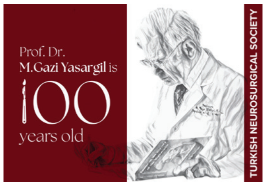
Turk Neurosurg 35(6):817-829, 2025
DOI: 10.5137/1019-5149.JTN.47512-24.2



Review

Received: 26.08.2024
Accepted: 25.12.2024
Published Online: 30.10.2025

Neurotoxicity of Microplastic Particles in the Human Brain: A Systematic Review

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ABSTRACT

AIM: To systematically review the existing literature on the neurotoxic effects of microplastics (MPs) on the brain.

MATERIAL and METHODS: This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The following keywords were used for the literature search “microplastics” and “human brain” in PubMed and “microplastics,” “health,” and “neurotoxicity” in Web of Science. Risk of bias was assessed using the Revised Risk of Bias Tool for Randomized Trials.

RESULTS: We identified 72 records from the databases and 12 records from the citation search. After exclusion, 11 records were included in this review, which revealed various effects of MPs on the human body at the molecular, cellular, and clinical levels. We observed that oxidative stress and energy disruption are the main toxic effects of MPs; in addition, they can induce neuroinflammation, alter biochemical pathways such as amino acids and neurotransmission, and cause cell death.

CONCLUSION: MPs are a significant global health problem. With the widespread use and accumulation of plastic materials, MPs can reach the nervous system and exert neurotoxic effects manifesting in behavioral and cognitive changes. The current evidence is insufficient to delineate the possible long-term outcomes of MP exposure. Further clinical studies are warranted to elucidate the mechanisms underlying these neurotoxic effects.

KEYWORDS: Microplastics, Neurotoxicity, Brain, Health, Memory

INTRODUCTION

Plastics are “lifesavers” for our industrial world owing to their resistance to environmental agents, cost of manufacturing, resulting in widespread use across the world. Considering their wide range of applications, from food packaging to medical products (31), the associated wastage and accumulation are inevitable. A recent study reported the total plastic waste generated between 2018 and 2022 to be 4.20 million tons (51).

Microplastics (MPs) are smaller plastic particles created by the breakdown of larger plastic particles through ultraviolet (UV) radiation and mechanical disintegration (18) or originate from manufactured products including cosmetics, sunscreens, and detergents (23). So far, there is no consensus on the definition of MPs by size, especially considering the sizes, in which they can exist. The most acceptable definition was given by Gigault et al. which considers MPs as plastic particles measuring between 1 μm and 5 mm (5,34).

Many recent studies have reported detecting MPs in the environment, such as oceans, rivers, sewage, soil (3), and even foods, such as seafood, tap water, table salt, sugar, honey, beer, and anything packaged with plastics (13,45,86,94). The marine environment is a major route for the distribution of MPs (56); given their widespread presence, it is inconceivable that these MPs do not affect living organisms. Both *in vivo* and *in vitro* studies indicate that MP exposure in marine organisms

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and humans results in their accumulation in several organs like kidneys, liver, gut, placenta, heart, lungs, brain, blood, feces, and urine (23,39,49,50,53,66,70,76), with cytotoxicity being the ultimate point of adverse effects at the cellular level (20,23,54,75,81). This accumulation and cytotoxicity are related to several factors, including MP size (23,54,75), type (81), surface shape (20), and concentration (17).

This accumulation of MPs and the associated cytotoxicity in the brain results in neurotoxicity; however, there is a lack of consensus regarding the neurotoxic effects of MPs because of conflicting evidence. This study systematically reviews the existing literature on the neurotoxic effects of MPs and presents further perspectives.

MATERIAL and METHODS

Search Strategy and Study Selection

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for conducting this systematic review (63,64). The PubMed and Web of Science databases were searched for relevant literature using the following keywords - “microplastics” and “human brain” in PubMed and “microplastics,” “health,” and “neurotoxicity” in Web of Science; no publication limit was set.

The studies were screened in two phases, first and second-level screening. Studies obtained using the aforementioned keywords that accepted MPs as plastics ranging between 1 µm and 5 mm and established any outcomes concerning the neurotoxicity of MPs were considered eligible in the screening process. The first-level screening evaluated the study titles and abstracts; we excluded studies with only “nanoplastic” or “nano-” in the title. If the title also included “microplastics” or “micro-”, only the MP findings were included in this systematic review. The second-level screening process included reviewing the full texts of all eligible studies.

We also examined the reference list of the included studies; the references related to the neurotoxicity of MPs according to their titles were searched on PubMed. Through this process, we found five other relevant studies, all of which met the eligibility criteria; these studies were included in this systematic review.

Data Synthesis

Table I presents a summary of the included studies explaining the possible underlying mechanisms of neurotoxicity caused by MPs. The characteristics of MPs, such as type, size, and shape, and the exposure process (dosage and exposure time) were sectioned to expand the review process. For this study, we used the size range of 1 µm–5 mm for MPs and excluded studies using a size range other than this (Table I). However, some studies used other particle sizes (2 and 10 µm) that were still in our specified size range (33,47); therefore, these studies were determined eligible for inclusion in the systematic review.

Table I: General Information of the Included Studies

Author, year	Type	Particle Size	Characteristics	Exposure process	Cell/animal model	Results
Gaspar et al., 2023 (33)	PS	0.1* and 2 µm	Unspecified**	*in vitro* 0.01, 0.1, 1, 10, 100, 1000 µg/mL; 24, 48, 72 h *in vivo* 0.0025, 0.025, 0.125 mg/mL; 3 weeks	U-2 OS cell line Young (4 month-old) and old (21 month-old) female mice	Intracellular accumulation Decreased cell viability Decreased GFAP expression Behavioral changes
Garcia et al., 2024 (32)	PS and mixed (PS, PE, PLGA)	PS: 5 µm PE: 1-4 µm PLGA: 5 µm	Spheric shape	2 and 4 mg/ week; 4 weeks	Female and male mice (2-3 month-old)	Tissue accumulation Altered metobolic pathways
Yang et al., 2022 (95)	PS	1 µm	Spheric shape	*in vitro* 0.6, 0.12, 0.24, 0.48 µg/mL; 24, 48 h *in vivo* 1 mg/day; 17 days	JEG-3 cell line N2A cell line Female and male mice (2 month-old)	No specific results for MPs
Hua et al., 2022 (38)	PS	1 and 10 µm	Spheric shape	5, 50, 100 µg/mL; 4-10 and 4-30 days	iPSC cell line	Oxidative stress Increased neuronal proliferation Increased neuronal progenitor genes’ expression Decreased cell viability Impaired neural development and maturation

Table I: Cont.

Author, year	Type	Particle Size	Characteristics	Exposure process	Cell/animal model	Results
Yin et al., 2022 (96)	PS	5 µm	Unspecified**	1, 10, 100 mg/ L; 6 weeks	120 day-old chicks	Decreased number of purkinje cells Neuroinflammation Intracerebral hemorrhage Impaired energy metabolism Pyroptosis
So et al., 2023 (79)	PS	2 µm	Spheric shape	*in vitro* 1 and 10 mg/L; 12 h *in vivo* 1 mg/L; 24 weeks	Primary cortical neurons of 2 month-old mouse embryos Female and male mice (2 month-old) mice	Increased neuronal proliferation Apoptosis in neuronal cells Decreased length of primary dendrites No impaired behavioral changes
Lee et al., 2023 (49)	PS	2 µm	Unspecified**	0.008 mg/g and 0.016 mg/g (based on body weight); 4 and 8 weeks	Female and male mice (6 weeks-old)	Tissue accumulation Neuroinflammation Increased BBB permeability Impaired learning and memory ability
Wang et al., 2024 (89)	PE	>2 µm	Oxidized/ non- oxidized, irregular shape	5 mg/L; 4 weeks	Male mice (6 weeks-old)	Oxidative stress Neuroinflammation Disruption of BBB integrity Impaired cholinergic pathways Increased anxiety-like behaviors Coginitive dysfunction
Wang et al., 2022 (90)	PS	5-5.9 µm	Unspecified**	0.01, 0.1, 1 mg/day; 4 weeks	Male mice (5 weeks-old)	Oxidative stress Inhibited CREB/BDNF pathway Decreased acetylcholine level Impaired learning and memory abilities
Ding et al., 2023 (24)	PS	10 µm	Photo-aged/ virgin, shape was unspecified**	0.1, 1, 10, and 100 µg/L; 5 days (120 hours post-fertilization)	Zebrafish larvae (Danio rerio)	Oxidative stress Impaired locomotor activity Dysregulation on neurotransmitter system
Kwon et al., 2022 (47)	PS	0.2*, 2, 10 µm	Spheric shape	*in vitro* 1, 5, 10 µg/ mL; 24, 48, 72 h *in vivo* 2.5 and 10 µg/mL; 1 and 7 days	HMC-3 cell line Mice (8 weeks-old)	Tissue accumulation Apoptosis Increased microglial activation

Notes: PS: *Polystyrene;* ***PE:*** *Polyethylen;* ***PLGA:*** *Polylacticcoglycolic acide;* ***U2 OS:*** *Human osteosarcome;* ***JEG-3:*** *Human choriocarcinoma;* ***N2A:*** *Mouse neuroblastoma;* ***iPSC:*** *Human induced pluripotent stem cell;* ***HMC-3:*** *human microglial cell that was isolated from the brain of a patient;* ***GFAP:*** *Glial fibrillary acidic protein;* ***BBB:*** *Blood-brain barrier;* ***CREB/BDNF:*** *Cyclic AMP Response Element-Binding Protein/ Brain-Derived Neurotrophic Factor*

**The result for this size were not included in this review. The reason for this was explained in "Materials and Methods" section.*

***This data was not found in the relevant study.*

The eligible studies were categorized based on three dimensions according to their outcomes – molecular, cellular, and clinical level. Table II presents a summary of the molecular level analysis for better understanding.

Risk of Bias Assessment

The included studies were assessed for risk of bias using the Revised Risk of Bias Tool for Randomized Trials (ROB 2) (80). While two of the studies had some concerns, the rest were all considered to have a low risk of bias (Figure 1).

RESULTS

Study Selection

We identified 72 records in the literature search (59 in PubMed and 13 in Web of Science); two records, Wang et al. (89), and So et al. (79), were duplicated. Hence, a total of 70 records were screened, of which 63 were excluded after first-level screening; seven articles were sought for retrieval in full text. During the second-level screening, one study, Suman et al. (82), was excluded because they used an MP size of 500 nm, and six studies were included in the review.

Table II: Detailed Informations of Molecular Level Outcomes

Author, year	Related outcomes	
Gaspar et al., 2023 (33)	GFAP expression ↓	
Garcia et al., 2024 (32)	Altered amino acid pathways	
Hua et al., 2022 (38)	*short-term effects* MK167 expression ↑ CASP3 expression ↑ SOD2 and CAT expression ↑ ATF4, Pax-6, Nestin expression ↑ CDKN1B expression ↑	*long-term effects* TBR2/TBR1, TUBB3 expression ↓ CASP3 expression ↑ Nestin expression ↑
Yin et al., 2022 (96)	Mitochondrial dynamics-related protein expression ↓ Inflammatory response proteins expression ↑ Pyroptosis related proteins expression ↑ (specificially Caspase 1 and IL-18) NLRP3 expression ↑ AMPK pathway-related proteins expression ↑	
So et al., 2023 (79)	Genes expression of brain cell markers and synaptic organization ↔ Genes expression of glutamaergic and GABAergic receptors ↔	
Lee et al., 2023 (49)	IEG expression ↓ Altered hippocampal synaptic proteins TNF-α and IL-1β ↑ Aif1 gene expression ↑, Iba1 levels ↑	
Wang et al., 2024 (89)	Cholinergic synaptic pathway regulating genes ↓ SOD, GSH-px ↓ TNF-α and IL-1β/6 ↑ ACH ↓, ACHe ↑	
Ding et al., 2023 (24)	CAT and SOD ↓, MDA and GST ↑ Oxidative stress and neurotransmission related genes ↓ DA, Ach, 5-HT and GABA levels ↑	
Kwon et al., 2022 (47)	Pro-apoptotic markes ↑ Anti-apoptotic markers(Bax, cleaved-Caspase3/8) ↓ Immune response gene transcription ↑ STAT3 / NFκβ pathway activation ↑	

***Notes: GFAP:** Glial fibrillary acidic protein; **MK167:** marker of proliferation Ki-67; **CASP3:** the gene encodes cysteine-aspartic acid protease 3; **SOD2,** superoxide dismutase 2; **CAT:** catalase; **ATF4:** activating transcription factor 4; **PAX-6:** paired box protein 6; **TBR2/TBR1:** T-box brain protein; **CDKN1B:** Cylin dependent kinase inhibitor 1B; **TUBB3:** tubulin beta class III; **NLRP3:** NLR family pyrin domain-containing protein 3; **AMPK:** 5' adenosine monophosphate-activated protein kinase; **IEG:** immediate early gene; **TNF-α:** tumor necrosis factor alfa; **Aif1:** allograft inflammatory factor 1; **Iba1:** ionized calcium-binding adapter molecule; **GSH-px:** glutathione peroxidase; **Ach,** acetylcholine; **AchE,** acetylcholine esterase; **MDA:** Malondialdehyde; **GST:** Glutathione S-transferase; **DA:** Dopamine; **5-HT:** 5-hydroxytryptamine; **GABA:** gamma-aminobutyric acid; **Bax:** Bcl-2-associated X protein; **STAT3:** signal transducer and activator of transcription 3; **NFκβ:** nuclear factor kappa B*

We further identified 12 relevant records by searching the reference lists of the included studies. These records were searched on the PubMed database, of which, seven were excluded based on title and abstract screening. Full texts of the remaining five studies were retrieved and assessed for eligibility; all five studies met the eligibility criteria. Finally, 11 studies were included in this review. All the identification, screening, and assessment eligibility processes can be seen in the flow diagram (Figure 2).

Study Characteristics

Four studies (33,47,79,95) examined MPs both *in vivo* and *in vitro*, six studies only conducted *in vivo* analysis (24,32,49,89,90,96), while one study (38) contained only *in vitro* analysis (Table I). Seven studies (24,33,49,79,89,90,96) reported clinical outcomes, as well as behavioral and cognitive functions, learning, and memory abilities, whereas two studies (49,89) specifically evaluated blood-brain barrier (BBB) integrity.

Neurotoxicity of MPs at the Molecular Level

Ten studies presented molecular level outcomes of the neurotoxicity caused by MPs (Table II). In particular, Gaspar et al. reported diminishing expression of glial fibrillary acidic protein (GFAP) in the hippocampus and prefrontal cortex of both young and older mice as a result of MP exposure (33). GFAP is a type of protein found in mature astrocytes, which is in charge of astrocyte development, regeneration, synaptic plasticity, and reactive gliosis (57), and is used as a marker of neuroinflammatory processes and reactive astrocytes (19). A recent study described that astrocyte atrophy could be seen in the onset of some diseases like Alzheimer's disease (AD), indicating that GFAP decrease may be an early sign in neurodegenerative diseases (87).

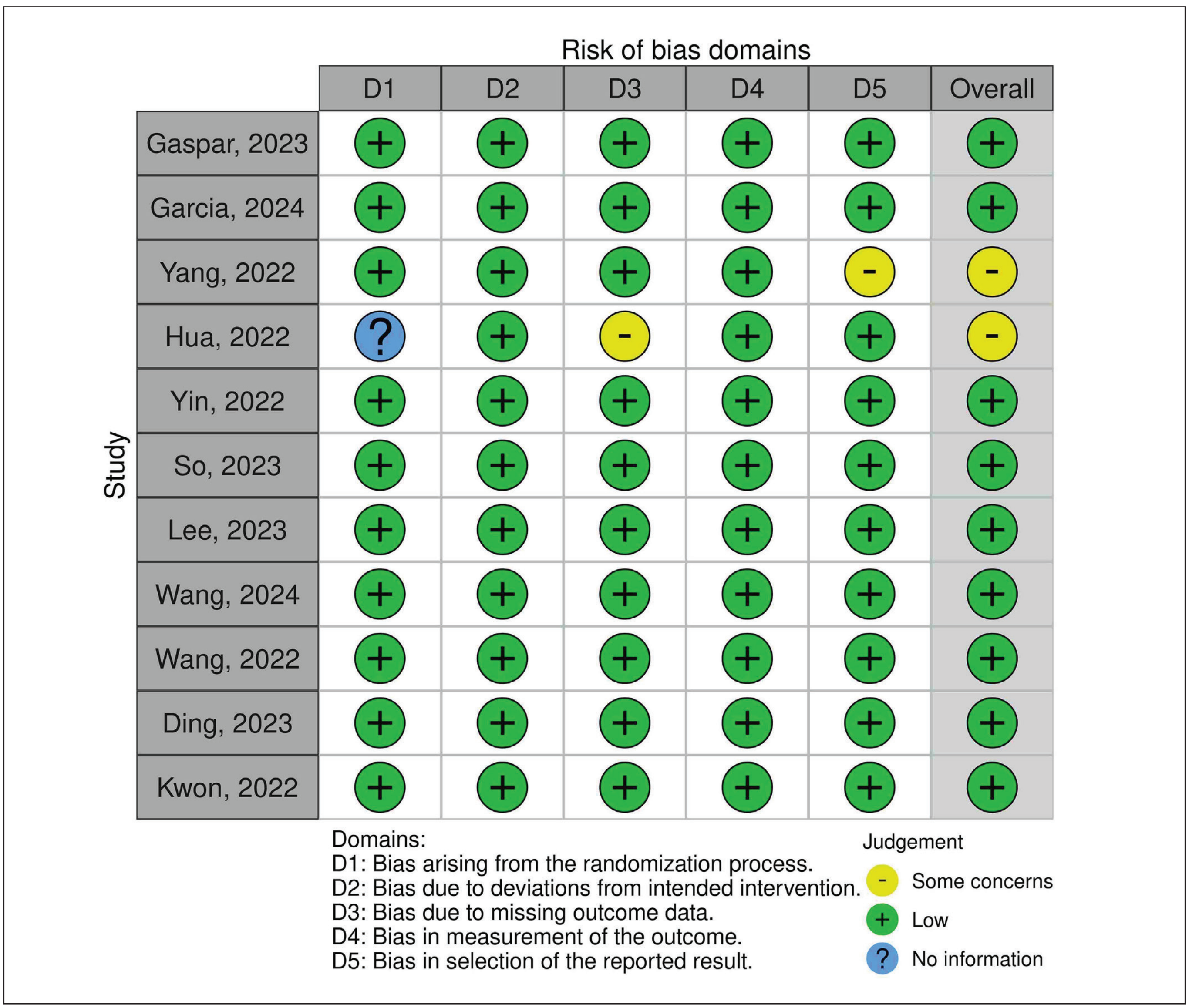

Figure 1: Risk of bias.

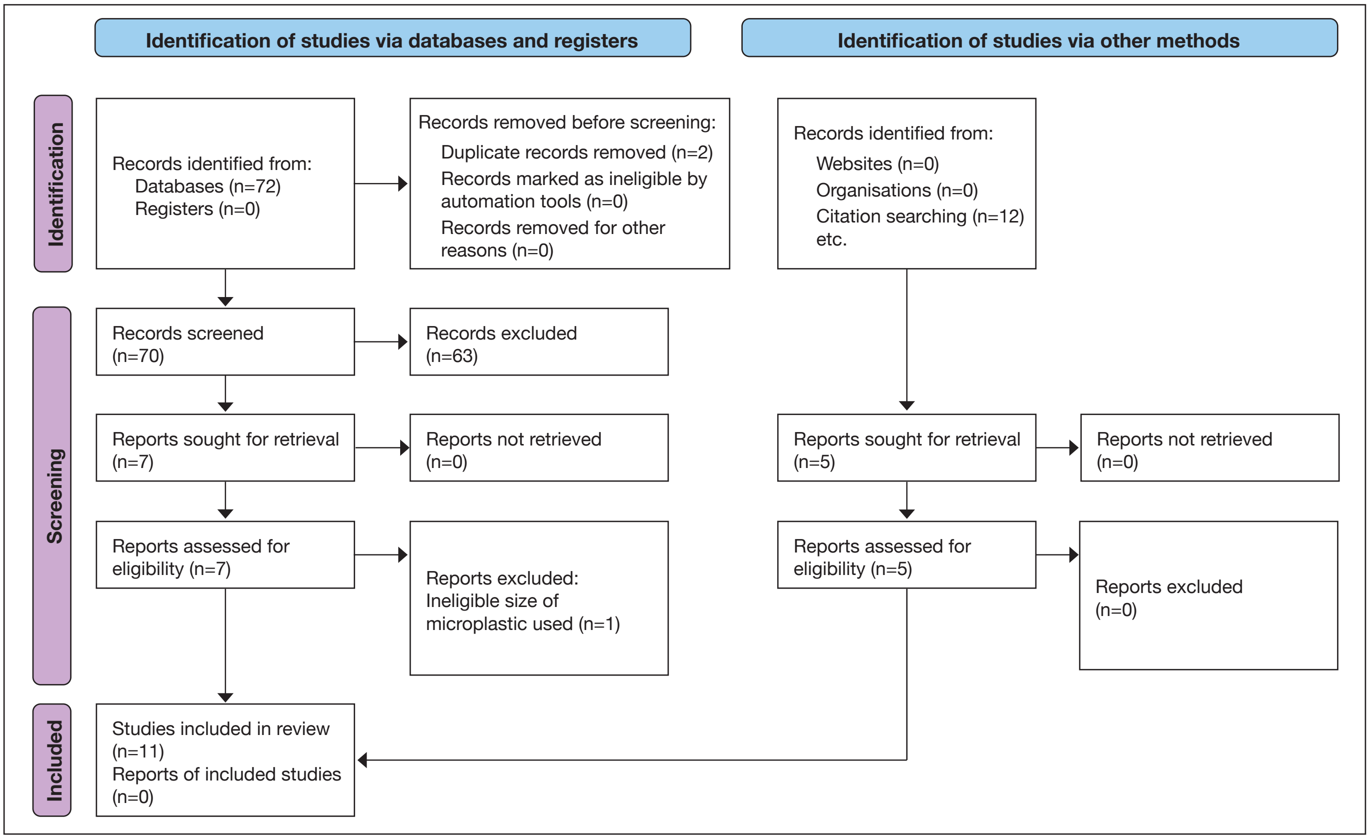

Figure 2: Flow diagram.

Garcia et al. observed changes in amino acid metabolism in mice treated with only polystyrene (PS) and mixed MP exposure (32). The alteration of the xenobiotic metabolism regulated by cytochrome P450 enzymes was also established, a mechanism underlying the detoxification and elimination of any foreign compounds in the brain. Damage to this system may prolong the elimination of xenobiotics from the brain (27) and potentially lead to neurotoxicity; however, it is noteworthy that this change was only observed in mice treated with the 4 mg/week dose (Table I).

Hua et al. reported certain changes that could be differentiated based on the exposure time to MPs *in vitro* – 4–10 days and 4–30 days (38). With short-term exposure, the expression of the neural progenitor genes, activating transcription factor 4 (ATF4), paired box protein 6 (PAX-6), and nestin was up-regulated; these genes modulate neural development and neural plasticity (10,52,97). A cell proliferation gene, marker of proliferation Ki-67 (MK167), and a cell death-related gene, which encodes cysteine-aspartic acid protease 3 (CASP3) were also up-regulated, as were superoxide dismutase 2 (SOD2) and catalase (CAT), which are antioxidant enzyme genes (60), yet no significant changes were observed at their protein levels. In terms of long-term exposure, a decreasing expression of T-box brain protein (TBR2/TBR1) genes, which regulate cell migration and projection in the cortex (58) was observed. Expression of the tubulin beta class III (TUBB3) gene, which is crucial in neuronal structure and function (48), was down-regulated with long-term exposure, as was with nestin, which is in contrast with the results for short-term exposure. Overall, especially long-term exposure to MPs may result in neurotoxic effects due to impaired neural maturation, oxidative stress, and increased risk of apoptosis.

Yin et al. highlighted the role of two genes, NLR family pyrin domain-containing protein 3 (NLRP3) and 5’ adenosine monophosphate-activated protein kinase (AMPK) (96). The NLRP3 inflammasome is functional in the host immune defense (43) and was activated by neuroinflammation due to MP-induced intracerebral hemorrhage (96). AMPK is an enzyme activated due to limited ATP production by cellular stress (71) and was also up-regulated. Some studies have identified that NLRP3 activation may be associated with neurodegenerative diseases like AD and Parkinson’s disease (PD) (2), and energy disruption due to cellular stress may be crucial in neurotoxicity.

So et al. (79) did not observe significant alterations of brain cell markers or synaptic organization in mice. Lee et al. (49) observed down regulation of the immediate early gene (IEG) and up-regulation of the allograft inflammatory factor 1), tumor necrosis factor-alfa (TNF-α), and interleukin 1 beta (IL-1β) genes in the hippocampus of male and female mice, with IEG down regulation being more significant in male mice. IEG expression is a commonly used marker for neuronal plasticity and indicates the formation of long-term memory (59). The Aif1 gene encodes the ionized calcium-binding adapter molecule (Iba1) protein which is a marker for microglial activation

(21,41). TNF-α and IL-1β are inflammatory cytokines with neuroprotective effects exerted by mitigating toxic changes in the brain (15). All these alterations suggest that the toxic effects of MP exposure may develop via neuroinflammation, potentially leading to impaired memory and learning ability in humans.

Wang et al. observed that cholinergic synaptic signaling pathways in the mice hippocampus and cortex were disrupted with down regulation of genes regulating this pathway, leading to increased acetylcholine (Ach) and decreased AchE (acetylcholine esterase) expression (89). The cholinergic system is crucial for memory, learning ability, and maintaining attention (36). Some studies have shown that deficiencies in neurotransmission pathways like the cholinergic system are associated with neurodegenerative diseases, such as AD, suggesting that the neurologic adverse effects of MPs may be one of the underlying causes of neurodegenerative diseases (36,40). Furthermore, dysregulation in the balance of oxidants/anti-oxidants and increased neuroinflammation markers are also noted as significant contributors.

In another study, Wang et al. observed decreased Ach levels, increased AchE levels, and oxidative stress in the brain tissue of mice (90), similar to the previous findings (89). They also found that the cyclic AMP response element binding protein (CREB)/brain-derived neurotrophic factor (BDNF) pathway was inhibited in a dose-dependent manner. CREB is a transcription factor crucial for structuring long-term memory, regulating neurodevelopment, and synaptic plasticity (73), meanwhile, BDNF is a neurotrophin and a target gene of CREB, vital for cognitive function, memory development, and synaptic plasticity in the central nervous system (CNS) (72,98). Accordingly, some studies have demonstrated that decreased BDNF and CREB levels may be one of the underlying mechanisms responsible for cognitive dysfunction and impaired memory in AD (1,9,25).

Ding et al. observed that exposure to MPs caused decreased expression of genes related to neurotransmission and oxidative stress (24). Levels of both excitatory neurotransmitters (dopamine [DA] and Ach) and inhibitory neurotransmitters (5-hydroxytryptamine [5-HT] and gamma-aminobutyric acid [GABA]) were increased in zebrafish in a dose-dependent manner (14,37,74). Presumably, dysregulation of neurotransmission may result from MP-related neurotoxicity and cause some neurological disorders (84).

Kwon et al. observed increased pro-apoptotic markers and decreased anti-apoptotic markers in the human microglial cell (HMC-3) cell line treated with 2 μm PS for 24-h; however, no significant findings were reported for the 10-μm particles (47). Furthermore, they examined two immune response signaling pathways in microglial cells, nuclear factor kappa B (NFκβ) and signal transducer and activator of transcription 3 (STAT3). NFκβ is a transcription factor that regulates the innate and adaptive immune systems (29), in addition to its role in providing neuronal maintenance and synaptic growth in the CNS (26). It has also been reported that excessive glial activation of the NFκβ may expose the cells to neurotoxicity (12). Likewise, STAT3 is another transcription factor contributing to cell growth and apoptosis (29), and the STAT3 signaling pathway underlies the inflammation-mediated astrogliogenesis via the activation of microglia (16,61). Therefore, induced cell apoptosis and increased immune response may lead to microglial activation, eventually causing neurotoxicity.

Neurotoxicity of MPs at the cellular level

Typically, humans are exposed to MPs via ingestion, inhalation, and dermal contact (7,65,68,93). Due to their small size, some of them can be eliminated through stool and urine (66,76); however, larger particles can reach into the other organs and accumulate in the brain through the circulatory system (95). MP accumulation in the brain tissue has been mostly detected in the prefrontal cortex and hippocampus of mice (32,47,49). Notably, the accumulation of MPs in the brain tissue was colocalized to the region where the Iba-1 (a microglial marker) is found (57). Intracellular accumulation in brain samples has also been detected in mice (33); however, So et al. did not find any such accumulation in size and type (79).

It has been shown that nanoplastics (<100 nm) can penetrate the BBB due to their size and toxic effects (44,78). Lee et al. reported that BBB permeability is affected even with exposure to 2-μm PS-MPs (49), that is, they found an increase in BBB leakage in PS-MP-treated mice. Wang et al. also observed down regulation at the level of tight junction-associated markers, such as claudin-1, occludin, and zonula occludens 1 (ZO-1) in the messenger RNA (mRNA) of MP-treated mice (89). The BBB is an enormously selective barrier that includes many types of tight junctions, which limit paracellular transport (8,55); damage to the integrity of the BBB can render the CNS undefended against harmful substances.

Gaspar et al. and Hua et al. showed that cell viability in *in vivo* cell lines decreased with MP exposure (33,38). The viability of the U-2 OS (human osteosarcoma) cell line did not show a linear trend at different exposure times but was highest at the 72-h exposure with MP (33). Similarly, in the human induced pluripotent cell (iPSC) cell line, which was differentiated into forebrain cortical spheroids, cell viability decreased after long-term exposure (4–30 days) (38), suggesting that cell viability decreases in an exposure-time-dependent manner.

Hua et al., observed increased neural proliferation, including increased apoptosis markers, at short-term exposure *in vitro* (4–10 days) (38). So et al. observed the same findings *in vivo* (79). These findings indicate that damage caused by MP exposure may lead to acute cell proliferation, but the opposite occurs with long-term exposure. Another study found a decrease in the number of Purkinje cells in the cerebellum of chicks at all different doses, and no Purkinje cells were left at the 100 mg/L dose (96).

Oxidative stress is an imbalance between oxidant and antioxidant agents that affects many cellular structures, such as plasma membrane substances and mitochondria (11,35,36,67). It also plays an important role in the underlying mechanisms of neurodegenerative diseases such as AD and PD (30,46,83). Two studies (89,90) have reported increased oxidative stress markers in the brain tissue. Hua et al. also observed increased antioxidant enzyme expression *in vitro* (38). These findings highlight the probability of MP-exposure-induced oxidative stress and activation of antioxidant mechanisms to prevent cellular damage.

Neurotoxicity of MPs at the Clinical Level

A variety of animal experiments aimed at determining if MP exposure can cause any behavioral, cognitive, or learning and memory impairments have achieved significant results. Gaspar et al. observed anxiety-like behaviors, such as increased distance traveled and locomotion activity, in young and old mice after MP exposure (33). In contrast, another study observed increased time spent in the central area, indicating anxiolytic behaviors; these outcomes were more prominent in older mice (69).

Lee et al. did not observe any anxiety-like behavior or impairments in locomotor activity but rather observed damages to learning and memory ability in mice treated with PS-MP (49). One study used a novel object recognition test to examine hippocampus-dependent memory – in this test, the mice were supposed to spend less time with the old object than the new object after recognition training (4). The time spent with the old object did not decrease in male mice treated with PS-MP, whereas the control group showed a significant time difference; no changes were observed in the female mice. They also compared the effects of a truncal vagotomy versus sham surgery (control group) considering that the vagal pathway-mediated gut-brain axis is a potential route for the neurotoxicity of MPs. Mice that underwent vagus nerve ablation showed improved recognition and hippocampus-dependent memory.

Likewise, Wang et al. observed impaired learning and memory abilities in mice treated with PS-MP by using the Morris water maze test for spatial learning and memory abilities (89). In this test, rats were subjected to finding the escape platform, and the time spent finding the platform was expected to decrease over time (88,92). However, the time and distance spent by the mice to find the platform were increased. Furthermore, the group that received lactobacillus plantarum DP189 and galacto-oligosaccharides-probiotic supplementations (91) along with PS-MP reversed the effects caused by PS-MP exposure. Another study by Wang et al. (90) observed similar results, noting that the results were dose-dependent and that mice treated with Vit E, an antioxidant, showed improvements in learning, memory abilities, as well as in other impairments and dysfunctions.

Ding et al. observed impaired locomotor activity after MP exposure (24). Locomotor activity is considered an indicator of neurotoxicity in zebrafish (77); however, it is worth mentioning that the photo-aged particles used in this study had more significant adverse effects.

Yin et al. observed intracerebellar hemorrhage in chicks after MP exposure in a dose-dependent manner (96). At lower doses, there were only microthrombi in different spots of the cerebellum, whereas the hemorrhage became more apparent at higher doses.

So et al. (79) observed no behavioral, locomotor, learning, or memory changes with MP exposure.

DISCUSSION

In this systematic review, we scrutinized the findings of the included studies from a molecular, cellular, and clinical aspect. A variety of neurotoxic effects have been identified as a consequence of exposure to MPs at the molecular level, which can be observed in different cell cultures and animal models. Furthermore, these effects can be attributed to several mechanisms, including oxidative stress, induced immune response, increased inflammatory cytokine levels, microglial activation, altered cholinergic function, and energy deficiency.

From the cellular aspect, disruption of the BBB due to MPs is the primary concern. The BBB is one of the most selective barriers in the human body comprising a major defensive force of the brain, and MPs are particularly hazardous in diseases that damage the integrity of the BBB, such as tumors, ischemia, and hemorrhages (8). According to the preliminary study (42), MPs were found in the brain cells of a patient with a grade four tumor; the surgeons took intraoperative samples from brain areas where the BBB was intact and where it was not. However, examination of the samples revealed that MPs were found in all brain cells (damaged and undamaged). The accumulation of MPs in the brain, mostly in the prefrontal cortex and hippocampus, can also be a consequence of this process, which can lead to many behavioral and cognitive alterations at the clinical level (6).

Another significant finding from a clinical perspective is MP-induced intracerebral hemorrhage (ICH) and secondary brain injury. While the mechanisms underlying ICH-induced brain injury involve various pathways at the molecular level, such as the activation of pro-inflammatory cytokines and microglia/macrophages (98,99), MPs may also cause these impairments. According to Yin et al. (96), exposure to MPs causes ICH through physical injury and provokes inflammation; they also observed tissue hemorrhage and hemolysis at various levels. The existing literature provides insufficient evidence to substantiate an association between MPs and ICH; further research is warranted to gain a more comprehensive understanding of this topic.

Limitations of the Study

Most of the included studies used PS-MP particles in their reports, except Garcia et al. (32) and Wang et al. (89), as PS is one of the most used types of plastic (28). The surface shape most commonly used among the included studies is spherical, whereas, in nature, the most abundant forms are particles with irregular shapes, fibers, and fragments (22). Hence, it is not clear whether other types of MPs (such as polypropylene, polyethylene, and polyethylene terephthalate) can cause neurotoxicity, or if neurotoxicity may alter with different structures of MPs; this factor was not considered in this review.

CONCLUSION

MPs are neurotoxic to the human brain, most commonly affecting the prefrontal cortex and hippocampus. These particles may cause memory disturbances, learning difficulties, and behavioral changes in the human body by disrupting the BBB permeability and inducing oxidative stress. More clinical and laboratory studies are needed to elucidate the mechanisms of the neurotoxicity of MPs.

ACKNOWLEDGEMENTS

Preparation for publication of this review is partly supported by Turkish Neurosurgical Society.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors have no personal, financial, or institutional interest in any of the drugs or materials described in this article.

AUTHORSHIP CONTRIBUTION

Study conception and design: SK, EY, OT, YI

Data collection: SK, EY, OT, YI

Analysis and interpretation of results: SK, EY, OT, YI

Draft manuscript preparation: SK, EY, OT, YI

Critical revision of the article: YI, OT

All authors (SK, EY, OT, YI) reviewed the results and approved the final version of the manuscript.

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