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Oxidative Stress and Neuroinflammation Mechanisms in Rodent Brain Induced by $PM_{2.5}$ Exposure

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ABSTRACT

Exposure to fine particulate matter ($PM_{2.5}$) has been linked to various health disorders, including adverse effects on the nervous system. Rodent models provide a controlled platform to explore the pathophysiological mechanisms of $PM_{2.5}$-induced neurotoxicity. This systematic review synthesized evidence from 15 peer-reviewed studies retrieved from academic databases, focusing on: (1) impacts on brain health, (2) mechanisms of oxidative stress and neuroinflammation, (3) effects of combined exposures, and (4) potential therapeutic interventions. Findings showed that $PM_{2.5}$ exposure was associated with oxidative stress, neuroinflammation, and cognitive dysfunction, marked by beta-amyloid accumulation, microglial activation, and blood–brain barrier disruption through multiple molecular pathways. Interactions with other factors—such as high-cholesterol diets and co-exposure to pollutants like formaldehyde—exacerbated these effects. Several antioxidants, including melatonin, vitamin E, red ginseng, and baicalin-geniposide, demonstrated neuroprotective potential by modulating inflammatory pathways and improving cognition. Species differences (rats vs. mice) indicated variability in outcomes and limit generalizability. Overall, current evidence highlights the need for long-term and integrative research on $PM_{2.5}$ neurotoxicity and the development of

multi-target interventions. These findings may inform public health policies to reduce population-level exposure and emphasize the importance of integrating environmental monitoring with clinical research to protect vulnerable populations.

INTRODUCTION

Air pollution is one of the major environmental issues which adversely affects human health. Among various air pollutants, fine particulate matter with a diameter of less than 2.5 micrometers ($PM_{2.5}$) has received particular attention due to its ability to penetrate deep into the respiratory system. Once inhaled, $PM_{2.5}$ can enter systemic circulation and exert widespread effects throughout the body (Lu, Ling and Bian, 2017; Chen *et al.*, 2020; Xie *et al.*, 2021; Cano-Granda *et al.*, 2022; Peng, Li and Xu, 2022; Thangavel, Park and Lee, 2022; Garcia *et al.*, 2023; McCarron *et al.*, 2023; Zhang *et al.*, 2023).

A growing body of research has shown that $PM_{2.5}$ exposure contributes not only to respiratory and cardiovascular disorders but also has detrimental effects on the central nervous system (Cano-Granda *et al.*, 2022; Peng, Li and Xu, 2022; Garcia *et al.*, 2023). The primary mechanisms underlying the adverse effects of $PM_{2.5}$ on the brain include oxidative stress, neuroinflammation, and the blood-brain barrier disruption (Lu et al. 2017; Peng et al. 2022; Thangavel et al. 2022). $PM_{2.5}$-induced oxidative stress can lead to increased production of reactive oxygen species (ROS), which contributes to neuronal damage (Lu, Ling and Bian, 2017). In addition, $PM_{2.5}$-triggered neuroinflammatory responses play a role in the development of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases (Gong *et al.*, 2023; Xie *et al.*, 2025). Although the link between $PM_{2.5}$ and neurological disorders has been recognized, comprehensive understanding of the specific molecular mechanisms and the effects of combined exposures remains limited.

In recent years, studies using animal models—particularly rodents (rats and mice)—have provided valuable insights into how $PM_{2.5}$ affects brain health, as they allow precise control over dosage, duration, and exposure conditions, which is difficult to achieve in human epidemiological studies. Rodent models enable systematic exploration of pathophysiological mechanisms as well as potential therapeutic interventions in a controlled environment. However, despite the in-depth understanding gained from animal studies, there remain significant challenges in generalizing these findings to humans. Differences in metabolism, exposure duration, and the complexity of human living environments pose distinct barriers to translating experimental results into clinical contexts. Therefore, a more holistic approach is needed to fully understand the effects of $PM_{2.5}$ on the brain and to develop effective mitigation strategies.

This review aimed at systematically synthesizing and analyzing the existing literature on the effects of $PM_{2.5}$ exposure on the rodent brain in order to identify consistent patterns, knowledge gaps, and directions for future research. The analysis focuses on four main aspects: (1) the impact on brain health, (2) mechanisms of oxidative stress and neuroinflammation, (3) interactions with other environmental factors, and (4) potential

therapies or interventions which may mitigate the adverse effects of $PM_{2.5}$. Accordingly, the findings of this review were expected to contribute to a deeper understanding of how air pollutants affected the nervous system and to provide an evidence-based foundation for the development of more effective mitigation strategies in the future.

2. MATERIALS AND METHODS

This study was conducted using the Systematic Literature Review (SLR) method, following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The article selection process was systematically carried out through several stages, including identification, screening, eligibility assessment, and inclusion of relevant studies in the final analysis.

Several software tools and databases were utilized in this study, including Publish or Perish, Microsoft Excel, Mendeley Desktop, and the Scopus database. Publish or Perish was used to extract article metadata from Scopus, Microsoft Excel was employed to manage and filter the search results, and Mendeley Desktop was used for reference management. Scopus was selected as the sole database due to its credibility in indexing over 24,000 high-quality peer-reviewed journals. In addition, Scopus provided various scientific metrics, such as the h-index and citation counts, which supported the evaluation of publication impact and facilitate trend analysis relevant to this review.

The selection of articles in this review was based on predefined inclusion and exclusion criteria to ensure that only relevant studies were analyzed. Included articles were original research papers published in peer-reviewed scientific journals. Only studies written in English, available in full-text format, and published between 2015 and 2025 were considered for analysis. The primary focus of this review was the impact of $PM_{2.5}$ exposure on brain health in rodents (rats and mice); therefore, only studies which used rodent models (Rattus or Mus) met the inclusion criteria.

Of the 15 included studies, 13 employed mice as the primary in vivo model, one study used rats exclusively, and one combined rat in vivo experiments with mouse-derived microglial cell lines in vitro. To accommodate this distribution, the present review uses the broader term “rodents,” while stratifying results and noting inter-species differences where relevant.

Conversely, several categories of articles were excluded from this review. Literature reviews, editorials, and opinion pieces were not included, as they did not present empirical research findings. Studies involving subjects other than rodents—such as humans or other animal models—were also excluded from the analysis. In addition, articles available only in abstract form or those not accessible in full text, as well as studies published before 2015, were not considered in this review.

Search and Selection Strategy

The systematic review process began with a literature search conducted on the 5th of March 2025 using the Scopus database accessed via the Publish or Perish application. The keywords *"$PM_{2.5}$" AND "BRAIN"* were entered in the title field to ensure that only articles specifically addressing $PM_{2.5}$ and brain outcomes were identified. The initial search yielded 35 articles. After preliminary screening, 7 articles were excluded due to the unavailability of full-text access. Of the remaining 28 articles, full-text assessment was conducted, and 13 articles were eliminated: 2 were review papers and 11 did not specifically address $PM_{2.5}$ exposure in rodents. In total, 15 original research articles met all inclusion criteria and were included in this review.

The selection process was independently performed by two reviewers, with disagreements resolved through discussion and, when necessary, consultation with a third reviewer. The complete selection pathway was illustrated in the PRISMA flow diagram (Figure 1), which detailed the number of records identified, screened, excluded, and included, along with reasons for exclusion at each stage. A supplementary table (Supplementary Table S1) provided the full list of excluded full-text articles together with the corresponding reasons for their exclusion.

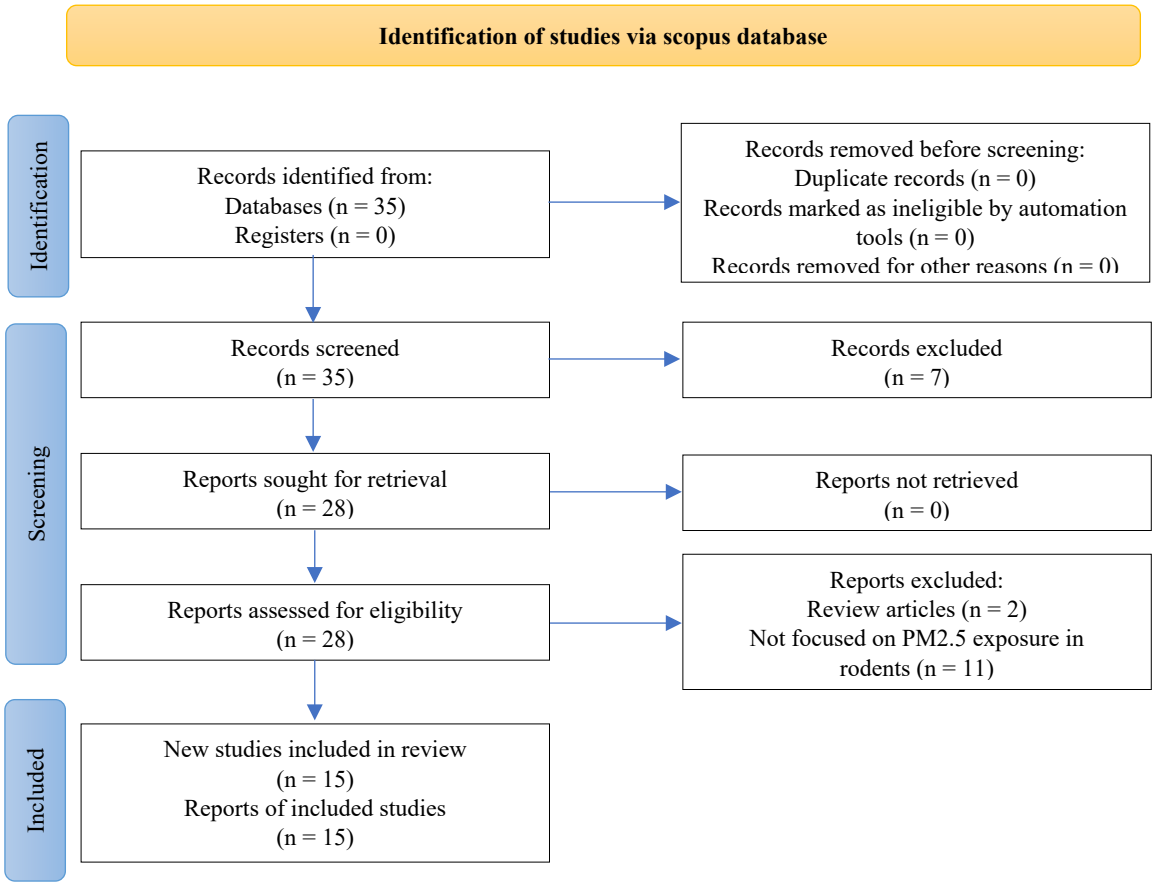

Fig. 1: PRISMA flow diagram of article selection in the systematic review on the effects of $PM_{2.5}$ on brain health in rodents

To enhance transparency and reproducibility, the key study-level characteristics of the 15 included articles were summarized in Supplementary Table S2. This table provided structured information for each study, including author and year, species/strain, sex and age of the animals, exposure type and dose, $PM_{2.5}$ source, sample sizes, endpoints, and principal findings.

The methodological quality of the included studies was further evaluated using the SYRCLE risk-of-bias tool, specifically adapted for animal intervention studies. Each study was assessed across domains such as random sequence generation, baseline characteristics, allocation concealment, random housing, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. The detailed study-level evaluations were presented in Supplementary Table S3, whereas an aggregated visual summary was provided in Figure 2.

Data Extraction and Analysis

After the selection process, the retrieved articles were exported to Microsoft Excel for preliminary screening based on duplication, title relevance, and abstract content. Articles which passed this stage were then further analyzed to ensure their compliance with the predefined inclusion and exclusion criteria. Eligible articles were then extracted to obtain information related to study design, $PM_{2.5}$ exposure methods, measured parameters, and key findings. The extracted data were descriptively analyzed to identify patterns of findings and the relationships between $PM_{2.5}$ exposure and its effects on the rodent brain.

To improve transparency, species information (rat vs. mouse) was explicitly extracted for each study. Results were stratified according to species when possible, and inter-species differences were highlighted in the synthesis, acknowledging that mouse models dominated the dataset while rat studies were relatively limited.

Based on the analysis, the studies included in this review were categorized into four main subthemes. The first subtheme addressed the effects of $PM_{2.5}$ exposure on rodent brain health, with a focus on neurological parameters such as brain morphological changes, cognitive function, and biomarkers of neural damage. The second subtheme explored the mechanisms of oxidative stress and neuroinflammation, highlighting molecular pathways involved in inflammatory and oxidative responses to $PM_{2.5}$ exposure. The third subtheme examined the impact of combined $PM_{2.5}$ exposure with other factors, noting the interactive effects of $PM_{2.5}$ with environmental stressors, co-pollutants, or genetic predisposition. The final subtheme evaluated therapeutic or interventional strategies to mitigate the adverse effects of $PM_{2.5}$ on the rodent brain, including both pharmacological and non-pharmacological approaches aimed at counteracting $PM_{2.5}$-induced neurotoxicity.

3. RESULTS

3.1. Effects of $PM_{2.5}$ Exposure on Rodent Brain Health

Exposure to fine particulate matter ($PM_{2.5}$) had been shown to exert multidimensional effects on rodent brain health, including significant structural, functional, and cellular alterations. Various studies had demonstrated that the neurotoxic effects of $PM_{2.5}$ could manifest across a broad spectrum, ranging from morphological changes in brain tissue to complex cognitive and behavioral impairments.

A total of 15 experimental studies met the inclusion criteria and were analyzed in this review. These studies varied in terms of rodent species, sex, age, exposure protocols, and sources of $PM_{2.5}$. A structured summary of the study-level characteristics, including exposure types, sample sizes, endpoints, and principal findings, was provided in Supplementary Table S2. This table served as the foundation for the thematic synthesis presented in the following subsections.

3.1.1. Structural and Morphological Effects on the Brain

$PM_{2.5}$ exposure had been associated with significant structural alterations in various regions of the mouse brain. Chronic exposure over 16 weeks was reported to induce morphological changes in neurons in several critical areas, including neuronal swelling in the dentate gyrus of the hippocampus and a reduction in the number of Purkinje cells in the cerebellum (Qin *et al.*, 2023). These structural damages were not limited to the cellular level but also affected the macroscopic architecture of the brain, as evidenced by a reduction in corpus callosum volume in mice exposed to $PM_{2.5}$ during the gestational period (Di Domenico *et al.*, 2020). Histopathological damage to brain tissue had also been reported in other studies, with untreated group showing more pronounced tissue injury, as demonstrated in a rat model (Zhang *et al.*, 2025). Furthermore, subchronic $PM_{2.5}$ exposure had been shown to cause significant neuronal loss in the cortical area, even in the absence of immediately detectable functional impairments (Lee *et al.*, 2021). These findings suggested that structural damage might precede overt functional deficits, underscoring the importance of early detection and long-term evaluation of the effects of $PM_{2.5}$ exposure.

3.1.2. Functional and Cognitive Impairments

Cognitive dysfunction was frequently reported as consequences of $PM_{2.5}$ exposure in mice. Studies utilizing the Morris Water Maze (MWM) had consistently demonstrated declines in spatial memory and learning abilities, with exposed mice requiring more time to locate the target platform (Liu, Zhang and Yang, 2019; Kang *et al.*, 2023; Panda *et al.*, 2023). These cognitive deficits were further supported by results from the Novel Object Recognition Test (NORT), which showed reduced cognitive performance following long-term exposure (90 days) to $PM_{2.5}$ containing high concentrations of polycyclic aromatic hydrocarbons (PAHs) at 25.48 ± 5.63 ng/m³, with an average $PM_{2.5}$ concentration of 54 ± 9.71 μg/m³ (Panda *et al.*, 2023). Synergistic effects on cognitive function were also observed under multi-pollutant exposure, where a combination of $PM_{2.5}$ and formaldehyde (FA) resulted in more pronounced impairments than single-pollutant exposure (Liu *et al.*, 2017; Liu, Zhang and Yang, 2019).

Cognitive disturbances were not limited to memory functions but also extended to other behavioral domains. Mice exposed to $PM_{2.5}$ during gestational and postnatal periods were reported to exhibit behavioral alterations, including increased locomotor activity and heightened exploratory behavior compared to control group. Studies employing the Y-maze and passive avoidance tests further suggested disruptions in the brain's cholinergic system, as evidenced by altered expression of AChE and ChAT proteins, both of which played critical roles in cognitive function (T. Y. Kim *et al.*, 2023). Combined exposure to a high-cholesterol diet (HCD) and $PM_{2.5}$ also appeared to induced more complex impairments, with increased latency in the buried pellet test, indicating deficits in cognitive and olfactory functions in female mice (Chen *et al.*, 2024). Other studies linked long-term exposure to $PM_{2.5}$ was associated with a heightened risk of neurological disorders such as Alzheimer's disease, Parkinson's disease, and other neurodegenerative conditions, as well as suggesting potential contributions to abnormal brain development which increased the risk of autism spectrum disorders (Wang *et al.*, 2020).

3.1.3. Cellular Impact and Neuroinflammation

At the cellular level, $PM_{2.5}$ exposure was frequently associated with a complex inflammatory response within mouse brain tissue. Mice exposed to $PM_{2.5}$ during gestational and postnatal periods were reported to show an increased number of microglia and astrocytes in the cortex, indicating activation of neuroinflammatory responses as a defense mechanism against pollutant-induced damage (Di Domenico *et al.*, 2020). In rats, exposure to the coarse $PM_{2.5–10}$ fraction was linked to greater biological toxicity compared to ultrafine particles (UFPM), particularly through elevated inflammatory and oncogenic biomarkers, as well as the accumulation of heavy metals in the brain (Ljubimova *et al.*, 2018).

Cellular changes also included evidence of antioxidant and mitochondrial dysfunction, which were associated with impairments in learning and memory performance in mouse models (J. H. Kim *et al.*, 2023). In Alzheimer's disease mouse models (APP/PS1), $PM_{2.5}$ exposure was observed to produce more complex effects, including significant alterations in lipid composition in the cortex and hippocampus (Lee *et al.*, 2022), as well as elevated levels of Aβ-42 protein and acetylcholinesterase (AChE), which were commonly regarded as hallmarks of Alzheimer's pathology. These biochemical changes were accompanied by behavioral impairments and ultrastructural brain alterations (Fu *et al.*, 2022).

This wide spectrum of damage—ranging from structural to functional levels—had prompted further research to further explore the molecular mechanisms underlying $PM_{2.5}$ neurotoxicity. Understanding oxidative stress and neuroinflammatory pathways remained key to explaining how particulate exposure might initiate the cascade of neural alterations identified in these studies.

3.2. Mechanisms of Oxidative Stress and Neuroinflammation

Exposure to $PM_{2.5}$ triggered a complex cascade involving oxidative stress and neuroinflammation as the primary mechanisms underlying neurological damage. These two pathological processes interacted and reinforced mutually one another, creating a vicious cycle which contributed to progressive neurodegeneration. A comprehensive understanding of the molecular pathways involved was essential for developing effective intervention strategies.

3.2.1. Oxidative Stress Pathways and Damage Biomarkers

Exposure to $PM_{2.5}$ was consistently associated with increased production of reactive oxygen species (ROS), which had been implicated as potential triggers of oxidative damage in mouse brain tissue. Elevated levels of oxidative stress biomarkers, such as malondialdehyde (MDA), had been detected in the olfactory bulb and hippocampus, accompanied by the accumulation of phosphorylated tau proteins—key indicators of neuronal damage (Lee *et al.*, 2021). The systemic effects of oxidative stress were further confirmed in studies where exposure to $PM_{2.5}$ at a concentration of 60 μg/mL enhanced significantly oxidative stress in various cell types, including microglial cells (HMC-3), indicating that polycyclic aromatic hydrocarbons (PAHs) in $PM_{2.5}$ played a crucial role in inducing both systemic and neural oxidative injury (Panda *et al.*, 2023). This oxidative damage was exacerbated by disturbances in cellular energy pathways and mitochondrial dysfunction, as evidenced by research showing a decline in mitochondrial activity essential for neuronal function (Kang *et al.*, 2023; T. Y. Kim *et al.*, 2023). Combined exposure to formaldehyde (FA) and $PM_{2.5}$ was reported to further aggravated ROS production and was associated with increased levels of Aβ1–42 and phosphorylated tau (Tau-P) proteins—two biomarkers linked to neurodegenerative conditions such as Alzheimer's disease (Liu, Zhang and Yang, 2019).

3.2.2. Activation of Neuroinflammatory Pathways

The neuroinflammatory response to $PM_{2.5}$ exposure was mediated through the activation of multiple complex molecular pathways. Several studies reported activation of NF-κB and JNK inflammatory signaling pathways, two critical routes involved in oxidative stress and apoptosis pathogenesis, following $PM_{2.5}$ exposure (J. H. Kim *et al.*, 2023). This activation was further supported by increased expression of inflammatory proteins such as TLR-4, MyD88, and TNF-α in mouse brain tissues, indicating a broad activation of inflammatory cascades (T. Y. Kim *et al.*, 2023). Microglia, the resident immune cells of the brain, played a central role in this neuroinflammatory response. An increase in the number of microglia and astrocytes in the cortex of mice exposed to $PM_{2.5}$ during gestational and postnatal periods was interpreted as reflecting an active inflammatory process, accompanied by an elevated frequency of micronuclei in glial cells—highlighting genotoxic effects (Di Domenico *et al.*, 2020). However, microglial responses appeared to be context-dependent. In certain conditions, the expression of Iba1—a marker of microglial activation—was found to be reduced, suggesting that neuroinflammatory signaling via microglia might be limited or biologically context-specific, particularly in aged mouse models which were physiologically more vulnerable (Lee *et al.*, 2021).

3.2.3. The Role of Proinflammatory Cytokines and Blood–Brain Barrier Disruption

$PM_{2.5}$ exposure was consistently associated with elevated levels of proinflammatory cytokines in mice, particularly IL-6 and TNF-α, which were considered key mediators in propagating systemic inflammatory responses to neural tissues (Fu *et al.*, 2022; Chen *et al.*, 2024). The elevated levels of these cytokines not only reflected localized activation of immune cells in the brain but also contributed to the disruption of blood–brain barrier (BBB) integrity. The combination of a high-cholesterol diet (HCD) and $PM_{2.5}$ exposure elevated synergistically inflammatory proteins such as COX-2 and MMP-9, directly impairing BBB integrity and exacerbating neurodegenerative conditions (Chen *et al.*, 2024). This BBB disruption was suggested to facilitate penetration of toxic molecules and systemic inflammatory mediators into the brain parenchyma potentially contributing to a self-perpetuating pathological loop. Evidence of this mechanism was demonstrated by studies showing the accumulation of pathological biomolecules such as beta-amyloid and α-synuclein—two critical indicators in the pathogenesis of Alzheimer's and Parkinson's diseases—which were mediated through the activation of oxidative stress-sensitive TRPM2 ion channels (Wang *et al.*, 2020).

3.2.4. Dysregulation of Lipid Metabolism and Membrane Integrity

A more subtle yet equally critical mechanism of damage involved the dysregulation of lipid metabolism and the disruption of neuronal cell membrane integrity. Widespread alterations in gene expression and lipid metabolism across various brain regions—particularly the hippocampus—indicated the involvement of cellular stress pathways and subchronic inflammation (Qin *et al.*, 2023). This dysregulation encompassed essential fatty acid metabolism, including alpha-linolenic acid, arachidonic acid, and linoleic acid, all of which played key roles in inflammatory regulation and neuronal homeostasis. The reduction of glycerophospholipids and sphingolipids, which were crucial for maintaining neuronal membrane integrity and signal transduction, reflected fundamental impairments at the structural cellular level (Lee *et al.*, 2022). This imbalance was associated with energy pathway dysregulation and myelin system disruption, phenomenon also observed in chronic neurodegenerative conditions linked to oxidative stress.

3.2.5. Specificity of Particle Size in Inflammatory Response

Research had revealed that the inflammatory response was not uniform across different particle size fractions of $PM_{2.5}$. In rats, exposure to $PM_{2.5}$–PM10 was specifically associated with increased expression of genes related to inflammation and carcinogenic processes, indicating the activation of molecular inflammatory pathways in response to toxic components within the particles—particularly heavy metals and endotoxins (Ljubimova *et al.*, 2018). Interestingly, this inflammatory response was not observed following exposure to ultrafine particles (UFPM), reinforcing the hypothesis that specific chemical constituents present in the $PM_{2.5}$–PM10 fraction might play an important role in triggering neuroinflammatory mechanisms.

3.2.6. Effects on Neurotrophic Factors and the Cholinergic System

$PM_{2.5}$ exposure in mice also had been associated with disruptions in endogenous regulatory systems responsible for neuroplasticity and neuroprotection. Gene expression analysis revealed a reduction in brain-

derived neurotrophic factor (BDNF) levels in the hippocampus—a critical factor for neuronal survival, dendritic growth, and synapse formation (Di Domenico *et al.*, 2020). This disruption was compounded by a decrease in choline acetyltransferase (ChAT) levels, which was essential for acetylcholine synthesis and often considered indicative of cholinergic system impairment—a feature linked to chronic oxidative stress and Alzheimer's disease pathology (Fu *et al.*, 2022).

Understanding these molecular mechanisms provided a foundation for exploring how the complexity of real-world exposure—particularly involving $PM_{2.5}$ in combination with other pollutants and biological factors—might modulate or exacerbate the identified pathological pathways.

3.3. Combined Effects of $PM_{2.5}$ Exposure with Other Factors

In real-world conditions, exposure to $PM_{2.5}$ rarely occured in isolation. Instead, it interacted with various environmental, biological, and chemical factors which could modulate or exacerbate its neurotoxic effects. Understanding these synergistic interactions was crucial for accurately assessing the true neurological risks posed by particulate air pollution, particularly given the multifactorial exposure complexity faced by populations in everyday life.

3.3.1. Combination with Other Atmospheric Pollutants

Simultaneous exposure to $PM_{2.5}$ and other air pollutants had been reported to exert significant synergistic effects on neurological health in mice. The combination of formaldehyde (FA) and $PM_{2.5}$, in particular, demonstrated more detrimental outcomes compared to single exposures, exacerbating oxidative stress, histological damage, and the accumulation of neurotoxic proteins. These effects extended beyond the hippocampus to include the cerebral and prefrontal cortex (Liu, Zhang and Yang, 2019). This synergy manifested as more severe cognitive impairments, as evidenced by prolonged escape latency in the Morris Water Maze test compared to both control group and those exposed to $PM_{2.5}$ or FA alone (Liu *et al.*, 2017). One of the most concerning aspects of this multi-pollutant exposure was the disruption of blood–brain barrier (BBB) integrity. Increased BBB permeability was exclusively observed in the multi-pollutant group, as indicated by Evans Blue dye accumulation and depletion of the tight junction protein ZO-1 (zonula occludens-1), suggesting that pollutant combinations cause both structural and functional damage to the brain's protective barrier (Liu *et al.*, 2017). Such BBB compromise was suggested to facilitated the infiltration of harmful molecules into the brain parenchyma, potentially contributing to progressive neurodegenerative processes.

3.3.2. Interaction with Intrinsic Chemical Components of $PM_{2.5}$

The toxicological complexity of $PM_{2.5}$ stemed not only from its combination with external pollutants but also from the synergistic interactions among its intrinsic chemical constituents. The presence of polycyclic aromatic hydrocarbons (PAHs) within $PM_{2.5}$ played a key role in enhancing the particle's toxicity, inducing more severe oxidative stress and inflammation compared to $PM_{2.5}$ with lower PAH content (Panda *et al.*, 2023). These

effects were not limited to the nervous system but also impacted the respiratory and gastrointestinal systems, indicating that combinational exposure exerts complex, multi-organ effects. Further research highlighted the significance of combinational exposure by demonstrating that inflammatory responses and tumorigenic potential only emerged in rats exposed to $PM_{2.5}$–PM10 particles containing a mixture of heavy metals and endotoxins (Ljubimova *et al.*, 2018). High endotoxin concentrations in air samples were suspected to be a key factor in triggering molecular pathways leading to inflammation and possible tumorigenesis, suggesting that interactions among chemical constituents within airborne particulate fractions played a determining role in their overall toxicity.

3.3.3. Modulation by Dietary and Metabolic Factors

The interaction between $PM_{2.5}$ and dietary factors introduced additional complexity into the pathogenesis of neurotoxicity. The combination of a high-cholesterol diet (HCD) and $PM_{2.5}$ had been reported to exert synergistic effects in exacerbating brain damage and cognitive dysfunction, which were significantly more severe than those caused by each factor alone (Chen *et al.*, 2024). This synergistic effect was manifested not only in cognitive deficits but also in more extensive pathological alterations in the brain tissue of female mice, including a more dramatic reduction in neuronal count. The underlying mechanism of this diet-pollutant interaction involved dysregulation of complex metabolic pathways. Analyses reveal that $PM_{2.5}$ might affect various interconnected biochemical routes, including bile acid biosynthesis, de novo fatty acid synthesis, and beta-oxidation of saturated fatty acids (Qin *et al.*, 2023). The strong correlation between differentially expressed genes (DEGs) and lipid profiles suggested that $PM_{2.5}$ interacted with biological predisposition factors, particularly the susceptibility of specific brain regions to metabolic dysregulation.

3.3.4. Influence of Age and Biological Vulnerability

Age played a crucial role in determining the magnitude of neurological responses to $PM_{2.5}$ exposure. Early-life exposure had a disproportionately large impact on brain development, suggesting a critical interaction between age and $PM_{2.5}$ exposure (Wang *et al.*, 2020). This window of vulnerability suggested that the timing of exposure might be an important determinant to the severity of neurological outcomes. At the opposite end of the age spectrum, studies using aged mouse models—biologically predisposed to vulnerability—had shown that physiological conditions could modulate responses fundamentally to $PM_{2.5}$ exposure (Lee *et al.*, 2021). Interestingly, in older mice, the lack of microglial activation typically observed following $PM_{2.5}$ exposure suggested that age or physiological status might alter the nature of the neuroinflammatory response. This finding opened avenues for further investigation into how $PM_{2.5}$ interacted with age-related or genetic susceptibility factors.

3.3.5. Interaction with Genetic Predisposition

The use of transgenic mouse models provided critical insights into the interaction between genetic vulnerability and environmental exposure. The APP/PS1 transgenic mouse model for Alzheimer's disease had demonstrated that $PM_{2.5}$ exposure exacerbated conditions already genetically predisposed to neurodegeneration (Fu *et*

al., 2022). These findings suggested that genetic susceptibility might act as an amplifying factor, intensifying the neurotoxic effects of $PM_{2.5}$ and resulting in more severe phenotypes compared to exposure in individuals with a normal genetic background. This gene–environment interaction had significant clinical implications, as populations with genetic predispositions to neurodegenerative disorders might experience accelerated decline when exposed to particulate air pollution. These insights underscored the importance of risk stratification based on genetic profiles in public health assessments of air pollution impacts.

3.3.6. Systemic Effects and Inter-Organ Interactions

The complexity of $PM_{2.5}$ exposure was further manifested through inter-organ interactions which could amplify neurological impacts. Although not involving explicit combinations of pollutants, studies had highlighted the lung–brain axis as a systemic consequence of $PM_{2.5}$ exposure (J. H. Kim *et al.*, 2023). Pulmonary dysfunction induced by fibrosis had the potential to exacerbate cerebral hypoxia, which in turn might contribute to cognitive decline—an exemplar of how a single type of environmental exposure could be linked to cross-organ pathological cascades. These systemic interactions underscored the importance of a holistic approach in understanding $PM_{2.5}$ toxicology, where primary effects on one organ could induce secondary impacts on target organs through systemic mediators or disruptions in physiological homeostasis.

The multifactorial complexity of these interactions reinforced the need for intervention strategies which not only addressed the isolated effects of $PM_{2.5}$ but also took into account combinational exposure scenarios and individual vulnerability factors having been identified.

3.4. Effective Therapies or Interventions to Mitigate the Adverse Effects of $PM_{2.5}$ Exposure on the Mouse Brain

Given the complexity of the pathological mechanisms induced by $PM_{2.5}$ exposure, the development of therapeutic intervention strategies was crucial for mitigating its neurotoxic effects. Various approaches had been explored, ranging from conventional antioxidant interventions to phytotherapies which simultaneously target multiple molecular pathways. The effectiveness of these interventions was evaluated not only by improvements in biochemical parameters but also through the restoration of cognitive function and structural protection of brain tissue.

3.4.1. Interventions of Conventional Antioxidant

- Melatonin as Neuroprotectant

Melatonin was reported to demonstrate protective effects against the neurotoxic impact of $PM_{2.5}$ through multiple mechanisms of action. At the cellular level, treatment with 100 μM melatonin reduced significantly microglial activation and inflammation in cell cultures, indicating a direct anti-inflammatory effect (Panda *et*

al., 2023). Translation to in vivo models yielded similarly promising outcomes, with administration of 50 mg/kg melatonin for 90 days in mice resulting in substantial reductions in neuroinflammation and neurodegeneration.

Most notably, melatonin treatment not only provided protection at the molecular and histological levels but also was reported to ameliorate cognitive deficits in $PM_{2.5}$-exposed mice. Improved performance in the Morris Water Maze (MWM) and Novel Object Recognition Test (NORT) reinforced the potential of melatonin as a therapeutic intervention for mitigating the effects of air pollution on the central nervous system (Panda *et al.*, 2023).

- Vitamin E and Antioxidant Protection

Vitamin E demonstrated a complementary neuroprotective profile through classical antioxidant mechanisms which targeted oxidative stress as an upstream trigger of neuronal damage. Treatment with vitamin E reduced significantly histological damage, reactive oxygen species (ROS) activation, and the accumulation of pathological proteins Aβ1–42 and phosphorylated Tau (Tau-P) (Liu, Zhang and Yang, 2019). These protective effects were manifested in better preservation of cellular architecture, with significantly higher neuronal counts observed in the cerebral cortex and prefrontal areas of the vitamin E-treated group. These findings reinforced the therapeutic potential of vitamin E as an effective antioxidant, particularly in addressing the effects of combined exposure to formaldehyde and $PM_{2.5}$. This suggested that conventional antioxidant approached remain relevant in multi-pollutant exposure scenarios (Liu, Zhang and Yang, 2019).

3.4.2. Phytotherapy and Multi-Target Natural Extracts

- Red Ginseng Extract (RGE) and Systemic Protection

Red Ginseng Extract (RGE) demonstrated a comprehensive therapeutic approach by modulating multiple molecular pathways simultaneously. RGE improved endogenous antioxidant systems and mitochondrial function while suppressing inflammation and apoptosis through the regulation of the NF-κB and JNK signaling pathways—both of which were critical in the pathogenesis of oxidative stress (J. H. Kim *et al.*, 2023). Remarkably, RGE also prevented pulmonary fibrosis by modulating the TGF-β1 pathway, a key regulator of tissue responses to injury, indicating that its protective effects extended beyond the nervous system to include $PM_{2.5}$'s primary target organs. The cognitive efficacy of RGE had been validated through improvements in learning and memory performance in mice, as evidenced by enhanced outcomes in the Morris Water Maze and Y-maze tests. This combination of neuroprotective and pulmonary protective effect suggested RGE's potential as a natural intervention which might address the systemic neurotoxicity induced by $PM_{2.5}$ exposure (J. H. Kim *et al.*, 2023).

- Herbal Mixture of Artemisia argyi and Saururus chinensis (AASC)

A combinatorial herbal approach using extracts of *Artemisia argyi* and *Saururus chinensis* (AASC) was reported to be effective in ameliorating $PM_{2.5}$-induced cognitive dysfunction through multifaceted mechanisms (Kang *et al.*, 2023). AASC significantly improved long-term memory and learning ability in mice, reduced

oxidative stress and inflammation levels, and inhibited amyloid beta accumulation and the inflammation-apoptosis signaling cascade. Bioactive component analysis identified key compounds such as dicaffeoylquinic acid isomers and quercetin-3-glucoside, which exerted potent antioxidant and anti-inflammatory effects. The synergistic contribution of these various bioactive compounds supported a comprehensive neuroprotective effect, underscoring the advantages of complex phytochemical strategies over single-compound interventions (Kang *et al.*, 2023).

- Baicalin and Geniposide (BC/GD) as Anti-Neuroinflammatory Agents

The combination of Baicalin and Geniposide (BC/GD) was reported to exert neuroprotective effects through targeted modulation of neuroinflammation. Treatment with BC/GD led to measurable improvements in cognitive function and memory in rats and mice, as assessed by the Morris Water Maze, accompanied by a reduction in brain tissue damage caused by $PM_{2.5}$ exposure (Zhang *et al.*, 2025). BC/GD attenuated specifically microglial inflammation by downregulating pro-inflammatory M1 markers such as iNOS and TNF-α, while upregulating anti-inflammatory M2 markers including Arg-1 and IL-10. Furthermore, BC/GD modulated leukotriene signaling by suppressing the expression of the 5-LOX gene, which was responsible for leukotriene B4 production, thereby reducing central nervous system inflammatory responses (Zhang *et al.*, 2025). This mechanistic precision suggested BC/GD's potential as a targeted therapeutic agent against air pollution-induced neuroinflammation and cognitive impairment.

3.4.3. Innovative Approaches: Marine Organism-Based Therapy

- Codium fragile and Gut-Brain Axis Modulation

Aqueous extract of *Codium fragile* (AECF) represented an innovative therapeutic approach through modulation of the gut-brain axis as a novel intervention target (T. Y. Kim *et al.*, 2023). AECF demonstrated significant protective effects against $PM_{2.5}$-induced cognitive dysfunction via multiple integrated mechanisms. Directly, AECF was able to downregulate inflammatory protein expression and reduce oxidative stress by enhancing mitochondrial activity and lowering reactive oxygen species (ROS) levels. Additionally, AECF restored cholinergic system protein expression, improved cognitive function, and preserved gut health through modulation of the gut microbiota and increased production of short-chain fatty acids (SCFAs). This modulation of the gut-brain axis suggested that interventions targeting the gut microbiome might offer indirect yet significant neuroprotective effects, indicating a possible holistic therapeutic approach (T. Y. Kim *et al.*, 2023).

3.4.4. Biomarkers and Molecular Targets for Precision Intervention

A more forward-looking approach involved identifying specific molecular targets for precision medicine interventions. Recent studies had successfully identified seven microRNAs (miRNAs) and six genes whose expression levels were significantly altered following $PM_{2.5}$ exposure (Fu *et al.*, 2022). These molecules might serve dual potential: as biological markers for early detection and as potential molecular targets for therapeutic

intervention. The identification of these molecular signatures might serve as a foundation for developing personalized intervention strategies or monitoring the efficacy of ongoing therapeutic treatments. Furthermore, these molecular targets might form the basis for the development of more specific drug discovery efforts in the context of air pollution-induced Alzheimer's disease (Fu *et al.*, 2022).

3.4.5. Comparative Evaluation of Efficacy and Mechanism

A comparative analysis of various intervention strategies revealed that multi-target approaches generally exhibited superior efficacy compared to single-pathway interventions. While conventional antioxidants such as melatonin and vitamin E were effective in mitigating oxidative damage, complex phytotherapeutic agents like Red Ginseng Extract (RGE) and the Artemisia argyi–Saururus chinensis combination (AASC) demonstrated more comprehensive protection by modulating multiple biological pathways simultaneously.

Notably, the most effective interventions appeared to be those that not only directly targeted brain tissue but also addressed systemic effects and other vulnerable organs. RGE's ability to concurrently protect both lung and brain tissues, and AECF's modulation of the gut–brain axis, indicated that holistic strategies accounting for the interconnection of biological systems yielded optimal therapeutic outcomes.

The diversity of identified intervention strategies—from conventional antioxidants to gut–brain axis modulation—provided a foundation for an integrative analysis which linked the spectrum of $PM_{2.5}$-induced effects, their underlying mechanisms, the complexity of multifactorial exposures, and the potential therapeutic solutions within a broader biomedical context.

A structured summary of therapeutic interventions, including dose, route, timing, sample size, effect sizes, and risk-of-bias scores, was presented in Table 1. While most interventions demonstrated neuroprotective effects against $PM_{2.5}$ exposure, the methodological limitations—particularly small sample sizes and incomplete blinding—necessitated cautious interpretation of efficacy.

Table 1: Detailed summary of therapeutic interventions evaluated in rodent models of $PM_{2.5}$-induced neurotoxicity

Intervention	Type	Dose & Route	Timing (relative to $PM_{2.5}$ exposure)	Rodent model (species/strain, n/group)	Primary Mechanism of Action	Key Outcomes (effect size if reported)	Risk-of-bias (SYRCLE)
Melatonin	Pharmacological	50 mg/kg, oral	Co-treatment during 90 days $PM_{2.5}$ exposure	Mouse (C57BL/6), n=20/group	Antioxidant, anti-inflammatory; inhibits microglial activation, improves mitochondrial function	↓ IL-6, TNF-α, ROS; improved MWM and NORT performance	High concern (no blinding, unclear randomization)

Vitamin E	Pharmacological	50 mg/kg, oral	Co-treatment during 7-day $PM_{2.5}$ + FA exposure	Mouse (C57BL/6), n=3/group	Reduces ROS and oxidative stress; inhibits Aβ and Tau accumulation	↓ ROS, MDA, COX-2; ↓ GFAP/Iba1 activation; improved cognition	Some concern (very small n, randomization not reported)
Red Ginseng Extract (RGE)	Phytotherapy	50 & 100 mg/kg, oral	Co-treatment for 12 weeks $PM_{2.5}$ exposure	Mouse (Balb/c), n not specified	Antioxidant, anti-inflammatory; modulates NF-κB/JNK and TGF-β1 pathways; prevents apoptosis	↓ Aβ, p-tau, TNF-α; improved memory; lung protection	Some concern (unclear blinding, incomplete reporting)
Codium fragile Extract (AECF)	Marine algae extract	50 & 100 mg/kg, oral	Co-treatment for 12 weeks $PM_{2.5}$ exposure	Mouse (Balb/c), n=8/group	Antioxidant, modulates gut–brain axis via microbiota and SCFAs	↓ MPO, MDA, IL-6; restored microbiota; improved cholinergic function & cognition	Some concern (no blinding, small n)
AASC (Artemisia argyi & Saururus chinensis)	Combined phytotherapy	50 & 100 mg/kg, oral	Co-treatment for 12 weeks $PM_{2.5}$ exposure	Mouse (Balb/c), n=9/group	Antioxidant, anti-inflammatory; reduces Aβ accumulation; regulates apoptosis	Reduced neuroinflammation, improved memory tasks	Some concern (randomization reported, blinding unclear)
Baicalin & Geniposide (BC/GD)	Flavonoid & iridoid	7.5–30 mg/kg, oral	Co-treatment for 2–4 months $PM_{2.5}$ exposure	Rat (Sprague-Dawley), n=150 across 12 groups; mouse-derived microglial cells in vitro	Anti-inflammatory and neuroprotective; modulates M1/M2 microglial polarization, reduces 5-LOX/LTB4	Improved MWM; ↓ TNF-α, ↑ IL-10; reduced neuroinflammation	Moderate concern (randomization reported, dropouts not explained)
miRNA & Gene Target Identification	Molecular biomarker	n/a	n/a	Mouse (C57BL/6), n not specified	Biomarker discovery rather than intervention	Identified 7 miRNAs & 6 gene targets relevant to $PM_{2.5}$-induced Alzheimer pathology	n/a (not an intervention efficacy study)

Abbreviations:

- MWM: *Morris Water Maze*
- NORT: *Novel Object Recognition Test*
- ROS: *Reactive Oxygen Species*
- Aβ: *Beta-amyloid Protein*
- Tau: *Phosphorylated Tau Protein*
- SCFAs: *Short-Chain Fatty Acids*
- 5-LOX: *5-Lipoxygenase*
- RGE: Red Ginseng Extract

- AASC: *Artemisia argyi* and *Saururus chinensis*
- BC/GD: Baicalin and Geniposide
- AECF: Aqueous Extract of *Codium fragile*

The pathways of $PM_{2.5}$-induced neurotoxicity in rodents—encompassing oxidative stress and neuroinflammation, the compounded effects of multi-pollutant exposures, and various therapeutic strategies to counteract these impacts—are illustrated in Figure 2.

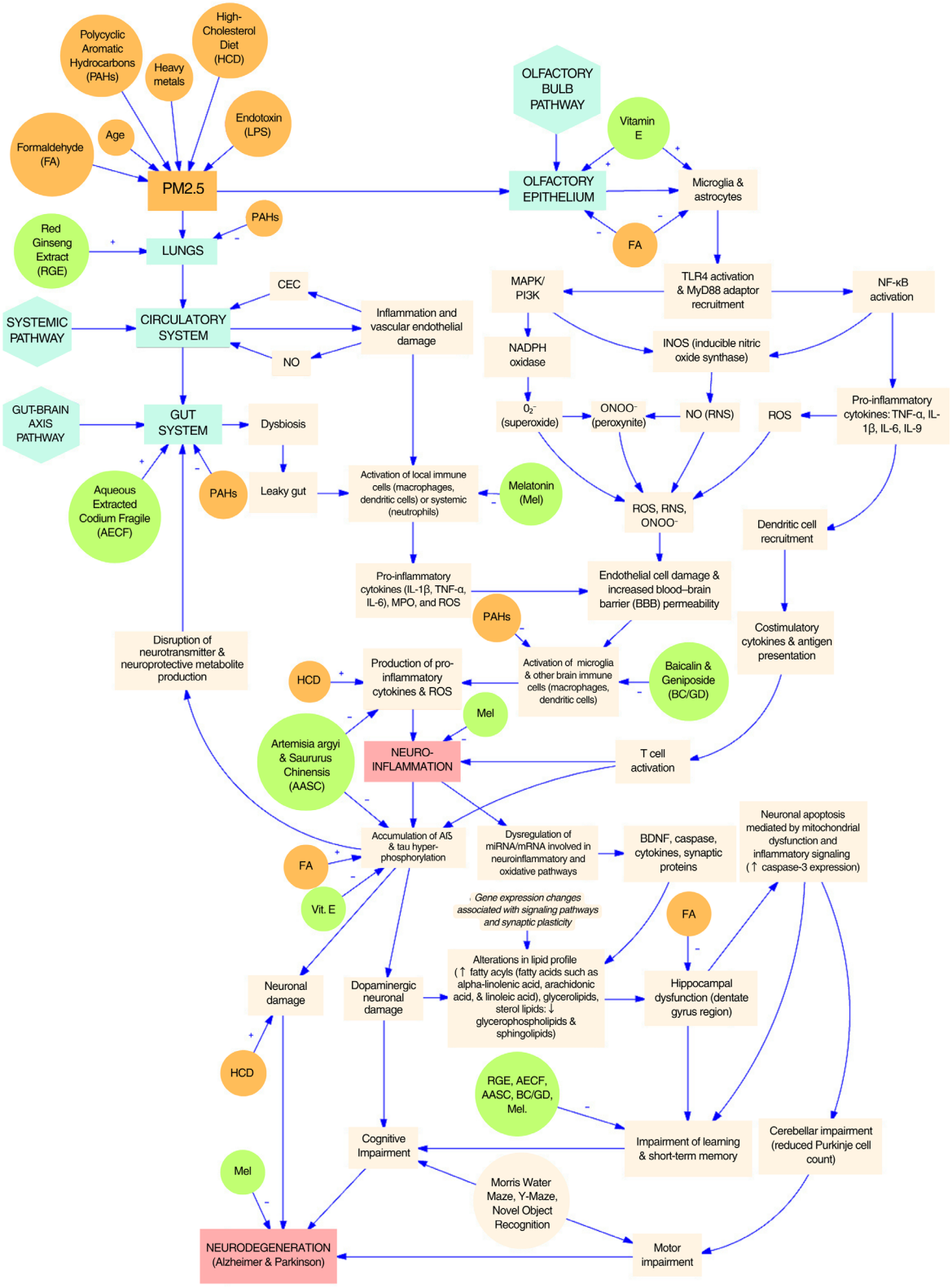

Fig. 2: Pathways of $PM_{2.5}$ Exposure Impact on Brain Health in Rodents.

3.5. Risk of Bias Assessment

The methodological quality of the included studies was evaluated using the SYRCLE risk-of-bias tool, which was specifically adapted for animal intervention studies. Overall, most studies did not provide sufficient details regarding random sequence generation or allocation concealment, and blinding of outcome assessment was seldom described. Random housing procedures were also infrequently reported. By contrast, baseline characteristics and completeness of outcome data were generally adequate, and selective outcome reporting was rarely evident. These patterns suggested a moderate overall risk of bias across the body of evidence, highlighting the need for more rigorous methodological reporting in future experimental studies. A detailed, study-level evaluation was provided in Supplementary Table S3, whereas an aggregated summary of domain-level assessments was illustrated in Figure 3.

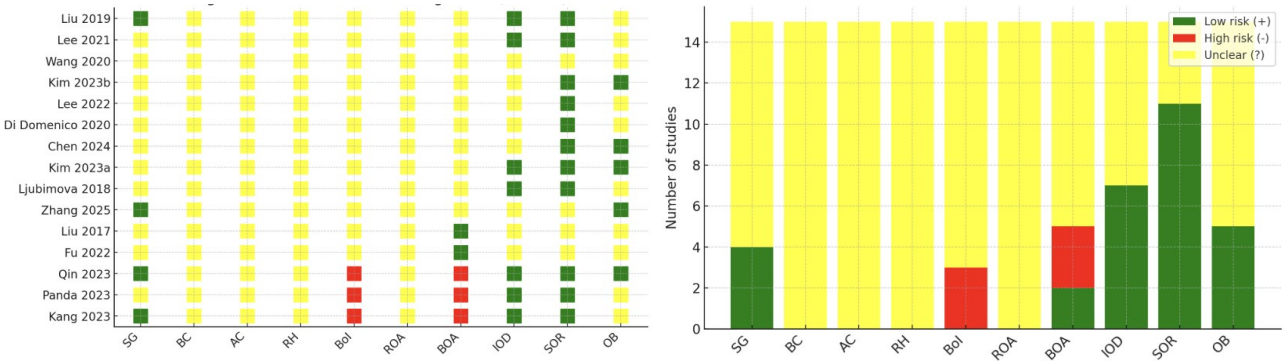

Fig. 3: Risk-of-bias assessment of included studies using the SYRCLE tool. (A) Traffic-light plot showing judgments across 10 domains. (B) Summary bar chart indicating frequent underreporting of randomization, allocation concealment, and blinding, consistent with a moderate overall risk of bias.

3.6. Variation by Exposure Type and Duration

The included studies employed diverse exposure modalities, including whole-body inhalation, intranasal instillation, and real-ambient exposure models. Inhalation studies, which most closely mimic physiological exposure pathways, consistently demonstrated neuronal and behavioral impairments at environmentally relevant concentrations (e.g., Kang et al., 2023; Qin et al., 2023). Instillation models, although advantageous for delivering controlled doses, frequently applied supra-environmental concentrations that induced pronounced but often acute oxidative and inflammatory responses (e.g., Liu et al., 2017). In contrast, real-ambient exposure studies provided ecological validity by capturing complex pollutant mixtures, yet introduced variability due to fluctuating environmental conditions and co-pollutant interactions (e.g., Ljubimova et al., 2018).

Differences were also apparent with respect to exposure duration and concentration. Acute exposures (ranging from a single instillation to ≤2 weeks of inhalation) generally produced transient oxidative stress, inflammatory changes, and mild behavioral alterations (e.g., Fu et al., 2022). Subchronic exposures (4–12

weeks) revealed more sustained oxidative damage, glial activation, and early signs of synaptic impairment (e.g., Lee et al., 2022). Chronic exposures (>12 weeks), particularly those involving inhalation or real-ambient models, were most strongly associated with progressive cognitive decline, structural brain alterations, and molecular signatures of neurodegeneration (e.g., Di Domenico et al., 2020; Lee et al., 2021). Collectively, these findings indicated that both the modality and duration of exposure substantially influence the observed neurotoxic outcomes of $PM_{2.5}$.

3.7. Critical Appraisal of Outcomes

The 15 included studies employed a broad range of behavioral, histological, and biochemical endpoints to evaluate the neurotoxic effects of $PM_{2.5}$. Behavioral tests were reported in 8 studies, of which 7 documented significant impairments in memory, learning, or anxiety-like behaviors, while 1 study found no clear functional deficits despite histological evidence of neuronal damage. Histological analyses were performed in 10 studies, with nearly all reporting structural abnormalities such as neuronal loss, corpus callosum thinning, or mitochondrial damage. Biochemical and molecular assays were the most frequently applied, appearing in 13 studies; these consistently demonstrated oxidative stress, inflammatory responses, and altered expression of proteins linked to neurodegeneration (e.g., β-amyloid, phosphorylated tau, TNF-α, IL-6).

Despite this consistency, several methodological weaknesses might affect the reliability of outcomes. Many studies used small sample sizes (often <10 animals per group), limiting statistical power. Blinding of outcome assessment was rarely reported, raising concerns about observer bias, particularly in behavioral scoring and histological evaluations. Furthermore, the heterogeneity of assays—ranging from diverse behavioral paradigms to variable biochemical markers—complicated direct comparison across studies.

A detailed breakdown of endpoints and findings was available in Supplementary Table S2, while methodological limitations identified through the SYRCLE risk-of-bias tool were summarized in Supplementary Table S3 and Figure 3.

4. DISCUSSION

4.1. Synthesis of Findings

This systematic literature review indicated that $PM_{2.5}$ exposure was associated with significant neurotoxic effects on the brains of rodents (rats and mice), with oxidative stress and neuroinflammation serving as the primary underlying mechanisms. Analysis of 15 selected studies consistently reported that direct exposure to $PM_{2.5}$ under controlled conditions was link to progressive structural and functional brain impairments, including synaptic damage, cognitive dysfunction, β-amyloid accumulation, and tau protein hyperphosphorylation—all

of which were hallmark features of neurodegenerative pathology. The spectrum of damage encompassed reduced corpus callosum volume, neuronal loss in cortical regions, and morphological alterations in the dentate gyrus of the hippocampus and the cerebellum.

Alarmingly, findings indicated that combined exposure to $PM_{2.5}$ and other environmental factors—such as high-cholesterol diets, formaldehyde, and heavy metals—appeared to produced synergistic effects exceeding simple additive outcomes. These interactions particularly exacerbated blood–brain barrier (BBB) disruption, amplifed systemic inflammatory responses, and accelerated neuronal apoptosis. Most notably, BBB integrity was specifically compromised only under combinational exposures, suggesting that single-pollutant risk assessments might substantially underestimate the true neurological threat. Age and genetic susceptibility further modulated these responses, with early-life exposure and genetic predispositions (e.g., APP/PS1 models) showing disproportionately heightened vulnerability.

On the intervention side, a spectrum of plant-derived bioactive compounds demonstrated promising protective effects through multi-target approaches. While conventional antioxidants such as melatonin and vitamin E were effective in mitigating primary oxidative damage, complex phytotherapeutic strategies exhibited superior protection by simultaneously modulating multiple pathological pathways. Particularly innovative were approaches targeting the gut–brain axis (e.g., AECF) and systemic protection (e.g., RGE, which concurrently safeguarded both the lungs and brain), indicating that holistic interventions accounting for the interconnection of biological systems yielded the most optimal therapeutic outcomes.

Nevertheless, although the overall evidence consistently supported $PM_{2.5}$-induced neurotoxicity in rodents, the reliability of specific outcomes required cautious interpretation. Behavioral assays, though widely applied, were often performed with small sample sizes and without reported blinding, raising concerns of observer bias. Histological analyses generally revealed structural damage, yet inconsistencies in staining protocols and semi-quantitative scoring methods might have introduced subjectivity. Biochemical endpoints proved the most reproducible, consistently demonstrating oxidative stress and neuroinflammatory responses, although variation in biomarker selection complicated direct cross-study comparisons. Together, these methodological weaknesses highlighted the need for larger, well-controlled studies employing standardized protocols and rigorous blinding to strengthen confidence in outcome reliability.

4.2. Comparison with Previous Studies

The findings of this review generally confirmed those of previous studies suggesting that $PM_{2.5}$ exposure was associated with detrimental effects on brain health in rodents (rats and mice), particularly through oxidative stress, microglial activation, and inflammatory pathways. Earlier studies (Kulas *et al.*, 2018; Zhang *et al.*, 2018; Liu *et al.*, 2019; Zheng *et al.*, 2019; Zhou *et al.*, 2020; Ferreira *et al.*, 2022; Thiankhaw, Chattipakorn and Chattipakorn, 2022; F. Liu *et al.*, 2023; Hou *et al.*, 2023; X. Q. Liu *et al.*, 2023; Gui *et al.*, 2024; Jaiswal and

Singh, 2024) highlighted that animal models in laboratory environments enabled controlled observation of potensial toxic effects—unlike epidemiological approaches in humans, which was prone to external confounders such as socioeconomic status, lifestyle, and multi-pollutant exposure.

However, there was notable variation in the biological responses reported across studies. Some previous research reported beta-amyloid accumulation and tau hyperphosphorylation as possible effects of $PM_{2.5}$ exposure, particularly in relation to Alzheimer's disease pathology (Wang *et al.*, 2020; Patten *et al.*, 2021; Liu *et al.*, 2024; Kang *et al.*, 2025). In contrast, other studies did not observe significant changes in these biomarkers, especially when animals were exposed to lower doses or for shorter durations (Chen *et al.*, 2022; Thiankhaw, Chattipakorn and Chattipakorn, 2022). These discrepancies suggested that the intensity and duration of exposure, along with the type and genetic background of the test animals (e.g., transgenic vs. wild-type strains), played a critical role in determining the observed outcomes.

Furthermore, although the activation of inflammatory pathways was a consistent finding, there remained significant differences in the mechanisms mediating the neurotoxic effects, particularly concerning the role of the peripheral immune system and the gut–brain axis. Recent studies suggested that $PM_{2.5}$-related gut microbiota dysbiosis might contribute to elevate cytokine production and neuroinflammation via systemic communication through the gut–brain axis. However, the specific mechanisms underlying this pathway remained poorly understood, and further research was needed to clarify whether these effects were primary (direct) or secondary (a consequence of systemic responses) to air pollution exposure.

Previous studies had also highlighted the interaction between $PM_{2.5}$ and other predisposing factors such as diet, age, metabolic status, and genetic background, which collectively appeared to amplify its neurotoxic effects. These findings supported the present review's observation which combined exposures—such as $PM_{2.5}$ with formaldehyde or a high-cholesterol diet—tend to produce synergistic and more damaging effects compared to single-agent exposures.

Thus, this review not only reinforced existing evidence but also expanded the current understanding of the biological complexity of responses to $PM_{2.5}$ exposure. It underscored the necessity of adopting a multidimensional approach when investigating the impact of air pollution on the central nervous system.

Our findings are broadly consistent with prior systematic reviews and narrative syntheses that highlighted the role of $PM_{2.5}$ in triggering oxidative stress, neuroinflammation, and subsequent cognitive impairments in animal models. Earlier studies have also emphasized the vulnerability of specific brain regions such as the hippocampus and cortex, which are particularly sensitive to particulate matter–induced injury. The present review extends these observations by incorporating evidence from more recent publications and by examining the synergistic effects of co-exposures and dietary factors, aspects which were not consistently addressed in earlier reviews. Nevertheless, the majority of included studies relied on short-term or subchronic exposure

models, which may not adequately reflect the cumulative impact of long-term $PM_{2.5}$ exposure. This limitation restricts the generalizability of current findings, underscoring the importance of longitudinal and chronic exposure studies to better capture progressive neurotoxic outcomes relevant to real-world conditions.

In line with our findings, previous systematic reviews also emphasized the consistent involvement of oxidative stress and neuroinflammation as central mechanisms of $PM_{2.5}$-induced neurotoxicity (Zhang et al., 2018; Patten et al., 2021). However, unlike earlier reviews which were limited to small sets of studies, the present synthesis incorporates more recent evidence and provided a broader comparison across exposure modalities and combined factors. This broader scope highlights both the robustness of key findings and the variability introduced by differences in study design, thereby refining the current understanding of how experimental evidence fits into the wider body of research.

4.3. Implications for Research and Practice

The findings of this systematic literature review had important implications for environmental toxicology research utilizing rodent models. Unlike epidemiological studies in humans, which faced challenges in controlling specific pollutant exposures, research using rodent enabled precise manipulation of $PM_{2.5}$ dose and exposure duration. This allowed for a more accurate understanding of the underlying pathophysiological mechanisms involved. Furthermore, the reported efficacy of antioxidant-based and bioactive compound interventions suggested that rodent models could serve as an initial platform for testing potential therapies targeting the effects of air pollution. Compounds such as melatonin, baicalin–geniposide glycosides, and red ginseng extract had been reported to attenuate oxidative stress and inflammation in these models, offering valuable insights for the development of future mitigation strategies.

Although bioactive compounds such as melatonin, vitamin E, RGE, AECF, AASC, and BC/GD consistently suggested protective effects across multiple studies, these conclusions should be tempered. The evidence base is constrained by small group sizes, variable dosing regimens, and methodological weaknesses identified in the risk-of-bias assessment. Thus, while promising, current findings remain preliminary and require validation in larger, rigorously designed studies before translation to clinical contexts.

4.4. Limitations of Study

Although rodent studies offered a more controlled understanding of the neurotoxic effects of $PM_{2.5}$, several methodological and interpretative limitations should be acknowledged with caution. One of the main challenges lied in the heterogeneity of study designs, including variations in exposure type (acute vs. chronic), dosage, duration, and analytical methods. This variability complicated direct comparison and limited the consistency of cross-study synthesis. Temporal constraints were also important to note, as most studies examined only short-term outcomes. In reality, $PM_{2.5}$ exposure was typically chronic and cumulative; thus, the long-term

consequences—such as progressive cognitive decline, neurodegeneration, and systemic dysfunctions—might be insufficiently represented in current rodent models.

Furthermore, the majority of studies relied on single-exposure models, whereas real-world environments involved complex interactions with other biological or environmental factors, such as chronic stress, high-fat diets, metabolic disorders, or systemic infections. These interacting conditions were common in human populations and might amplify or modulate the neurotoxic impact of $PM_{2.5}$, yet they were rarely modeled in animal studies. Another critical limitation lied on clinical relevance. Despite their utility, rodents differed significantly from humans in pollutant metabolism, brain structure and connectivity, and immune responses. These physiological differences raised concerns about the extern to which findings could be directly extrapolated to human contexts.

From a methodological perspective, the risk-of-bias assessment using the SYRCLE tool revealed several shortcomings. Most studies provided incomplete reporting of randomization procedures, lacked allocation concealment, and rarely described blinding of outcome assessment. Such methodological weaknesses might have introduced systematic bias, thereby lowering confidence in the the overall evidence base. Finally, this review relied solely on the Scopus database for literature retrieval. Although Scopus provided broad coverage of environmental and neuroscientific research, the use of a single database might have limited the identification of additional relevant studies available elsewhere.

Collectively, these limitations highlighted the need for more rigorous, long-term, and integrative experimental designs better approximate the complexity of real-world exposures, incorporate robust methodological safeguards, and employ multiple data sources.

Table 2: Limitations of Study

Aspect	Identified Limitation	Research Implication
Study Design	Variability in exposure type (acute vs. chronic), dosage, duration, and analytical methods	Hinders comparability and synthesis of findings across studies
Evaluation Duration	Most studies focused on short-term effects	Long-term and cumulative impacts remain underexplored
Combined Exposure	Limited studies investigating co-exposure with biological or environmental factors	Fails to reflect the real-world complexity of environmental exposures
Clinical Relevance	Physiological differences between rodents and humans (metabolism, brain structure, immunity)	Findings cannot be directly extrapolated to humans without further validation
Rodent Models Used	Diversity of rodent strains and genetic backgrounds often underreported	May influence response to $PM_{2.5}$ and introduce bias in outcomes
Database Coverage	Literature search relied solely on Scopus	May have limited identification of additional relevant studies
Risk-of-Bias Issues	Incomplete reporting of randomization, blinding, and allocation concealment	Reduces methodological rigor and weakens the certainty of the evidence base

These limitations emphasized the importance of future studies adopting standardized methodologies, incorporating long-term and multifactorial exposure models, and improving reporting practices to strengthen the robustness and translational value of findings.

Another important limitation related to the heterogeneity of exposure modalities across the included studies. Inhalation, instillation, and real-ambient exposures each had distinct advantages and drawbacks. Inhalation studies provided the highest translational relevance by simulating natural respiratory uptake (e.g., Kang et al., 2023; Qin et al., 2023), whereas instillation allowed for precise dosing but often employed supra-physiological concentrations which might exaggerate toxic responses (e.g., Liu et al., 2017). Real-ambient exposure models captured the complexity of environmental pollutant mixtures, yet their variability reduced reproducibility and complicated mechanistic interpretation (e.g., Ljubimova et al., 2018). Moreover, comparisons across these modalities were further confounded by differences in concentration and exposure duration, as studies ranged from acute instillations (Fu et al., 2022) to chronic multi-week inhalation and ambient exposures (Di Domenico et al., 2020; Lee et al., 2021). This heterogeneity hindered the establishment of standardized dose–response relationships and underscored the need for more harmonized experimental designs.

In addition, it is important to clarify how interaction effects were assessed in the included studies. Typically, synergistic or additive effects were inferred by comparing combined exposure group (e.g., $PM_{2.5}$ plus a high-fat diet or co-pollutant) with single-exposure group across behavioral, biochemical, and histological outcomes. While informative, these comparisons were inherently constrained by controlled laboratory conditions and might not fully reflect the multifactorial nature of human exposures.

Finally, although rodent models provided valuable mechanistic insights, their translational relevance must be interpreted with caution. Differences in lifespan, pollutant metabolism, brain complexity, and immune system responses limited the direct extrapolation of findings to human populations. Thus, these results should be considered as foundational evidence, requiring validation through longitudinal epidemiological and clinical studies to ensure applicability in real-world contexts.

4.5. Directions to Future Research

Based on the identified limitations, future research needs to focus on several key aspects to achieve a more comprehensive understanding of the effects of $PM_{2.5}$ on the brain. One crucial direction is the implementation of longitudinal studies in rodents to explore the long-term impacts of $PM_{2.5}$ exposure on neurodevelopment. Such studies will provide provide valuable insights into how cumulative effects evolve over time and contribute to progressive neurodegeneration—processes often undetectable in short-term experiments.

In addition, further exploration of the interaction between $PM_{2.5}$ and the gut microbiota remains essential, given the gut-brain axis's role in neuroinflammatory mechanisms. A deeper understanding of this relationship could open new avenues for mitigating air pollution-induced brain damage through microbiota-based strategies, including probiotic, prebiotic, or postbiotic interventions aimed at modulating neuroinflammatory responses.

Studies examining combined exposures to $PM_{2.5}$ and other factors—such as psychosocial stress, high-fat or high-sugar diets, obesity, or co-pollutants like nitrogen dioxide, ozone, and heavy metals—are also necessary to reflect the complex realities of environmental exposures. These variables may interact synergistically with $PM_{2.5}$ to exacerbate neurological disturbances, necessitating more integrative and multifactorial experimental designs to unravel the underlying mechanisms.

Moreover, research into the molecular pathways underlying the neuroprotective effects of antioxidant compounds such as melatonin, baicalin-geniposide, vitamin E, and other phytochemicals should continue to be prioritized. Detailed mechanistic insights will support the development of effective intervention strategies and accelerate the translation of these findings into early-stage clinical studies.

Finally, the development and use of transgenic or humanized rodent models should be further considered to enhance the clinical relevance of experimental outcomes. These models could be particularly valuable in studying neurodegenerative diseases such as Alzheimer's or Parkinson's, which have shown links to air pollution exposure. Employing more representative models may help facilitate the translational potential of preclinical findings and bridge the gap to human health applications.

5. CONCLUSIONS

Overall, this review indicates that direct exposure to $PM_{2.5}$ in rodents under controlled laboratory conditions is associated with significant neurological impairments, primarily through mechanisms involving oxidative stress and neuroinflammation. The combination of $PM_{2.5}$ with additional environmental risk factors—such as unhealthy diets or co-exposure to other pollutants— was reported to further exacerbates brain damage through synergistic effects. On the other hand, various interventions based on antioxidant and anti-inflammatory compounds, particularly those derived from natural sources, demonstrate promising protective potential in mitigating $PM_{2.5}$-induced neurotoxicity. Accordingly, this systematic literature review highlights the critical role of rodent models as experimental platforms for evaluating environmental toxicity and investigating potential therapeutic strategies. Further research is urgently needed to clarify the long-term effects of $PM_{2.5}$ exposure, to elucidate the role of the gut–brain axis in mediating these effects, and to assess the translational potential of interventions in human health contexts.

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