



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 problems, including negative effects on the nervous system. Rodent models offer a controlled way to study the mechanisms underlying PM_{2.5}-induced neurotoxicity. This systematic review combined evidence from 15 peer-reviewed studies found in academic databases, focusing on (1) the effects on brain health, (2) mechanisms of oxidative stress and neuroinflammation, (3) impacts of combined exposure, and (4) potential treatment options. The results showed that PM_{2.5} exposure is associated with oxidative stress, neuroinflammation, and cognitive problems, characterized by beta-amyloid buildup, microglial activation, and blood-brain barrier disruption through various molecular pathways. Interactions with other factors, such as high-cholesterol diets and co-exposure to pollutants such as formaldehyde, worsen these effects. Several antioxidants, including melatonin, vitamin E, red ginseng, and baicalin-geniposide, have shown potential to protect the brain by modulating inflammatory pathways and enhancing cognition. Differences between species (rats vs. mice) indicated variability in the results and limited broad application. Overall, the current evidence underscores the need for long-term comprehensive research on PM_{2.5} neurotoxicity and the development of multi-target therapies. These findings can guide public health policies to reduce population exposure and highlight the importance of combining environmental monitoring with clinical research to safeguard vulnerable groups.

INTRODUCTION

Air pollution is a major environmental issue that negatively impacts the health of humans. Among various air pollutants, fine particulate matter with a diameter of less than 2.5 micrometers (PM_{2.5}) has gained particular attention because of its ability to penetrate deeply into the respiratory system of humans. Once inhaled, PM_{2.5} can enter the bloodstream and exert widespread effects throughout the body (Lu et al. 2017, Chen et al. 2020, Xie et al. 2021, Cano-Granda et al. 2022, Peng et al. 2022, Thangavel et al. 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 et al. 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 et al. 2017). In addition, PM_{2.5}-triggered



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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, a comprehensive understanding of the specific molecular mechanisms and effects of combined exposure 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 the dosage, duration, and exposure conditions, which is difficult to achieve in human epidemiological studies. Rodent models enable the systematic exploration of pathophysiological mechanisms and 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 human studies. Differences in metabolism, exposure duration, and 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} in the brain and develop effective mitigation strategies.

This review aimed to systematically synthesize and analyze the existing literature on the effects of PM_{2.5} exposure in the rodent brain 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 that may mitigate the adverse effects of PM_{2.5}. Accordingly, the findings of this review are expected to contribute to a deeper understanding of how air pollutants affect the nervous system and provide an evidence-based foundation for the development of more effective mitigation strategies in the future.

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) statement. 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 used 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 because of its credibility in indexing over 24,000 high-quality peer-reviewed journals. In addition, Scopus provides various scientific metrics, such as the h-index and citation counts, which support 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. The 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 included in the 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 that 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 study. Literature reviews, editorials, and opinion pieces were excluded 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 assessed. The initial search yielded 35 relevant articles. After preliminary screening, seven articles were excluded because of the unavailability of full-text access. Of the remaining 28 articles, full-text assessments were conducted, and 13 articles were eliminated: two were review papers, and 11 did not specifically address PM_{2.5} exposure in rodents. In total, 15 original research articles met the 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, by consulting a third

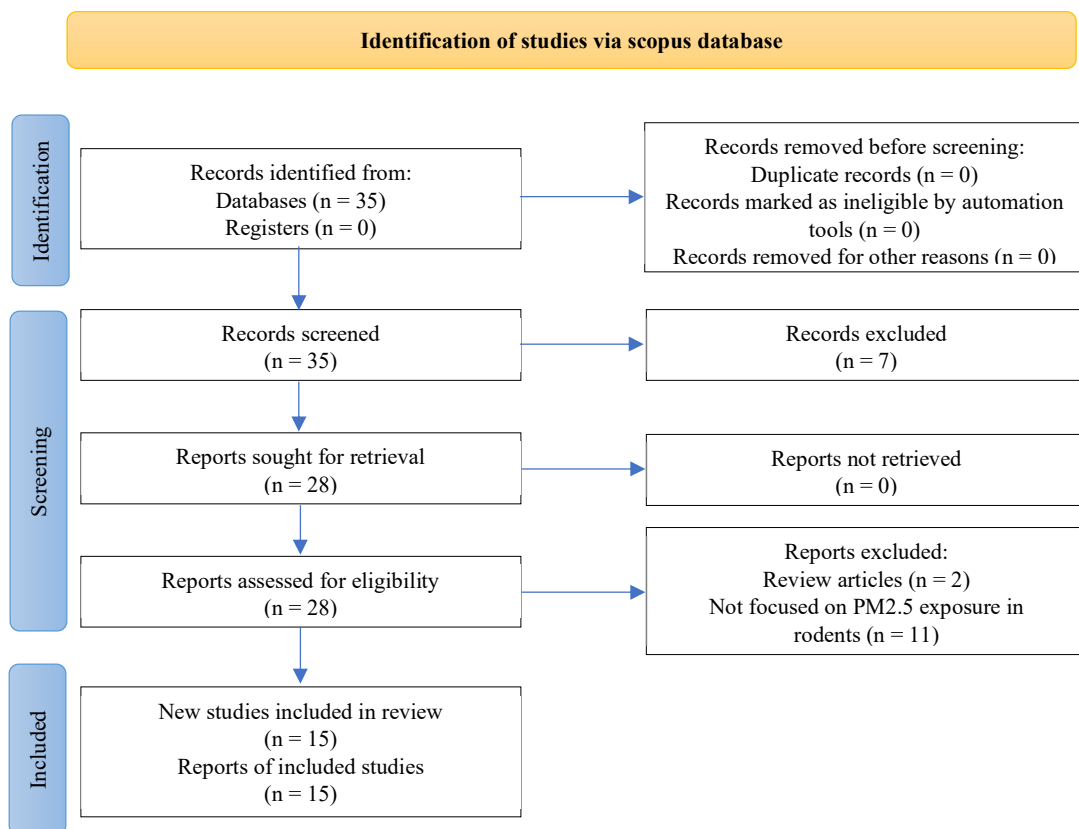


Fig. 1: PRISMA flow diagram of article selection in the systematic review on the effects of PM_{2.5} on brain health in rodents.

reviewer. The complete selection pathway is illustrated in the PRISMA flow diagram (Fig. 1), which details the number of records identified, screened, excluded, and included, along with the reasons for exclusion at each stage. A supplementary table (Supplementary Table S1) provides a full list of excluded full-text articles, along with the corresponding reasons for their exclusion.

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

The methodological quality of the included studies was further evaluated using the SYRCLE risk of bias tool, which was 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 bias sources. Detailed study-level evaluations are presented in Supplementary Table S3, and an aggregated visual summary is shown in Fig. 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. Articles that passed this stage were further analyzed to ensure compliance with the predefined inclusion and exclusion criteria. Eligible articles were then extracted to obtain information related to the study design, PM_{2.5} exposure methods, measured parameters and key findings. The extracted data were descriptively analyzed to identify patterns and relationships between PM_{2.5} exposure and its effects on rodent brains.

To improve transparency, species information (rat vs. mouse) was explicitly extracted from each study. The 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 this 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, focusing 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 the 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}, environmental stressors, co-pollutants, or genetic predisposition. The final subtheme evaluated therapeutic or interventional strategies to mitigate the adverse effects of PM_{2.5} in the rodent brain, including both pharmacological and non-pharmacological approaches aimed at counteracting PM_{2.5}-induced neurotoxicity in mice.

RESULTS

Effects of PM_{2.5} Exposure on Rodent Brain Health

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

Fifteen 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, is provided in Supplementary Table S2. This table serves as the foundation for the thematic synthesis presented in the following subsections.

Structural and Morphological Effects on the Brain

PM_{2.5} exposure was associated with significant structural alterations in various regions of the mouse brain. Chronic exposure for over 16 weeks has been 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 has also been reported in other studies, with the untreated group showing more pronounced tissue injury, as demonstrated in a rat model (Zhang et al. 2025). Furthermore, subchronic

PM_{2.5} exposure has been shown to cause significant neuronal loss in the cortical area, even in the absence of immediately detectable functional impairment (Lee et al. 2021). These findings suggest that structural damage may precede overt functional deficits, underscoring the importance of early detection and long-term evaluation of the effects of PM_{2.5} exposure.

Functional and Cognitive Impairments

Cognitive dysfunction is frequently reported as a consequence of PM_{2.5} exposure in mice. Studies utilizing the Morris Water Maze (MWM) have 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 the results of 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 $25.48 \pm 5.63 \text{ ng.m}^{-3}$, with an average PM_{2.5} concentration of $54 \pm 9.71 \text{ }\mu\text{g.m}^{-3}$ (Panda et al. 2023). Synergistic effects on cognitive function have also been 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, 2019).

Cognitive disturbances are not limited to memory functions but also extend to other behavioral domains. Mice exposed to PM_{2.5} during the gestational and postnatal periods exhibited behavioral alterations, including increased locomotor activity and heightened exploratory behavior, compared to the 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 play critical roles in cognitive function (Kim et al. 2023b). Combined exposure to a high-cholesterol diet (HCD) and PM_{2.5} also appeared to induce 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} 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 increases the risk of autism spectrum disorders (Wang et al. 2020).

Cellular Impact and Neuroinflammation

At the cellular level, PM_{2.5} exposure is frequently associated with a complex inflammatory response within the mouse

brain tissue. Mice exposed to PM_{2.5} during the gestational and postnatal periods showed an increased number of microglia and astrocytes in the cortex, indicating the 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 (UFP), 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 (Kim et al. 2023a). 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 A β -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, has prompted further research to explore the molecular mechanisms underlying PM_{2.5} neurotoxicity. Understanding oxidative stress and neuroinflammatory pathways is key to explaining how particulate exposure might initiate the cascade of neural alterations identified in these studies.

Mechanisms of Oxidative Stress and Neuroinflammation

Exposure to PM_{2.5} triggers a complex cascade involving oxidative stress and neuroinflammation as the primary mechanisms underlying neurological damage. These two pathological processes interact and mutually reinforce each other, creating a vicious cycle that contributes to progressive neurodegeneration. A comprehensive understanding of the molecular pathways involved is essential for developing effective intervention strategies.

Oxidative Stress Pathways and Damage Biomarkers

Exposure to PM_{2.5} was consistently associated with increased production of reactive oxygen species (ROS), which have 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 that exposure to tM_{2.5} at a concentration of 60 $\mu\text{g}\cdot\text{mL}^{-1}$ significantly enhanced oxidative stress in various cell types, including microglial cells (HMC-3), indicating that polycyclic aromatic hydrocarbons (PAHs) in PM_{2.5} play 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, Kim et al. 2023a). Combined exposure to formaldehyde (FA) and PM_{2.5} was reported to further aggravate ROS production and was associated with increased levels of A β 1-42 and phosphorylated tau (Tau-P) proteins, two biomarkers linked to neurodegenerative conditions such as Alzheimer's disease (Liu et al. 2019).

Activation of Neuroinflammatory Pathways

The neuroinflammatory response to PM_{2.5} exposure is mediated through the activation of multiple complex molecular pathways. Several studies reported activation of NF- κ B and JNK inflammatory signaling pathways, two critical routes involved in oxidative stress and apoptosis pathogenesis, following PM_{2.5} exposure (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. 2023b). Microglia, the resident immune cells of the brain, play a central role in neuroinflammatory responses. 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. Under 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).

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 synergistically elevates inflammatory proteins such as COX-2 and MMP-9, directly impairing BBB integrity and exacerbating neurodegenerative conditions (Chen et al. 2024). BBB disruption was suggested to facilitate the 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).

Dysregulation of Lipid Metabolism and Membrane Integrity

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

Specificity of Particle Size in Inflammatory Response

Research has revealed that the inflammatory response is not uniform across different particle size fractions of PM_{2.5}. In rats, exposure to PM_{2.5}, PM₁₀ is 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 is not observed following exposure to ultrafine particles (UFP), reinforcing the hypothesis that specific chemical constituents present in the PM_{2.5}–PM₁₀ fraction

play an important role in triggering neuroinflammatory mechanisms.

Effects on Neurotrophic Factors and the Cholinergic System

PM_{2.5} exposure in mice has also 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 laid a foundation for exploring how the complexity of real-world exposure, especially involving PM_{2.5} along with other pollutants and biological factors, could influence or worsen the identified pathological pathways.

Combined Effects of PM_{2.5} Exposure with Other Factors

In real-world conditions, exposure to PM_{2.5} rarely occurred in isolation. Instead, it interacted with various environmental, biological, and chemical factors that could influence or worsen its neurotoxic effects. Understanding these synergistic interactions was essential for accurately assessing the true neurological risks of particulate air pollution, especially given the multifactorial exposure complexity faced by populations in daily life.

Combination with Other Atmospheric Pollutants

Simultaneous exposure to PM_{2.5} and other air pollutants has been reported to produce significant synergistic effects on neurological health in mice. The combination of formaldehyde (FA) and PM_{2.5}, in particular, showed more harmful outcomes compared to individual exposures, worsening oxidative stress, histological damage, and the buildup of neurotoxic proteins. These effects extended beyond the hippocampus to include the cerebral and prefrontal cortex (Liu et al. 2019). This synergy manifested as more severe cognitive impairments, as evidenced by prolonged escape latency in the Morris Water Maze test compared to both the 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 the 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 a BBB compromise may facilitate the infiltration of harmful molecules into the brain parenchyma, potentially contributing to progressive neurodegenerative processes.

Interaction with Intrinsic Chemical Components of PM_{2.5}

The toxicological complexity of PM_{2.5} stems 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} plays 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 are not limited to the nervous system but also impact the respiratory and gastrointestinal systems, indicating that combinational exposure exerts complex, multi-organ effects. Further research highlights the significance of combinational exposure by demonstrating that inflammatory responses and tumorigenic potential only emerge 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 are 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 play a determining role in their overall toxicity.

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.

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 of the severity of neurological outcomes. At the opposite end of the age spectrum, studies using aged mouse models, biologically predisposed to vulnerability, have 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 is 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.

Interaction with Genetic Predisposition

The use of transgenic mouse models has provided critical insights into the interaction between genetic vulnerability and environmental exposure. The APP/PS1 transgenic mouse model of Alzheimer's disease demonstrated that PM_{2.5} exposure exacerbated conditions already genetically predisposed to neurodegeneration (Fu et al. 2022). These findings suggest that genetic susceptibility may act as an amplifying factor, intensifying the neurotoxic effects of PM_{2.5}, resulting in more severe phenotypes than those in individuals with a normal genetic background. This gene-environment interaction has significant clinical implications, as populations with genetic predispositions to neurodegenerative disorders may experience accelerated decline when exposed to particulate air pollution. These insights underscore the importance of risk stratification based on genetic profiles in public health assessments of the impact of air pollution.

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 have highlighted

the lung–brain axis as a systemic consequence of PM_{2.5} exposure (Kim et al. 2023a). Pulmonary dysfunction induced by fibrosis has 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 underscore the importance of a holistic approach to understanding PM_{2.5} toxicology, where primary effects on one organ can induce secondary impacts on target organs through systemic mediators or disruptions in physiological homeostasis.

The multifactorial complexity of these interactions reinforces the need for intervention strategies that not only address the isolated effects of PM_{2.5} but also consider combinational exposure scenarios and individual vulnerability factors having been identified.

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 is crucial for mitigating its neurotoxic effects. Various approaches have 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 by the restoration of cognitive function and structural protection of brain tissue.

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 μ M melatonin significantly reduced 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⁻¹ melatonin for 90 days in mice resulting in substantial reductions in neuroinflammation and neurodegeneration.

Most notably, melatonin treatment not only protected 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 significantly reduced histological damage, reactive oxygen species (ROS) activation, and the accumulation of pathological proteins A β 1–42 and phosphorylated Tau (Tau-P) (Liu et al. 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 approaches remain relevant in multi-pollutant exposure scenarios (Liu et al. 2019).

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- κ B and JNK signaling pathways—both of which were critical in the pathogenesis of oxidative stress (Kim et al. 2023a). Remarkably, RGE also prevented pulmonary fibrosis by modulating the TGF- β 1 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 effects suggested RGE's potential as a natural intervention that might address the systemic neurotoxicity induced by PM_{2.5} exposure (Kim et al. 2023a).

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 Neuro-inflammatory 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.

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 (Kim et al. 2023b). 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 (Kim et al. 2023a).

Biomarkers and Molecular Targets for Precision Intervention

A more forward-looking approach involved identifying specific molecular targets for precision medicine

interventions. Recent studies have 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 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).

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 that 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.

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 Fig. 2.

Risk of Bias Assessment

The methodological quality of the studies included was assessed using the SYRCLE risk-of-bias tool, which was specifically adapted for animal intervention studies. Overall, most studies lacked sufficient details about random sequence generation or allocation concealment, and descriptions of blinding in outcome assessment were rare. Random housing

procedures were also infrequently reported. Conversely, baseline characteristics and the completeness of outcome data were generally adequate, and evidence of selective outcome reporting was uncommon. These patterns indicate a moderate overall risk of bias across the evidence, emphasizing the need for more thorough methodological reporting in future experimental research. A detailed, study-level evaluation is provided in Supplementary Table S3, while an overall summary of domain-level assessments is shown in Fig. 3.

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 ⁻¹ , 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 ⁻¹ , 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 ⁻¹ , 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 (AEFC)	Marine algae extract	50 & 100 mg.kg ⁻¹ , 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 ⁻¹ , 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 & iri[DOI]d	7.5–30 mg.kg ⁻¹ , 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; AEFC: Aqueous Extract of *Codium fragile*

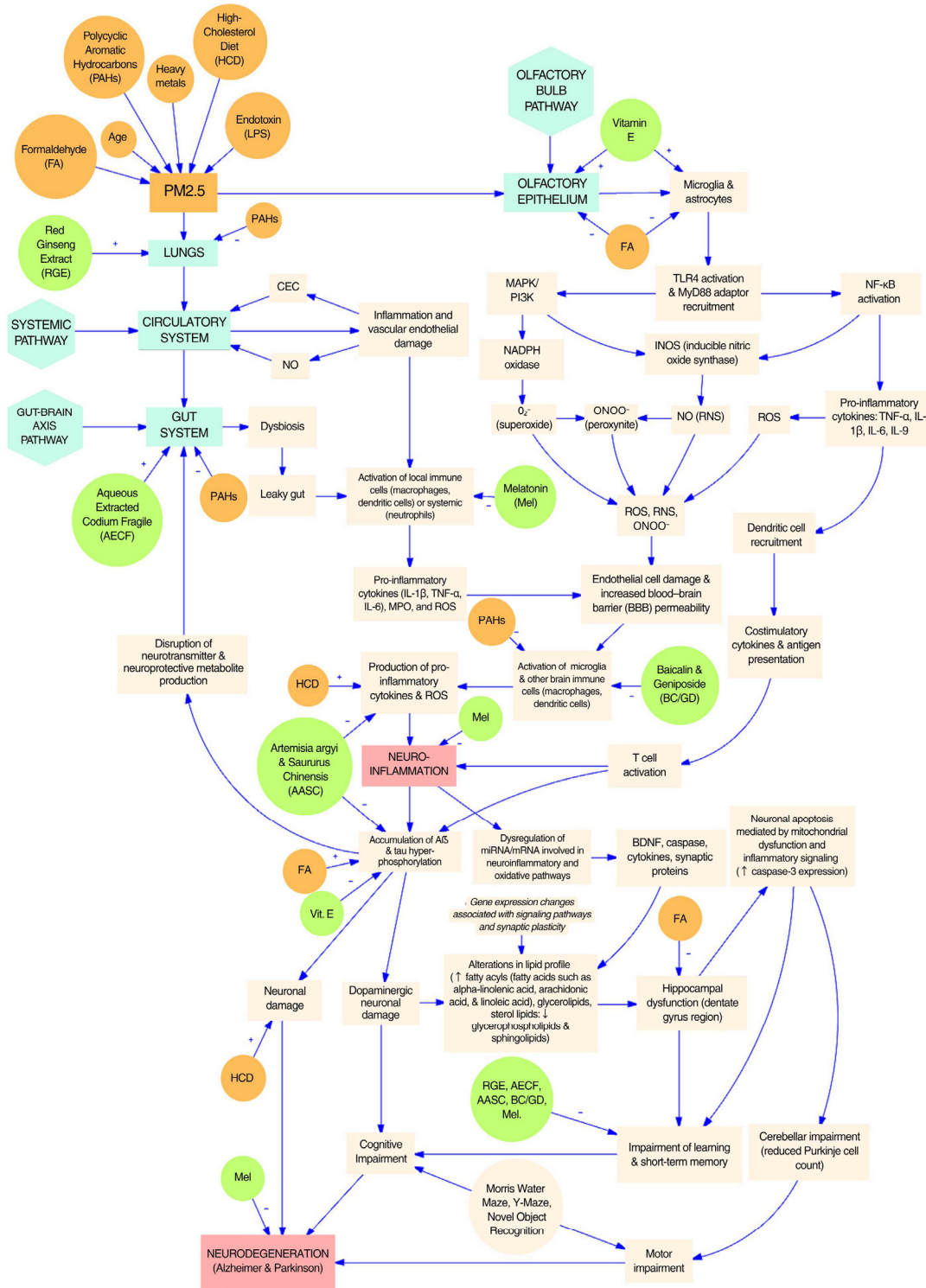


Fig. 2: Pathways of PM_{2.5} exposure impact on brain health in rodents.

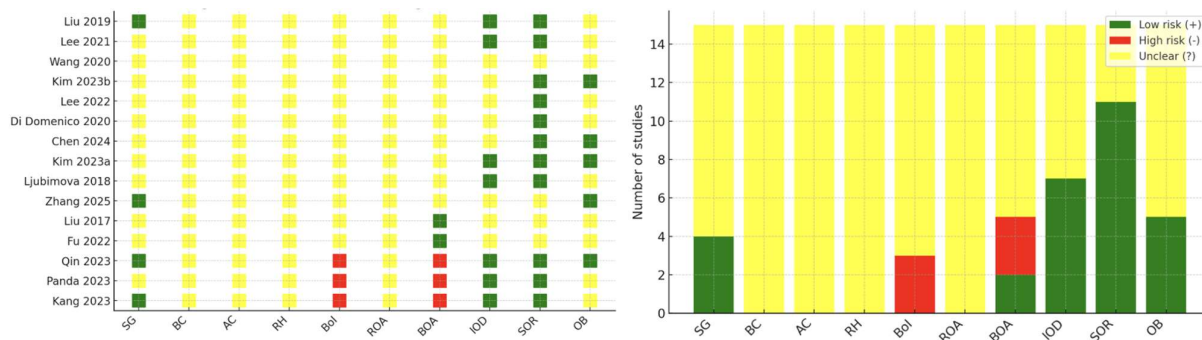


Fig. 3: Risk-of-bias assessment of included studies using the SYRCLE tool. (A) Traffic-light plot showing judgments across 10 domains. (B) Summary bar chart indicating frequent underreporting of randomization, allocation concealment, and blinding, consistent with a moderate overall risk of bias.

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}.

Critical Appraisal of Outcomes

The 15 studies included used a variety of behavioral, histological, and biochemical endpoints to assess the

neurotoxic effects of PM_{2.5}. Behavioral assessments were reported in 8 studies, with 7 showing significant impairments in memory, learning, or anxiety-like behaviors; 1 study found no clear functional deficits despite histological evidence of neuronal damage. Histological analyses were conducted in 10 studies, nearly all of which reported structural abnormalities such as neuronal loss, corpus callosum thinning, or mitochondrial damage. Biochemical and molecular assays were the most common, appearing in 13 studies, consistently indicating oxidative stress, inflammatory responses, and altered expression of proteins associated with neurodegeneration (e.g., β -amyloid, phosphorylated tau, TNF- α , IL-6). Despite these consistent findings, several methodological weaknesses may influence the reliability of results. Many studies employed small sample sizes (often fewer than 10 animals per group), which limits statistical power. Blinding of outcome assessment was infrequently reported, raising concerns about observer bias, especially in behavioral scoring and histological evaluations. Additionally, the heterogeneity of assays, ranging from different behavioral paradigms to diverse biochemical markers, complicates direct comparisons across studies. A detailed overview of endpoints and findings is available in Supplementary Table S2, while methodological limitations identified via the SYRCLE risk-of-bias tool are summarized in Supplementary Table S3 and Fig. 3.

DISCUSSION

Synthesis of Findings

This systematic literature review indicated that PM_{2.5} exposure was associated with significant neurotoxic effects in the brains of rodents (rats and mice), with oxidative stress and neuroinflammation serving as the primary underlying mechanisms. An analysis of 15 selected studies consistently reported that direct exposure to PM_{2.5} under controlled conditions was linked to progressive structural

and functional brain impairments, including synaptic damage, cognitive dysfunction, β -amyloid accumulation, and tau protein hyperphosphorylation, all of which are hallmark features of neurodegenerative pathology. The spectrum of damage encompasses reduced corpus callosum volume, neuronal loss in cortical regions, and morphological alterations in the dentate gyrus of the hippocampus and cerebellum.

Alarmingly, the findings indicated that combined exposure to PM_{2.5} and other environmental factors, such as high-cholesterol diets, formaldehyde, and heavy metals, appeared to produce synergistic effects that exceeded simple additive outcomes. These interactions particularly exacerbate blood–brain barrier (BBB) disruption, amplify systemic inflammatory responses, and accelerate neuronal apoptosis. Most notably, BBB integrity was specifically compromised only under combinational exposure, suggesting that single-pollutant risk assessments might substantially underestimate the true neurological threat. Age and genetic susceptibility further modulate 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 has demonstrated promising protective effects through multi-target approaches. While conventional antioxidants, such as melatonin and vitamin E, are effective in mitigating primary oxidative damage, complex phytotherapeutic strategies exhibit 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 yield the most optimal therapeutic outcomes.

Nevertheless, although the overall evidence consistently supported PM_{2.5}-induced neurotoxicity in rodents, the reliability of specific outcomes requires cautious interpretation. Although behavioral assays are widely applied, they are often performed with small sample sizes and without reported blinding, raising concerns about observer bias. Histological analyses generally reveal structural damage; however, inconsistencies in staining protocols and semi-quantitative scoring methods may introduce subjectivity. Biochemical endpoints proved to be the most reproducible, consistently demonstrating oxidative stress and neuroinflammatory responses, although variations in biomarker selection complicated direct cross-study comparisons. Together, these methodological weaknesses highlight the need for larger, well-controlled studies

employing standardized protocols and rigorous blinding to strengthen confidence in outcome reliability.

Comparison with Previous Studies

The findings of this review generally confirmed those of previous studies, suggesting that PM_{2.5} exposure has 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 et al. 2022, Liu et al. 2023, Hou et al. 2023, Liu et al. 2023, Gui et al. 2024, Jaiswal & Singh 2024) highlighted that animal models in laboratory environments enabled controlled observation of potential toxic effects—unlike epidemiological approaches in humans, which are prone to external confounders such as socioeconomic status, lifestyle, and multi-pollutant exposure.

However, there were notable variations in the biological responses reported across studies. Some previous studies have 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 et al. 2022). These discrepancies suggest 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), play a critical role in determining the observed outcomes.

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

Previous studies have also highlighted the interaction between PM_{2.5} and other predisposing factors, such as diet, age, metabolic status, and genetic background, which collectively amplify its neurotoxic effects. These findings support the present review's observation that combined exposures, such as PM_{2.5} with formaldehyde or

a high-cholesterol diet tend to produce synergistic and more damaging effects than single-agent exposures.

Thus, this review not only reinforces existing evidence but also expands our current understanding of the biological complexity of responses to PM_{2.5} exposure. This underscores 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 those of prior systematic reviews and narrative syntheses that highlighted the role of PM_{2.5}, triggering oxidative stress, neuroinflammation, and subsequent cognitive impairment 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 examining the synergistic effects of co-exposures and dietary factors, aspects that were not consistently addressed in earlier reviews. Nevertheless, the majority of the 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 the current findings, underscoring the importance of longitudinal and chronic exposure studies to better capture progressive neurotoxic outcomes relevant to real-world conditions.

Consistent with our findings, previous systematic reviews have emphasized the consistent involvement of oxidative stress and neuroinflammation as central mechanisms underlying 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 provides a broader comparison across exposure modalities and combined factors. This broader scope highlights both the robustness of the 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.

Implications for Research and Practice

The findings of this systematic literature review have important implications for environmental toxicology research utilizing rodent models. Unlike epidemiological studies in humans, which face challenges in controlling specific pollutant exposures, research using rodents has enabled the precise manipulation of PM_{2.5} dose, and exposure duration. This allowed for a more accurate understanding of the underlying pathophysiological mechanisms. Furthermore,

the reported efficacy of antioxidant-based and bioactive compound interventions suggests 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 have 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 suggest 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 risk-of-bias assessments. Thus, while promising, the current findings remain preliminary and require validation in larger, rigorously designed studies before being translated into clinical contexts.

Limitations of the Study

Although rodent studies offer a more controlled understanding of the neurotoxic effects of PM_{2.5}, several methodological and interpretative limitations should be acknowledged. One of the main challenges lies in the heterogeneity of study designs, including variations in exposure type (acute vs. chronic), dosage, duration, and analytical methods. This variability complicates direct comparisons and limits the consistency of cross-study synthesis. Temporal constraints were also important to note, as most studies examined only the short-term outcomes. In reality, PM_{2.5} exposure is typically chronic and cumulative; thus, the long-term consequences, such as progressive cognitive decline, neurodegeneration, and systemic dysfunctions, may be insufficiently represented in current rodent models.

Furthermore, most studies relied on single-exposure models, whereas real-world environments involve complex interactions with other biological or environmental factors, such as chronic stress, high-fat diets, metabolic disorders, or systemic infections. These interacting conditions are common in human populations and may amplify or modulate the neurotoxic effects of PM_{2.5}, yet they are rarely modeled in animal studies. Another critical limitation is the clinical relevance. Despite their utility, rodents differ significantly from humans in terms of pollutant metabolism, brain structure and connectivity, and immune responses. These physiological differences raise concerns about the extent to which the findings can 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 the outcome assessment. Such methodological weaknesses might have introduced systematic bias, thereby lowering confidence in the overall evidence base. Finally, this review relied solely on the Scopus database for literature retrieval purposes. Although Scopus provides 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 highlight the need for more rigorous, long-term, and integrative experimental designs that better approximate the complexity of real-world exposures, incorporate robust methodological safeguards, and employ multiple data sources.

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 the combined exposure group (e.g., PM_{2.5} plus a high-fat diet or co-pollutant) with a 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.

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 valuable

Table 2: Limitations of the 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

insights into how cumulative effects evolve 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.

CONCLUSIONS

Overall, this review shows that direct exposure to PM_{2.5} in rodents under controlled laboratory conditions causes significant neurological impairments, mostly through mechanisms involving oxidative stress and neuroinflammation. The combination of PM_{2.5} with other environmental risk factors, such as unhealthy diets or exposure to additional pollutants, further worsens brain damage through synergistic effects. On the other hand, various interventions using antioxidant and anti-inflammatory compounds, especially those from natural sources, show promising potential in protecting against PM_{2.5}-induced neurotoxicity. Therefore, this systematic review emphasizes the importance of rodent models as experimental platforms for evaluating environmental toxicity and exploring

potential therapies. More research is urgently needed to clarify the long-term effects of PM_{2.5} exposure, understand the role of the gut-brain axis in mediating these effects, and assess how interventions could be translated to human health.

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