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MICROPLASTIC NEUROTOXICITY-BBB-TARGETED PHARMACOTHERAPY

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ABSTRACT

Microplastic and nanoplastic exposure is now a plausible biological risk due to widespread contamination of air, drinking water, and food systems. Preclinical evidence increasingly indicates that micro-/nanoplastic particles may enter systemic circulation and interact with the neurovascular unit, weakening blood–brain barrier (BBB) integrity and promoting central nervous system (CNS) injury. Proposed mechanisms include tight junction remodeling, endothelial oxidative injury, mitochondrial dysfunction, microglial activation, and NLRP3 inflammasome–driven cytokine release, which collectively undermine synaptic plasticity and behavior. Because microplastic neurotoxicity involves multiple converging pathways, a rational therapeutic strategy should integrate BBB stabilization, oxidative stress control, neuroinflammation suppression, and synaptic rescue. This review consolidates current evidence on (i) exposure routes and systemic distribution, (ii) BBB penetration and disruption mechanisms, (iii) downstream molecular cascades associated with cognitive and affective impairment, and (iv) pharmacotherapeutic countermeasures with repurposing potential, including N-acetylcysteine, minocycline, memantine, retinoid-based BBB modulators, and selective inflammasome inhibitors. Finally, research gaps and a translational roadmap are presented, emphasizing standardized particle characterization, biomarker-guided outcome assessment, and targeted studies in high-exposure occupational cohorts.

KEYWORDS: Microplastics; Nanoplastics; Blood–Brain Barrier; Neuroinflammation; Oxidative Stress; NLRP3 Inflammasome; Drug Repurposing; Cognition; Behavior.

1. INTRODUCTION

Plastic materials degrade into secondary microplastics (<5 mm) and nanoplastics (often <1 μm), creating persistent particulate contaminants across ecosystems. Human exposure occurs through ingestion and inhalation, with polymer residues and microplastic particles reported in biological samples, raising concern over systemic distribution.[1–3] Although quantification approaches require rigorous contamination control, mechanistic studies suggest that sufficiently small particles can interact with vascular endothelium, alter immune signaling, and potentially reach the brain through BBB compromise or transport processes.[4–6] The BBB is maintained by endothelial tight junctions (claudin‑5, occludin, ZO‑1), pericytes, and astrocytic end-feet, enabling stringent control of CNS entry.[7,8] Disruption of this barrier is implicated in neuroinflammation and neurodegeneration; hence BBB-centric countermeasures may be pivotal for microplastic-associated neurological risk.[9] This review focuses on pharmacotherapeutic strategies that protect BBB function and restore behavioral outcomes after microplastic exposure.

2. Sources and routes of microplastic exposure

2.1 Ingestion exposure

Dietary intake arises from contaminated drinking water, seafood, salt, and food packaging-derived particulates.[10–12]

2.2 Inhalation exposure

Indoor and occupational airborne microplastics, including fibers, can be inhaled; smaller fragments may translocate from alveoli to circulation.[13–15]

2.3 High-risk populations

Plastic manufacturing and recycling workers may experience elevated exposure burdens, justifying targeted monitoring and preventive intervention research.[16]

3. BBB entry and disruption mechanisms

3.1 BBB architecture and function

The BBB restricts paracellular permeability through tight junctions and regulates solute exchange via selective transporters, maintaining CNS homeostasis.[7,17]

3.2 Particle translocation pathways

Experimental evidence supports endocytosis/transcytosis, inflammation-driven permeability increases, and tight junction remodeling as plausible pathways for micro-/nanoplastic entry.[4–6,18]

3.3 Endothelial injury and microvascular effects

Vascular particle interaction may promote endothelial dysfunction, altered perfusion, and pro-thrombotic signaling, amplifying neurovascular stress.[19]

4. Molecular cascade of microplastic neurotoxicity

4.1 Oxidative injury and mitochondrial dysfunction

Micro-/nanoplastics can amplify ROS generation via surface reactivity and immune activation. ROS overload damages lipids and proteins and disrupts mitochondrial respiration, reducing ATP availability and increasing neuronal susceptibility.[20–22]

4.2 Neuroinflammation and NLRP3 inflammasome activation

Microglial activation may stimulate NLRP3 inflammasome assembly, increasing caspase‑1 activity and IL‑1β maturation, sustaining inflammatory loops and functional deficits.[23–25]

4.3 CREB/BDNF suppression and synaptic impairment

Inflammatory mediators and oxidative signals can attenuate CREB phosphorylation and reduce BDNF expression, weakening synaptic maintenance and long-term potentiation (LTP), which contributes to learning and mood disturbances.[26–28]

4.4 Microglial polarization and chronic neurotoxicity

Pro-inflammatory (M1-like) microglial skewing elevates TNF‑α and iNOS, supporting persistent neuronal injury and behavioral dysfunction.[29]

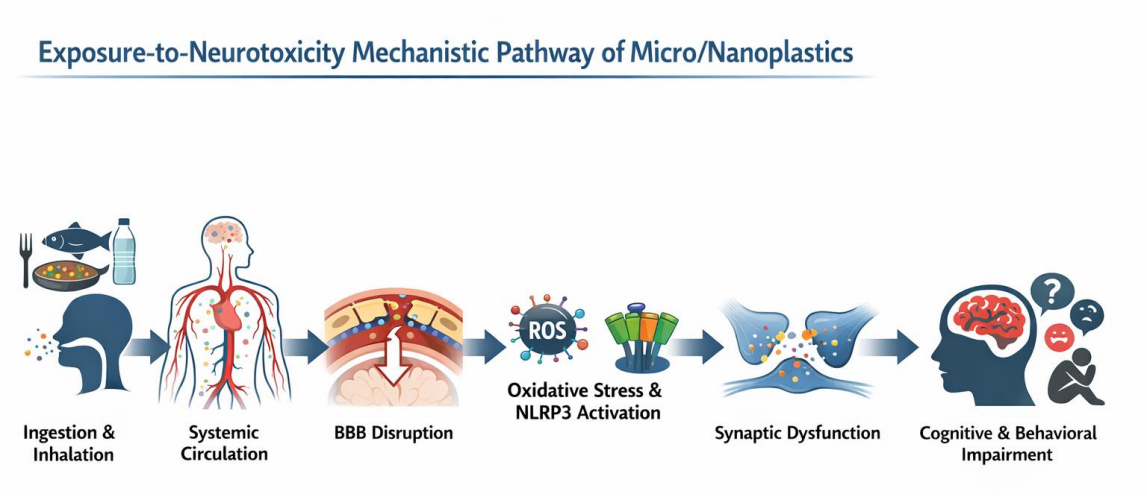

Figure 1: Exposure-to-neurotoxicity pathway.

5. Neurobehavioral outcomes

Animal models repeatedly report anxiety-like behaviors, depressive phenotypes, reduced locomotor activity, and learning/memory impairment after microplastic exposure, often with hippocampal inflammation and synaptic remodeling changes.[30–32]

Table 1: Key mechanistic pathways implicated in microplastic neurotoxicity.

Mechanism	Biomarkers/indicators	Functional consequence	Refs
BBB disruption	↓ZO-1/occludin/claudin-5; ↑permeability	Enhanced CNS entry; neurovascular stress	[7,17,18]
Inflammasome activation	↑NLRP3; ↑caspase-1; ↑IL-1β	Sustained neuroinflammation	[23–25]
Oxidative injury	↑ROS; ↓GSH; ↑lipid peroxidation	Mitochondrial dysfunction; neuronal vulnerability	[20–22]
Synaptic suppression	↓pCREB; ↓BDNF; ↓LTP	Cognitive and mood impairment	[26–28]
Microglial M1 shift	↑TNF-α; ↑iNOS	Chronic neurotoxicity progression	[29,37]

6. Pharmacotherapeutic counter measures

6.1 BBB stabilization strategies

Retinoid signaling enhances barrier phenotype and may upregulate tight junction proteins; retinoic acid derivatives have been explored to strengthen endothelial barrier properties.[33,34] Adjunct vascular protectants (e.g., statins) may reduce endothelial inflammatory activation.[35]

6.2 Neuroinflammation inhibition (NLRP3/IL-1β/microglia)

Selective NLRP3 inhibitors (e.g., MCC950) reduce inflammasome activity and IL‑1β release, improving outcomes in inflammatory CNS models.[24,36] Minocycline suppresses microglial activation and cytokine production beyond its antimicrobial use.[37] IL‑1 receptor blockade (anakinra) provides a rational approach where IL‑1β dominates neuroinflammatory signaling.[38]

6.3 Antioxidant restoration and mitochondrial support

N‑acetylcysteine (NAC) replenishes glutathione stores and reduces oxidative injury. Evidence from neuroinflammatory and neuropsychiatric contexts supports its neuroprotective potential.[39,40] Mitochondrial-targeted antioxidants and cofactor therapies remain promising adjuncts for evaluation in microplastic models.[41]

6.4 Synaptic rescue and cognitive protection

Memantine, an NMDA receptor antagonist, can attenuate excitotoxicity and preserve plasticity during oxidative-inflammatory stress.[42] TrkB agonists and BDNF enhancers (e.g., 7,8-dihydroxyflavone) may promote synaptic recovery and memory improvement.[43]

6.5 Combination therapy rationale

Neurological disorders and acute brain injuries arise from the concurrent interplay of multiple pathogenic mechanisms, rather than a single isolated process. Blood–brain barrier (BBB) dysfunction, excessive oxidative stress, glutamate-driven excitotoxicity, and persistent neuroinflammatory responses often develop in parallel and reinforce one another. As a result, therapeutic approaches directed at only one pathway frequently yield limited or transient benefits, underscoring the need for multitarget treatment strategies.

Combination therapy offers a mechanistically sound solution by enabling simultaneous modulation of distinct yet interconnected pathological processes. N-acetylcysteine (NAC) acts predominantly as a redox modulator, restoring intracellular glutathione reserves, neutralizing reactive oxygen species, and supporting vascular and endothelial stability, thereby contributing to preservation of BBB integrity. Complementing this, minocycline exerts broad neuroprotective effects through suppression of microglial overactivation, downregulation of inflammatory mediators, inhibition of apoptotic signaling, and

stabilization of mitochondrial function. Together, these agents may exert synergistic effects by concurrently attenuating oxidative injury and neuroinflammatory amplification.

Further enhancement of this therapeutic framework can be achieved with the addition of memantine, a moderate-affinity NMDA receptor antagonist. By selectively limiting pathological glutamate signaling and calcium overload, memantine reduces excitotoxic neuronal damage without disrupting normal synaptic activity. This action aligns functionally with the antioxidant and anti-inflammatory properties of NAC and minocycline, enabling broader neuroprotection across molecular, cellular, and synaptic levels.

In summary, combination regimens such as NAC + minocycline ± memantine represent a rational, integrated approach for addressing the multifactorial nature of neurological injury. By targeting overlapping yet distinct pathological pathways, such strategies may improve therapeutic outcomes, minimize compensatory disease mechanisms, and provide more sustained neuroprotection than single-agent interventions, highlighting their potential relevance for future translational and clinical applications.[44]

Table 2: Pharmacotherapeutic candidates and targeted pathways for microplastic-associated CNS injury.

Agent	Target	Proposed benefit	Refs
N-acetylcysteine	GSH replenishment/ROS control	Reduces oxidative injury; supports cognition	[39,40]
Minocycline	Microglial modulation	Decreases TNF-α/IL-1β; improves behavior	[37]
Memantine	NMDA modulation	Reduces excitotoxicity; preserves LTP	[42]
MCC950	NLRP3 inhibition	Suppresses IL-1β signaling axis	[24,36]
Retinoic acid derivatives	TJ stabilization	Strengthens BBB integrity	[33,34]
7,8-DHF	TrkB agonism	Enhances neuroplasticity	[43]

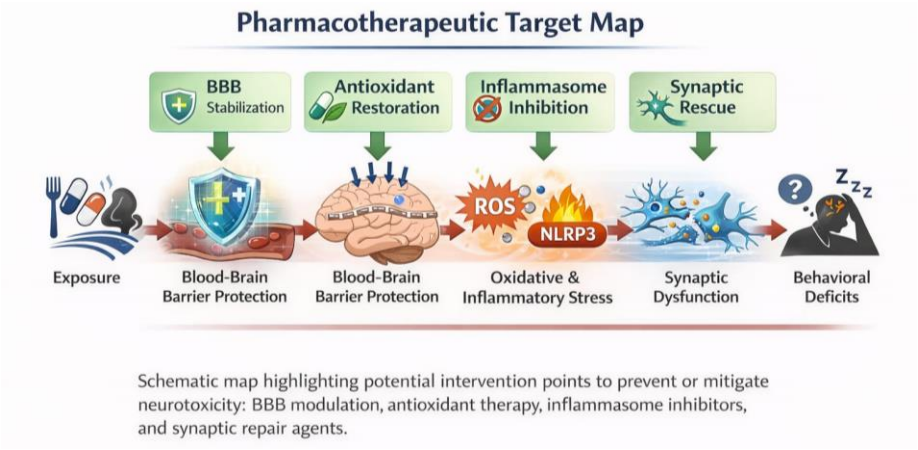

Figure 2: Pharmacotherapeutic target map.

7. Research gaps and future directions

Despite rapid growth in microplastic neurotoxicity studies, several limitations restrict translation into clinically actionable guidance.

- Standardization deficits: particle size distribution, polymer identity, surface chemistry, and additive contaminants are often inconsistently reported.[45]
- Exposure realism: many studies employ doses that may not reflect chronic human exposure; low-dose, long-duration models are needed.[46]
- Barrier quantification: robust BBB outcome panels (tight junction proteins, tracer permeability, transporter changes) should be systematically implemented.[7,17]
- Clinical biomarkers: validation of oxidative (8‑OHdG), neuronal injury (NfL), and inflammatory markers is required for human studies.[47,48]
- Mixture toxicity: co-exposures with heavy metals, pesticides, and persistent organics can modify neurotoxicity and should be addressed in systems-based models.[49]
- Therapeutic trials: head-to-head comparisons of single vs combination regimens and optimal timing (prevention vs post-exposure) remain sparse.[44]

  Future work should prioritize harmonized reporting frameworks, integrate multi-omics approaches, and evaluate drug-repurposing candidates using biomarker-guided endpoints in high-exposure cohorts.[16,50]

8. CONCLUSION

Micro-/nanoplastic exposure is increasingly linked to neurovascular dysfunction, with BBB disruption serving as a plausible gateway for CNS injury. Oxidative injury, mitochondrial impairment, and NLRP3 inflammasome-driven inflammation converge to weaken synaptic

plasticity and impair behavior. Therapeutic countermeasures should combine barrier protection, oxidative stress mitigation, and neuroinflammation suppression, with synaptic rescue strategies supporting functional recovery. Repurposed agents such as NAC, minocycline, and memantine offer pragmatic candidates for near-term evaluation, while selective inflammasome inhibitors and BBB-stabilizing retinoids represent targeted options for mechanistic intervention. Coordinated translational studies using standardized particle characterization and validated biomarkers are essential for direct clinical relevance.

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