

Experimental Study on the Systemic Toxic Effects of PM_{2.5} Exposure on Oxidative Stress and Systemic Toxicity

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Abstract

Particulate matter 2.5 (PM_{2.5}) refers to fine particulate matter with a diameter of 2.5 micrometers or less. It poses a serious threat to health, causing respiratory and cardiovascular diseases and potentially triggering other health problems. Its main sources include industrial emissions, vehicle exhaust, agricultural activities, and waste incineration. (PM_{2.5}) has emerged as a significant global health concern, contributing to substantial morbidity and mortality worldwide. This comprehensive review examines the mechanistic pathways through which PM_{2.5} exposure induces systemic oxidative stress and inflammation, leading to multi-organ toxicity. We synthesize evidence from recent toxicological, epidemiological, and experimental studies highlighting how PM_{2.5} components trigger cellular oxidative damage through direct generation of reactive oxygen species (ROS) and disruption of endogenous antioxidant systems. The complex relationship between PM_{2.5} physicochemical characteristics and their biological reactivity is explored, with particular emphasis on size-dependent deposition, chemical composition-dependent toxicity, and temporal patterns of exposure. Furthermore, we discuss emerging therapeutic approaches to mitigate PM_{2.5}-induced damage, including natural compounds and pharmaceutical agents targeting oxidative stress pathways. Current research gaps and future directions are identified, emphasizing the need for more precise exposure assessment, multi-organ system investigations, and translational studies to bridge experimental findings and clinical applications. This review underscores the urgent need for comprehensive strategies addressing air pollution-related health burdens through integrated environmental, public health, and biomedical approaches.

Keywords

Air Pollution, PM_{2.5}, Inflammation, Systemic Toxicity, Reactive Oxygen Species, Toxicology

1. Introduction

Air pollution, particularly fine particulate matter (PM_{2.5}), represents one of the most pressing environmental health challenges of our time. PM_{2.5} refers to airborne particles with an aerodynamic diameter of 2.5 micrometers or less, capable of penetrating deep into the respiratory system and entering the bloodstream. The Global Burden of Disease study has consistently identified ambient air pollution, with PM_{2.5} as the primary contributor, as a leading risk factor for global mortality, with cardiovascular deaths accounting for the highest proportion of these premature deaths. The physicochemical complexity of PM_{2.5} arises from its diverse sources, including industrial emissions, vehicle exhaust, biomass combustion, agricultural activities, and natural sources like dust storms. This compositional diversity significantly influences its biological reactivity and health impacts, creating substantial challenges for researchers and policymakers alike.

The threat of PM_{2.5} lies not only in its ability to cause pulmonary damage but also in its capacity to induce systemic effects. Once inhaled, these fine particles can traverse the alveolar-capillary barrier, entering systemic circulation and disseminating to various organs, where they can instigate oxidative stress and inflammatory responses. The oxidative stress paradigm posits that PM_{2.5}-induced health effects primarily stem from its ability to generate reactive oxygen species (ROS) directly through its chemical components or indirectly by activating cellular ROS-producing systems such as NADPH oxidases and mitochondrial electron transport chains. This oxidative burden, when exceeding cellular antioxidant capacity, leads to oxidative damage to lipids, proteins, and DNA, triggering cascades of inflammatory responses and cellular dysfunction.

Research over the past decade has substantially advanced our understanding of the molecular mechanisms linking PM_{2.5} exposure to diverse health outcomes. Epidemiological studies have established associations between PM_{2.5} exposure and increased incidence and severity of respiratory, cardiovascular, cerebrovascular, metabolic, and neurological diseases. Recent evidence suggests that PM_{2.5} may also contribute to adverse reproductive outcomes, accelerated aging, and increased cancer risk across multiple organ systems. Experimental models have been instrumental in elucidating the pathogenic sequences, revealing that PM_{2.5} components can induce mitochondrial dysfunction, activate inflammasome pathways, and cause epigenetic modifications, thereby altering gene expression and cellular phenotypes.

This review aims to provide a comprehensive analysis of current research directions on the systemic toxic effects of PM_{2.5} exposure, with particular emphasis on oxidative stress-mediated mechanisms. We will critically examine the evidence linking PM_{2.5} characteristics to differential biological effects, explore innovative methodological approaches in PM_{2.5} research, and discuss potential intervention strategies to mitigate its health impacts. Furthermore, we will identify key knowledge gaps and future research priorities in this rapidly evolving field, with the ultimate goal of informing scientific understanding, public health policies, and clinical approaches to address the global challenge of air pollution.

2. PM_{2.5} Exposure and Systemic Oxidative Stress

2.1 Mechanisms of PM_{2.5}-Induced Oxidative Stress

The pathogenesis of PM_{2.5}-induced organ damage primarily revolves around its capacity to instigate oxidative stress through multiple interconnected mechanisms. PM_{2.5} particles can directly generate reactive oxygen species (ROS) through their chemical constituents, including transition metals, quinones, and polycyclic aromatic hydrocarbons. These components can catalyze the formation of hydroxyl radicals via Fenton reactions or undergo redox cycling, perpetuating oxidative stress long after initial exposure. Additionally, PM_{2.5} can activate cellular ROS-producing systems, notably the NADPH oxidase (NOX) family of enzymes, which respond to particle phagocytosis and subsequent inflammatory signaling. Mitochondrial dysfunction represents another significant source of ROS production, as PM_{2.5} components can disrupt electron transport chain efficiency, leading to electron leakage and superoxide formation [1].

The cellular consequences of PM_{2.5}-induced oxidative stress are extensive and multifaceted. Lipid peroxidation of cellular membranes leads to the formation of reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which can further propagate oxidative damage and form protein adducts that disrupt cellular function. Oxidative DNA damage results in strand breaks and base modifications, potentially leading to mutagenesis and carcinogenesis if not adequately repaired. Protein carbonylation and nitration can alter enzymatic activities, receptor functions, and structural proteins, compromising cellular homeostasis. These molecular alterations activate stress-responsive signaling pathways, including nuclear factor kappa-B (NF- κ B), activator protein-1 (AP-1), and mitogen-activated protein kinase (MAPK) cascades, which orchestrate inflammatory gene expression and further amplify the oxidative stress response.

The variability in PM_{2.5}-induced oxidative potential depends largely on its physical characteristics and chemical composition. Smaller particles within the PM_{2.5} fraction typically exhibit greater oxidative potential due to their larger surface area-to-mass ratio, providing more sites for chemical interactions and biological reactivity. Particles from different sources demonstrate varying toxicities; for instance, those from traffic emissions often contain more redox-active components compared to dust-derived particles. Seasonal variations also influence PM_{2.5} composition and toxicity, with winter samples frequently exhibiting higher oxidative potential due to increased combustion products and atmospheric inversion events. Understanding these source-toxicity relationships is crucial for targeted emission control strategies aimed at reducing the most harmful components of PM_{2.5} [2].

2.2 Systemic Propagation of Oxidative Stress

While the initial oxidative burst occurs in the respiratory tract following PM_{2.5} inhalation, the effects rapidly extend to the systemic circulation and distant organs through multiple pathways. The direct translocation of ultrafine particles ($\leq 0.1 \mu\text{m}$) across the alveolar-capillary barrier allows them to enter the bloodstream and distribute throughout the body, where they can interact directly with endothelial cells and parenchymal tissues. Evidence from tracer studies has demonstrated that inhaled nanoparticles can reach the bloodstream within minutes of exposure, subsequently accumulating in organs such as the liver, spleen, heart, and brain.

Indirect mechanisms also contribute significantly to the systemic propagation of PM_{2.5} effects. Inflammatory mediators released from lung-based cells, including cytokines (IL-1 β , IL-6, TNF- α), chemokines, and acute-phase proteins, can enter the circulation and initiate endothelial activation and systemic inflammation. This "spillover" effect creates a pro-oxidative, pro-inflammatory milieu throughout the body. Additionally, autonomic nervous system activation by pulmonary irritant receptors can trigger imbalances in sympathetic-parasympathetic tone, promoting oxidative stress in cardiovascular tissues and other organs. These neural reflexes represent a rapid communication system between the lungs and distant organs, potentially explaining the almost immediate cardiovascular effects observed following PM_{2.5} exposure [3].

The consequences of systemic oxidative stress are particularly evident in the vascular endothelium, which serves as both a target and propagator of PM_{2.5}-induced damage. Exposure to PM_{2.5} components leads to reduced nitric oxide (NO \bullet) bioavailability through multiple mechanisms, including superoxide-mediated conversion to peroxynitrite (ONOO $^-$), uncoupling of endothelial nitric oxide synthase (eNOS), and decreased eNOS expression. The resulting endothelial dysfunction manifests as impaired vasodilation, increased vascular permeability, and pro-thrombotic tendencies, creating a permissive environment for the development and progression of atherosclerosis, hypertension, and other cardiovascular conditions. Similar oxidative damage mechanisms operate in other organ systems, explaining the multi-system morbidity associated with chronic PM_{2.5} exposure [4].

Table 1. Chemical Composition of PM_{2.5} and Associated Health Impacts

Component	Primary Sources	Major Health Effects	Oxidative Potential
Metals (Transition)	Industrial processes, brake wear	Cardiovascular dysfunction, respiratory inflammation	High (Direct ROS generation)
Polycyclic Aromatic Hydrocarbons	Incomplete combustion, vehicle exhaust	DNA damage, carcinogenesis, endocrine disruption	Moderate-High (Metabolic activation required)
Organic Carbon	Biomass burning, secondary formation	Pulmonary inflammation, systemic oxidative stress	Variable (Depends on specific compounds)
Sulfates/Nitrates	Secondary aerosols from SO ₂ /NO ₃	Respiratory symptoms, cardiovascular impairment	Low (Mainly through acidic pH)
Biological Components	Microbial origin, plant fragments	Allergies, exacerbations, asthma immune sensitization	Variable (Through inflammatory responses)

Table 1 reveals the complexity and multi-source nature of PM_{2.5}: chemical components from different sources cause oxidative stress and inflammatory responses through multiple mechanisms. Among them, metal-containing particles and PAHs typically have high oxidative potential and are key factors causing cellular oxidative damage and systemic inflammation. In contrast, sulfates and nitrates have lower oxidative activity, but can amplify the toxicity of other components through acidification and synergistic effects.

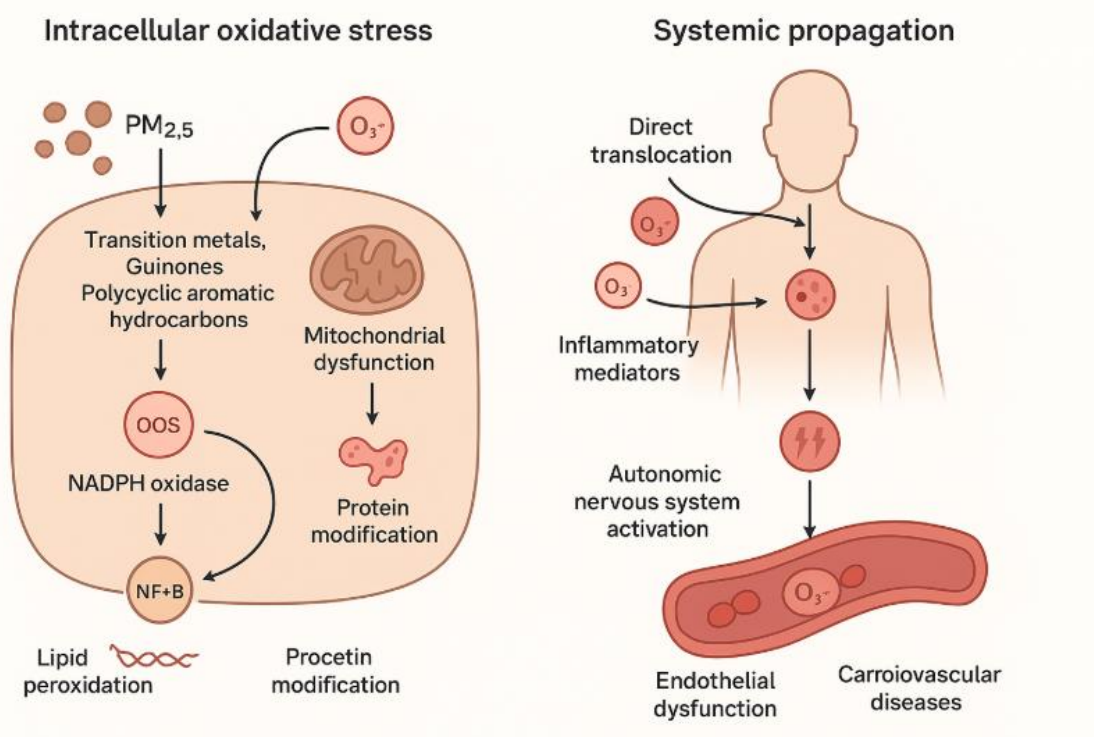


Figure 1. Schematic diagram illustrating PM_{2.5}-induced intracellular oxidative stress pathways and systemic propagation mechanisms

Figure 1 is show visually illustrates the pathological process of PM_{2.5} exposure from local (lung) to systemic oxidative stress. It begins with the direct generation of ROS from chemical components, progresses through the release of ROS during the intermediate stages, activates cellular signaling pathways leading to the spread of inflammatory responses, and ultimately results in multi-organ damage and systemic diseases.

3. Organ-Specific Oxidative Damage

3.1 Cardiovascular System

PM_{2.5} exposure has been strongly linked to cardiovascular morbidity and mortality through oxidative stress-mediated pathways. The vascular endothelium experiences significant oxidative burden, leading to decreased nitric oxide

bioavailability, increased endothelial permeability, and enhanced monocyte adhesion. These functional alterations accelerate the development and progression of atherosclerosis, with studies demonstrating more rapid plaque progression in animal models exposed to concentrated ambient PM_{2.5}. Atherosclerotic plaques in exposed subjects show characteristics of instability, including larger necrotic cores and thinner fibrous caps, potentially explaining the increased incidence of acute coronary syndromes following pollution episodes [5].

At the cardiac level, oxidative stress contributes to electrophysiological abnormalities and myocardial remodeling. PM_{2.5} components can directly affect cardiac ion channel function, potentially leading to arrhythmogenesis, particularly in individuals with pre-existing cardiac conditions. Chronic exposure promotes myocardial fibrosis and hypertrophy through angiotensin II activation and transforming growth factor-beta (TGF- β) signaling, pathways known to be redox-sensitive. These structural changes compromise cardiac function and increase vulnerability to ischemic injury and heart failure. The interplay between systemic inflammation, autonomic imbalance, and direct cardiac effects creates a perfect storm for cardiovascular events following both acute and chronic PM_{2.5} exposure [6].

3.2 Respiratory System

As the primary portal of entry, the respiratory system bears the initial brunt of PM_{2.5}-induced oxidative damage. In the airway epithelium, PM_{2.5} exposure triggers glutathione depletion, mitochondrial dysfunction, and activation of NADPH oxidases, leading to oxidative damage to cellular macromolecules. This oxidative burden activates transcription factors such as NF- κ B and AP-1, resulting in increased expression of pro-inflammatory cytokines (IL-8, TNF- α , IL-6), which recruit and activate immune cells, amplifying the inflammatory cascade. The repeated cycle of injury and repair can lead to altered remodeling of the airway architecture, contributing to chronic obstructive pulmonary disease (COPD) and asthma pathogenesis.

The alveolar compartment similarly experiences oxidative stress, with type II epithelial cells and alveolar macrophages being particularly vulnerable. Oxidative impairment of macrophage phagocytic function compromises clearance of particles and pathogens, creating a vicious cycle of persistent inflammation and tissue damage. In susceptible individuals, these processes can drive the development of pulmonary fibrosis through epithelial-mesenchymal transition and fibroblast activation, both of which are influenced by redox-sensitive pathways. The role of PM_{2.5} in lung cancer initiation and progression is similarly rooted in its ability to cause DNA damage through both direct oxidative adduct formation and inhibition of DNA repair mechanisms [7].

3.3 Reproductive Health and Development

Emerging evidence indicates that PM_{2.5} exposure adversely affects reproductive health and fetal development through oxidative stress mechanisms. During pregnancy, the placental barrier can be breached by fine and ultrafine particles, which have been detected in placental tissues. Once in the placental environment, PM_{2.5} components can induce oxidative stress, leading to trophoblast dysfunction and impaired placental vascular development. Recent research has identified a novel mechanism of PM_{2.5}-induced placental damage through ferroptosis, an iron-dependent form of regulated cell death characterized by excessive lipid peroxidation. This process depletes glutathione reserves and inactivates glutathione peroxidase 4 (GPX4), compromising antioxidant defenses.

The consequences of gestational PM_{2.5} exposure extend to the developing fetus, with epidemiological studies linking air pollution to adverse pregnancy outcomes including preterm birth, low birth weight, congenital anomalies, and stillbirth. The developing fetal nervous system appears particularly vulnerable to oxidative damage due to its high oxygen consumption, rich lipid content, and immature antioxidant defense systems. Animal studies demonstrate that gestational exposure to PM_{2.5} leads to persistent neuroinflammatory changes and behavioral abnormalities in offspring, suggesting that oxidative stress during critical developmental windows may have lifelong neurological consequences. These findings highlight the transgenerational health implications of air pollution exposure and the need for special protection of vulnerable populations [8].

4. Research Methods and Emerging Trends

4.1 Experimental Models in PM_{2.5} Research

Understanding the mechanistic pathways of PM_{2.5}-induced toxicity has relied heavily on complementary experimental approaches, each offering distinct advantages and limitations. In vitro systems using human bronchial epithelial cells (e.g., BEAS-2B), alveolar macrophages, and endothelial cells have been instrumental in delineating cellular signaling pathways and identifying specific molecular targets of PM_{2.5} components. These systems allow for precise control over exposure conditions, including particle concentration, composition, and timing, facilitating mechanistic studies. However, their simplicity often fails to recapitulate the complex cellular interactions occurring in intact organisms and may not accurately reflect realistic exposure scenarios. Recent advances in lung-on-a-chip technology and three-dimensional organoid cultures offer promising alternatives that better mimic the architecture and functionality of human tissues while maintaining experimental controllability [9].

Animal models, particularly rodents, have provided critical insights into the systemic physiological responses to PM_{2.5} exposure. These models enable researchers to study integrated cardiovascular, respiratory, and neurological responses under controlled conditions. The use of concentrated ambient particles (CAPs) systems represents a significant

methodological advancement, allowing animals to be exposed to real-world atmospheric particles through inhalation, the most physiologically relevant route. However, interspecies differences in anatomy, physiology, and metabolism necessitate cautious interpretation when extrapolating findings to humans. Complementary approaches, such as ex vivo lung perfusion models, offer opportunities to study human tissue responses while overcoming some limitations of cell culture systems.

Human exposure studies and panel investigations provide crucial translational bridges between experimental findings and clinical outcomes. Controlled exposure studies in human volunteers, typically employing concentrated air particles or specific PM_{2.5} components, allow detailed physiological monitoring under ethical constraints. These studies have demonstrated rapid cardiovascular changes following exposure, including increased blood pressure, endothelial dysfunction, and altered heart rate variability. Epidemiological investigations, particularly those incorporating personal exposure monitoring and biomarker assessments, have established important exposure-response relationships in diverse populations. The integration of biomarker approaches, including measurements of oxidative stress markers (8-isoprostane, malondialdehyde), inflammatory mediators, and epigenetic modifications, has strengthened the causal inference in observational studies and provided mechanistic insights into human toxicity pathways [10].

4.2 Advanced Analytical Approaches

The characterization of PM_{2.5} physicochemical properties has been revolutionized by advances in analytical techniques, enabling more precise source apportionment and toxicity attribution. High-resolution mass spectrometry allows detailed characterization of organic components, including polycyclic aromatic hydrocarbons, oxidized derivatives, and secondary organic aerosol markers. When coupled with oxidative potential assessments, such as the dithiothreitol (DTT) and ascorbic acid (AA) assays, these analytical approaches facilitate identification of the most toxic PM_{2.5} components. Such information is crucial for targeted emission control strategies, as all particles are not equally toxic, and regulatory efforts should prioritize sources with the highest health impacts per unit mass.

Omics technologies have transformed our ability to map the biological responses to PM_{2.5} exposure comprehensively. Transcriptomic profiling has revealed complex gene expression changes in pathways related to oxidative stress, inflammation, and cellular metabolism following PM_{2.5} exposure [11]. Epigenomic analyses have identified alterations in DNA methylation, histone modifications, and microRNA expression that may mediate long-term health effects and explain susceptibility differences. Proteomic approaches have detected protein carbonylation and nitration patterns specific to PM_{2.5} exposure, providing insights into molecular damage and adaptive responses. The integration of these multi-omics datasets through systems biology approaches offers unprecedented opportunities to identify master regulatory networks and key nodal points for therapeutic intervention.

Artificial intelligence and machine learning algorithms are increasingly being applied to predict PM_{2.5} toxicity and health impacts based on compositional data. These approaches can integrate complex exposure patterns with population health data to identify vulnerable subpopulations and critical exposure windows. Furthermore, the development of novel biosensors for real-time monitoring of oxidative stress biomarkers in exposed individuals promises to bridge the gap between environmental exposure assessment and biological effect monitoring. These technological advances, combined with traditional toxicological approaches, provide a powerful toolkit for deciphering the complex relationships between PM_{2.5} characteristics and biological responses.

Table 2. Advantages and Limitations of Current Research Methodologies in PM_{2.5} Studies

Methodology	Key Applications	Strengths	Limitations
In vitro systems	Mechanistic pathway analysis, high-throughput screening	Controlled conditions, cost-effective, detailed molecular data	Simplified systems, may not reflect in vivo complexity
Animal models	Systemic physiological responses, organ-organ interactions	Whole-organism responses, controlled genetics and environment	Species differences, ethical concerns, artificial exposure settings
Human chamber studies	Controlled human exposure, physiological monitoring	Direct human relevance, detailed temporal response patterns	Ethical constraints, limited to mild exposures and short durations
Epidemiological studies	Population risk assessment, real-world exposure scenarios	Population relevance, large sample sizes, long-term follow-up	Confounding factors, exposure misclassification, limited mechanistic insight
Omics technologies	Unbiased biomarker discovery, pathway mapping	Comprehensive coverage, hypothesis-generating	Data complexity, validation requirements, high costs

Table 2 is explain the current PM_{2.5} research employs a multi-layered methodology, initially focusing on mechanistic studies using in vitro systems and animal models, then moving to human and epidemiological studies to assess actual exposure and risk, and finally utilizing omics technologies to provide molecular-level systemic support to traditional models. However, each method has its limitations; therefore, interdisciplinary research integrating multiple models (such as "in vitro + animal + omics + human") is an important trend for future understanding of PM_{2.5} systemic toxicity.

4.3 Prediction Models and Air Quality Management

The development of sophisticated prediction models has enhanced our ability to forecast PM_{2.5} concentrations and their health impacts, enabling proactive public health interventions. Statistical models incorporating meteorological parameters, land use patterns, and emission source data have demonstrated reasonable accuracy in predicting PM_{2.5} levels across diverse geographic settings. The integration of satellite-based aerosol optical depth (AOD) measurements with ground monitoring data has been particularly valuable for estimating exposures in regions with sparse monitoring networks, facilitating global burden of disease assessments. Machine learning approaches, including random forest and neural network algorithms, have further improved prediction accuracy by capturing complex nonlinear relationships between predictor variables and PM_{2.5} concentrations [12].

Recent research has focused on combining prediction models to enhance forecasting precision. One study demonstrated that a hybrid model integrating complementary ensemble empirical mode decomposition (CEEMD), support vector regression (SVR), and generalized regression neural network (GRNN) outperformed individual models in predicting PM_{2.5}, NO₂, and SO₂ concentrations. Such advanced forecasting approaches provide more accurate information for air quality management and public health warnings, potentially reducing population exposure during high pollution episodes. The optimization of these models through particle swarm optimization (PSO) algorithms and other computational techniques represents an active research frontier with significant practical implications for air quality management.

Effective air quality management requires not only accurate forecasting but also evidence-based standard setting. Current regulatory standards for PM_{2.5} vary considerably worldwide, with the World Health Organization recommending an annual average of 5 µg/m³. However, recent evidence suggests that no threshold exists below which no adverse health effects occur, with studies demonstrating health benefits from continued reductions even at the lowest measurable concentrations. This continuous exposure-response relationship complicates regulatory decisions and underscores the importance of employing the ALARA (As Low As Reasonably Achievable) principle in air quality management. Future standards will need to balance technical feasibility, economic considerations, and public health protection while accounting for differential toxicity across PM_{2.5} components and sources [13].

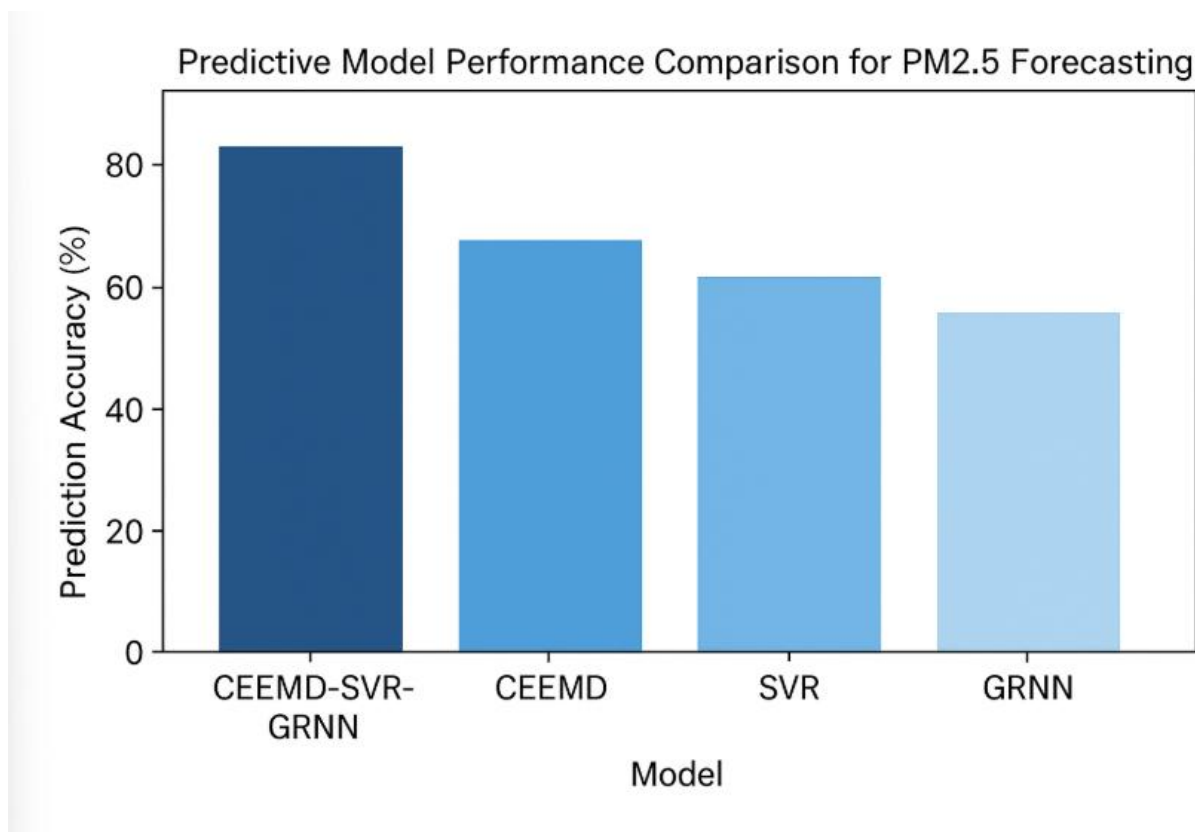


Figure 2. Predictive model performance comparison for PM_{2.5} forecasting using combined CEEMD-SVR-GRNN approach versus individual models

Figure 2 shows the significance of the combined model, CEEMD-SVR-GRNN, which significantly outperforms individual CEEMD, SVR, or GRNN models. This demonstrates that multi-model ensemble methods (combining the decomposition method CEEMD with machine learning models SVR and GRNN) can more effectively capture the complex patterns of PM_{2.5} time series data. Therefore, the CEEMD-SVR-GRNN model performs best in PM_{2.5} prediction tasks, exhibiting high prediction accuracy and reliability.

The Figure is shows that:

- The CEEMD-SVR-GRNN (combined model) has the highest prediction accuracy, exceeding 80%.
- The CEEMD model is second, at approximately 68%.
- SVR (Support Vector Regression) has an accuracy of approximately 60%.
- GRNN (Generalized Regression Neural Network) performs the worst, with an accuracy of approximately 55%.

5. Therapeutic Interventions and Future Research Directions

5.1 Mitigation Strategies Against PM_{2.5}-Induced Oxidative Stress

The identification of oxidative stress as a central mechanism in PM_{2.5} toxicity has stimulated research into interventions that bolster antioxidant defenses. Nutritional antioxidants, including vitamins C and E, N-acetylcysteine, and flavonoids, have demonstrated protective effects in both experimental and limited human studies. These compounds can directly scavenge ROS, regenerate endogenous antioxidants like glutathione, and modulate redox-sensitive signaling pathways. However, results from large-scale human trials have been inconsistent, possibly due to differences in exposure levels, genetic backgrounds, and baseline nutritional status. The timing and dosage of antioxidant supplementation appear critical, with pretreatment being more effective than post-exposure intervention in animal models. Personalized approaches based on genetic polymorphisms in antioxidant enzymes and transporters may improve the efficacy of nutritional interventions.

Pharmacological agents targeting specific oxidative stress pathways represent another promising approach. Metformin, a biguanide commonly used for type 2 diabetes, has shown protective effects against PM_{2.5}-induced placental damage and cardiovascular dysfunction in experimental models. Its mechanisms appear to involve activation of AMP-activated protein kinase (AMPK), reduction of mitochondrial ROS production, and inhibition of NADPH oxidases. Other drugs with antioxidant properties, including statins, angiotensin-converting enzyme inhibitors, and certain anti-inflammatory agents, may similarly mitigate PM_{2.5} effects, particularly in individuals with pre-existing conditions requiring these medications. The repurposing of approved drugs for pollution protection offers practical advantages but requires careful risk-benefit assessment, especially for long-term use in healthy populations.

Lifestyle factors and dietary patterns also influence susceptibility to PM_{2.5}-induced oxidative stress. Regular physical activity enhances endogenous antioxidant capacity through upregulation of mitochondrial biogenesis and antioxidant enzymes, potentially counteracting some pollution effects. However, exercise during high pollution episodes may increase inhalation rates and particle deposition, necessitating careful timing and location choices. Dietary patterns rich in fruits, vegetables, and whole grains provide complex mixtures of phytochemicals with synergistic antioxidant and anti-inflammatory properties. The Mediterranean diet, in particular, has been associated with attenuated responses to air pollution in several observational studies, possibly due to its high content of polyphenols and unsaturated fats. These non-pharmacological approaches offer accessible protection strategies while avoiding potential medication side effects [14].

5.2 Research Gaps and Future Perspectives

Despite significant advances in understanding PM_{2.5}-induced oxidative stress, important knowledge gaps remain. The differential toxicity of PM_{2.5} from various sources and chemical compositions is incompletely characterized, hindering targeted emission control strategies. While current regulations focus on mass concentrations, a component-based approach might more effectively protect public health. Research integrating detailed physicochemical characterization with biological responses using advanced statistical methods is needed to identify the most harmful PM_{2.5} components. This information would enable regulators to prioritize sources based on both quantity and toxicity, potentially increasing the efficiency of control measures.

The long-term consequences of chronic exposure, particularly during sensitive developmental windows, represent another critical research frontier. Epigenetic modifications induced by PM_{2.5} exposure may have transgenerational effects, an area that remains largely unexplored. Advanced life-course studies incorporating precise exposure assessment and molecular profiling are needed to map the temporal evolution of PM_{2.5}-induced damage and identify critical periods for intervention. Similarly, the interaction between air pollution and other environmental stressors, including noise, temperature, and non-PM pollutants, may produce synergistic effects that amplify toxicity. A multi-stressor approach better reflects real-world exposure scenarios and may explain heterogeneity in population responses.

From a methodological perspective, the development of advanced models that more accurately recapitulate human physiology is essential [15]. Organ-on-a-chip systems, humanized animal models, and sophisticated in silico approaches promise to bridge the gap between current experimental systems and human responses. The integration of high-resolution exposure data with biomarker measurements in large cohort studies will strengthen causal inference and facilitate precision prevention approaches targeting vulnerable subpopulations. Furthermore, the translation of mechanistic insights into effective clinical and public health interventions requires stronger collaboration between toxicologists, clinicians, epidemiologists, and policymakers.

Table 3. Promising Therapeutic Interventions for PM_{2.5}-Induced Oxidative Stress and Their Mechanisms of Action

Intervention Category	Specific Examples	Proposed Mechanisms	Evidence Level
Nutritional Antioxidants	Vitamin C, Vitamin E, N-acetylcysteine, Quercetin	Direct ROS scavenging, glutathione synthesis support, metal chelation	Moderate (Strong in vitro and animal evidence, variable human results)
Pharmaceutical Agents	Metformin, Statins, ACE inhibitors	AMPK activation, NOX inhibition, mitochondrial protection, anti-inflammatory effects	Moderate-High (Strong animal studies, limited human epidemiological support)
Dietary Patterns	Mediterranean diet, DASH diet, plant-based diets	Synergistic antioxidant and anti-inflammatory effects, gut microbiome modulation	Moderate (Observational epidemiological evidence, limited clinical trials)
Lifestyle Factors	Regular physical activity, stress reduction	Enhanced endogenous antioxidant defenses, reduced inflammation, improved resilience	Moderate (Observational evidence supporting modification of pollution effects)

Table 3 shows that potential interventions for PM_{2.5}-induced oxidative stress currently include: nutritional supplementation (such as antioxidants), drug therapy, healthy eating patterns, and active lifestyles.

While animal and epidemiological evidence suggests these interventions have protective effects, clinical research remains limited, resulting in an overall level of evidence that is mostly moderate to moderately high. This table provides direction for developing comprehensive intervention strategies to reduce the health hazards of air pollution.

6. Conclusion

The evidence reviewed in this article unequivocally establishes oxidative stress as a central mechanism underlying the systemic toxic effects of PM_{2.5} exposure. From its initial deposition in the respiratory tract to its dissemination to distant organs, PM_{2.5} instigates a complex cascade of molecular events that disrupt redox homeostasis, trigger inflammatory responses, and ultimately lead to cellular dysfunction and tissue damage. The physicochemical characteristics of PM_{2.5}, including its size, surface area, and chemical composition, significantly influence its biological reactivity and tissue-specific effects, creating challenges for both risk assessment and targeted interventions.

Recent methodological advances have substantially enhanced our ability to characterize PM_{2.5} exposure, model its health impacts, and identify susceptible populations and critical exposure windows. The integration of multi-omics approaches, sophisticated exposure assessment techniques, and systems biology frameworks has revealed the remarkable complexity of PM_{2.5}-induced pathophysiology while simultaneously identifying potential points for therapeutic intervention. Nevertheless, important knowledge gaps remain regarding the long-term consequences of exposure, particularly during vulnerable developmental periods, and the differential toxicity of PM_{2.5} from various sources.

Addressing the global health burden imposed by PM_{2.5} exposure requires a multi-pronged approach combining stringent emission controls, evidence-based regulatory standards, and targeted protective interventions for vulnerable populations. The continued refinement of air quality standards based on health evidence rather than solely technical feasibility represents an ethical imperative, given the absence of a safe exposure threshold. Simultaneously, research into pharmacological and lifestyle interventions that bolster antioxidant defenses and enhance resilience to pollution exposure offers hope for mitigating health impacts, particularly in regions where rapid improvement in air quality remains challenging. Through integrated efforts spanning scientific research, clinical practice, public policy, and individual protection, we can reduce the substantial health burden imposed by air pollution in an increasingly urbanized world.

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