MPS	PROBLEMS	MODE OF ACTION	REFERENCES
12	*B. breve* C50 *B. longum* subsp. *infantis* 35624	Mice	PE/PS with *Salmonella*	Intestinal Homeostasis Inflammation	CXCL8 secretion by epithelial cells via AP1 transcription factor subunit and IκB-α a decreased phosphorylation of p38-MAPK and IκB-α molecules attenuation of nuclear transcription factor κB (NF-κB) compete for receptors and binding sites with pathogen and restore intestinal barrier	[250,251]

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Table 2

MP INDUCED GUT MICROBIAL COMPOSITION VARIATION IN DIFFERENT SPECIES OF ANIMALS

MP	Species affected	Decreasing Phylum/ Genus	Increasing Phylum / Genus	Functional changes	Reference
PE	Zebrafish	*Firmicutes, Bacteroides, Actinobacteria, β-Proteobacteria, γ-Proteobacteria, Acidobacteria, Gemmatimonadetes* and *Cyanobacteria /Pseudomonas, Ralstonia, Stenotrophomonas, Chryseobacterium, Rhizobiaceae, Sphingomonas, Variovorax, Rhodococcus, Roseburia, Butyrivibrio, Lysobacter, Phascolarctobacterium, Mycobacterium, Micromonospora* and *Gaiella*	Proteobacteria, Chloroflexi and Fusobacteria /Aeromonas, Shewanella, Microbacterium, Nevskia and Methyloversatilis	The levels of ✓ Triglyceride (TG), ✓ Total cholesterol (TCHO), ✓ Non-esterified fatty acid (NEFA), ✓ Total bile acid (TBA), ✓ Glucose (GLU) ✓ Pyruvic acid Transcription of genes: ✓ Glycolipid ✓ Metabolism-related ✓ Genes and phospho-lipid metabolism-related genes Metabolites: ✓ Phospholipids	[19]
PS		*Bacteroidetes, γ-Proteobacteria /Sphaerotilus, Haliangium, Leptothrix, Pseudomonas, Methylobacterium*	Firmicutes /Methyloversatilis, Polynucleobacter, Legionella, Ottowia, Flectobacillus and Methylophilus	Metabolites: ✓ Carbohydrates, ✓ Fatty acids, ✓ Amino acids, ✓ Nucleic acid Transcription of genes: ✓ Glucose metabolism ✓ Glycolysis-related ✓ Lipid metabolism	[100] [252]
PP		*Actinobacteria / Aeromonas* and *Pseudomonas*	Proteobacteria / Gordonia	Enriched GO biological processes: ✓ Lipid metabolism, ✓ Hormone metabolism ✓ Protein secretion	
PS	Large yellow croaker	*Proteobacteria / Ruegeria, Vibrio* and *Microscilla*	Bacteroidetes, Firmicutes /Alloprevotella, Parabacteroides, Bifidobacterium, Alistipes, Bacteroides, Aliivibrio, Lactobacillus and Weissella	Bacterial gene functional prediction: ✓ Metabolism, ✓ Organismal systems, ✓ Biosynthesis of other secondary metabolites and circulatory system	[41]

PVC	Sea bass	No changes	no changes	Extracellular enzymatic activities decreased: ✓ Leucine ✓ Aminopeptidase, ✓ Beta- glucosidase ✓ Alkaline phosphatase Carbon sourceutilization: ✓ Complex carbon sources, ✓ Amino acids, ✓ Carbohydrates, ✓ Carboxylic acids	[72] [73]
MP	**Species affected**	**Decreasing Phylum/ Genus**	**Increasing Phylum / Genus**	**Functional changes**	**Reference**
PS <5µm	Crab	no change	Fusobacteria, Proteobacteria, Cyanobacteria and Chloroflexi / Pseudomonas and Rhodococcus	not specific	[19]
PS 5µm and above		*Firmicutes*, *Bacteroidetes* and *Nitrospirae* / *Dysgonomonas*and *Acinetobacter*	Cyanobacteria and Chloroflexi / Pseudomonas and Rhodococcus	not specific	[128]

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1547 **Table 3**

1548 **EFFECT OF MP ON VARIOUS MAMMALIAN GLANDS**

Gland/ System involved	Endocrine Disrupter	Species	Consequences	References
Thyroid Gland	**MP**	Human	• Thyroid dysfunction • Metabolic and developmental abnormalities	[64] [113] [115]
	PS MP	Rat	• T3 and circulating THs levels were decreased and TSH significantly increased. • Ectopic thymus Ultimobranchial cyst formation • Increased level of T3, FT3/FT4 ratio, and decreased level of TSH	
	MP+ Phthalates	Human	• Thyroid epithelial cell hypertrophy and hyperplasia • Thyroid hyperactivity, • Disruption of the hypothalamic-pituitary-thyroid [HPT] axis, • Thyroid antagonistic interaction, • Altered FT3 and FT4	
	MP+ Bisphenol A [BPA]	Rats	• Inhibits T3 receptor binding ability, • Thyroid antagonist, • Thyroid oxidative damage	
	MP+ Polybrominated diphenyl ethers [PBDEs]	Rats and Human	• Serum T4 reduction, • hypothyroidism, altered T4 levels in umbilical-cord blood, • altered T3 and T4 levels	
	MP+ Polychlorinated Biphenyls (PCBs)	Rat	• Reduced TT4 • Reduced FT4 levels	
	MP+ Mercury	Human	• Thyroid cancer, • Hypothyroidism, • Autoimmune thyroiditis	
Male Reproductive System	**MP**	Mice	• Recused sperm quality, • abnormal testicular spermatogenesis	[87] [115]
	MP	Swine	• Increased apoptosis and necrosis in testes, • decreased viability of testicular cells	
	PS-MPs	Mice	• Oxidative stress in testes • reduced sperm motility	
	MP+ Phthalates	Rats and Mice	• Oxidative stress in testes, • altered sperm's physiology, • anti-androgenic effects	

	MP+ TBT	Syrian hamsters	• Adverse steroidogenic enzymes activity, • impaired testosterone production, • defective spermatozoa	
	MP+ Chromium, lead and Mercury	Mice, Rabbits	• Leydig cell tumors, • Attenuates a) serum level of luteinizing hormone [LH], b) testosterone, c) folliclestimulating hormone, d) testicular strom	
Gland/ System involved	**Endocrine Disrupter**	**Species**	**Consequences**	**References**
Female Reproductive System	**MP**	Mice	• Oxidative stress in ovaries, • Decrease the number of ovarian antral follicles • Reduced malondialdehyde [MDA] levels in ovaries • Spontaneous abortion • Decreased uterine blood supply	[115] [82]
	MP	Rats	• Granulosa cell apoptosis, • Ovary fibrosis, and pyroptosis	
	MP+ BPA	Humans	• Inhibiting secretion of progesterone and oestradiol, • decreases expression of CYP11A1	
	MP+PCBs	Mice	• Follicular atresia, • Suppressed level of LH, progesterone	
	MP+ PBDEs	Humans	• Increased menstrual cycle, bleeding time	
Hypothalamus	**MP+ BPA**	Mice	• Significant decrease in hypothalamic neurons, • Astrocyte activation • Impairs the function of proopiomelanocortin [POMC] neurons in the hypothalamic arcuate nucleus [ARC], • Astrocyte-dependent inflammation	[64] [115] [118]
	MP+ Phthalates	Rats	• Dysregulation of the HPG axis, • induce early puberty by upregulating hypothalamic IGF-1 expression, • prolong the female estrous cycle, • affects mRNA and protein expression of KiSS1, GPR54, and GnRH	
	MP+ PCBs	Rats	• Oxidative stress in the hypothalamus, • decreased hypothalamic weight, • decreased acetylcholinesterase (AChE) activity	
	MP+ PBDEs	Rats	• Dysregulation of HPT and HPG axis	

Pituitary gland	**MP+ Phthalates**	Rats	• Altering levels of GnRH, LH, and FSH, • increases corticosterone and ACTH levels	[112] [115] [117] [118]
	MP+ PBDEs	Rats	• alter TH balance at HPT-axis, • disrupting normal HPT-axis, • carcinogenic effects in the pituitary of male rats and the uterus of female rats	
	MP+ Mercury	Humans	• Inhibits LH and FSH secretion, • menstruation disorders, • Leydig cells deformation, • impaired follicular development	
	MP+ Cadmium	Rats	• Decreased circulating levels of LH and FSH	
	MP+ Chromium	Rats	• Increased adrenal D53b-hydroxysteroid dehydrogenase [HSD] activity, • Increased adrenal weight, • serum corticosterone level increased	
	MP+ Phenols	Rats	• Damages the endogenous estrogenic cascade in the adrenal gland, • cause changes in the regions of the cortex medulla, • Causes cytoplasmic decomposition in cells of the cortex and hemorrhage in the tissue interface	
Gland/ System involved	**Endocrine Disrupter**	**Species**	**Consequences**	**References**
Digestive system	**MP+PS**	ICR mice	• Accumulate in kidneys, liver, and gut • Energy disturbance • Disturbance of lipid metabolism • Oxidative stress • Decrease amino acid in female mouse offspring but opposite in male offspring • Change in acyl-carnitine and free carnitine • Metabolic disorders in offspring	[112] [115]
	MP+PE	Mice C57BL/6	• Inflammation • Decrease the percentage of Th17 and Trey • Intestinal inflammation • Intestinal dysbacteriosis	
	MP+PS **MP+ Pristine PS**	ICR mice	• Reduce intestinal mucus secretion • Damage to the intestinal barrier function • Aactinobacteria load reduced • Metabolic disorder	

			• Alter gut microbiota • Increase TBA in the liver • Altered feeding behavior and growth rate	
CNS	**MP+DBP**	Mice	• Reduction protein expression levels of ✓ Nr4a3, ✓ Egr1, ✓ Arc, ✓ BDNF ✓ AKT phosphorylation • Decrease scores in negative geotaxis at PND 7 and swimming scores and olfactory orientation tests at PND 14 • Increase dark neurons • Delay pup development	[115] [118]
	MP+BPA	Inbred Swiss albino mice	• Anxiety • Alterations in the ratio of excitatory–inhibitory proteins • Inhibited PSD95 expression • Reduce morphological changes, spine stability • Blocked LTP induction	
	MP+BPA	Human Infants	• Increase oxidative stress • Mitochondrial dysfunction • Behavior complication in patients with ASD	
Gland/ System involved	**Endocrine Disrupter**	**Species**	**Consequences**	**References**
	MP+DBP	Rats	• Changes in sensory motor development • Reflex response • Low memory retention • Altered cyto-architecture in hippocampus • Disrupt neural and endocrine functions	[64]

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Declaration of interests

☒ 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.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: