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# Air-pollutant particulate matter 2.5 ($PM_{2.5}$)-induced inflammation and oxidative stress in diseases: Possible therapeutic approaches

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## Abstract

Today, air pollution is one of the greatest threats to organismal healthspan. The environmental air of earth is contaminated with a wide variety of artificially generated pollutants like fine particulate matter ($PM_{2.5}$) emitting from industry, fuel engine vehicles, biomass combustion, fumes from blasting, crop residue burning, and wildfire. The air pollutant $PM_{2.5}$ induces massive oxidative stress and inflammation, the major contributors in initiation and progression of numerous diseases including pulmonary, cardiovascular, renal, hepatic, reproductive, neurological, mental, and accelerated biological aging. The provocative question is the following: how can we solve this air pollution associated problem? As it is not realistic to clean the environment at once from artificially generated toxic pollution, initiatives have been undertaken to develop novel therapeutic approaches to control air-pollutant-induced oxidative stress and inflammation and associated devastating diseases. The primary goal of this review article is to discuss systematically the key findings of numerous recent preclinical studies documenting first, the role of air pollutant $PM_{2.5}$ in augmentation of inflammation, oxidative stress, and associated diseases; and second, the efficacies of different natural and synthetic compounds in amelioration of $PM_{2.5}$-induced oxidative stress, inflammation, pyroptosis, and associated pathologies. Further investigation on the safety of these compounds will be helpful to select effective and non-toxic compound(s) for clinical trial and drug development.

**Keywords:** Air pollution; $PM_{2.5}$; Inflammation; Nlrp3; Oxidative Stress; Nrf2; PAI-1; Aging; Drug Development

## 1. Introduction

While good air quality of our habitat has immense impact on our healthy life, air pollution is one of the greatest risk factors for development of numerous diseases resulting in accelerated aging and shortened healthspan [1]. It is noteworthy that initiation of every disease stems from impaired inflammation and oxidative stress responses. The key events of inflammation in response to stress, injury, and infection are vascular dysfunction, infiltration of mononuclear immune cells including monocytes and macrophages, inflammatory cytokine storm, and activation of downstream inflammatory signaling. Importantly, inflammation is an essential response for healing in the early stage of injury or infection, and thus preserves tissue homeostasis. Furthermore, inflammatory cells also contribute to oxidative stress and impaired antioxidant system, another key early cellular response required to protect organisms from further vascular, cellular and tissue damage. However, persistent uncontrolled inflammation and oxidative stress in response to external or internal stressors lead to initiation and progression of numerous diseases due to impaired cellular physiology and tissue homeostasis [2].

Inhaled air pollutant fine particulate matter ($PM_{2.5}$) is one of the major igniters of massive inflammation and oxidative stress in the body [3]. In recent years, the real time world's air pollution index exhibit that the air pollutant $PM_{2.5}$ levels

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of many highly populated cities in industrial belts exceeds >300-500 μg/cubic meter (m^3) compared to standard <50 μg/m^3 [World's Air Pollution: Real-time Air Quality Index @ https://waqi.info; Current Air Quality @ https://www.airnow.gov]. It is well documented that both short-term and long-term exposure to $PM_{2.5}$ cause massive inflammation and oxidative stress in lungs and other organs. Both impaired inflammatory and oxidative stress pathways ignite the onset of numerous human diseases including chronic obstructive pulmonary disease (COPD), allergic rhinitis, vascular thrombosis, hypertension, arrhythmia, stroke, dementia, hepatic and renal diseases, abnormal childbirth, autism spectrum disorder, anxiety, infertility, cancer, and accelerated biological aging [3-10].

In the last decade, many *in vitro* and *in vivo* studies have been conducted to understand the underlying molecular bases and to develop potential therapy to alleviate fine air-pollutant particulate matter ($PM_{2.5}$)-induced pathologies. The purpose of this review article is to discuss the significant findings by many recent investigations on the induction of massive inflammation, oxidative stress, and initiation of disease development in response to $PM_{2.5}$ exposure using different approaches in cellular and animal models. The promises of different therapeutic approaches using synthetic and natural compounds in amelioration of $PM_{2.5}$-induced inflammation and oxidative stress associated multi-organ pathogenesis at the preclinical level are discussed [Figure 1].

## 2. Air-pollutant particulate matter (PM) and its mode of action.

Particulate Matter (PM) is the most hazardous air pollutant that holds a wide range of toxic substances including radon, sulfates, nitrates, benzene, polycyclic aromatic hydrocarbons, heavy metals like lead, cadmium, arsenic, chromium, barium, organic carbon, elemental carbon, and airborne bacteria. Based on available published data, the composition of the PM varies in different cities in the world depending on the sources like generation from factory exhausts, vehicle fuel/diesel combustion, biomass burning, coal burning, crop residue burning, fumes from blasting, and wildfire, and the season of $PM_{2.5}$ collection [11-20]. The partial composition of air pollutants collected in various parts of the world are published [13-15, 17; also see NIST Certificate of Analysis, SRM 1649a, https://tsapps.nist.gov/srmext/ certificates/ archives/]. Based on its aerodynamic diameter, PM has been classified as coarse (10 μm or smaller in diameter $PM_{10}$), fine (2.5 μm or smaller in diameter $PM_{2.5}$), and ultrafine (0.1 μm or smaller in diameter $PM_{0.1}$) [4,7]. Upon short-term or long-term inhalation, these original or chemically modified forms of fine particles trigger induction of massive oxidative stress, inflammation, and associated pathologies. Among different PMs, the elevated level of fine $PM_{2.5}$ in the atmosphere is the most hazardous risk factor to human health. It has been demonstrated that acute harmful effects of $PM_{2.5}$ are direct where fine $PM_{2.5}$ crosses through the lung epithelium into circulation. In contrast, the chronic effects of $PM_{2.5}$ involve generation of oxidative stress, inflammation, cellular dysfunction in lungs, and secretion of elevated levels of inflammatory cytokines into circulation [21-24]. However, eventually, both direct and indirect effects of $PM_{2.5}$ ignite the onset of oxidative stress, inflammation, pyroptosis and progression of devastating pathologies.

## 3. $PM_{2.5}$ in induction of massive inflammation and oxidative stress: major causes for the initiation and progression of pathologies.

This section covers the accumulated experimental evidence from different independent study supporting the negative impact of air pollution $PM_{2.5}$ in ignition of massive inflammation, oxidative stress, and related pathogenesis including accelerated aging process [Figure 1].

### 3.1. $PM_{2.5}$ induces inflammation and oxidative stress: evidence from gene expression "profiling".

Several unbiased global gene expression profiling provide evidence that exposure to air-pollutant $PM_{2.5}$ causes activation of inflammatory and oxidative stress pathways. For example, the gene expression profiling of control and $PM_{2.5}$-exposed human bronchial epithelial cells (16HBE) by RNA seq analysis reveals that exposure to $PM_{2.5}$ (25 μg/cm2/for 24h) causes differential expression of 539 genes [25]. Gene ontology analysis illustrates that $PM_{2.5}$ induces many genes involved in inflammation, oxidative stress, metabolism, xenobiotic stimuli, and cytokine-cytokine receptor interaction pathways. Additionally, exposure of cells to $PM_{2.5}$ is strongly associated with secretion of inflammatory cytokine IL-6 [25]. Histological and electron microscopy imaging data reveal that short term-exposer (24h and 48h) of mice to $PM_{2.5}$ (200 μg/mouse) causes an increased infiltration of neutrophils and macrophages in the lung tissues but not in liver compared to untreated animals [26]. Moreover, microarray analysis reveals that while, $PM_{2.5}$ exposer alters gene expression profiling of different pathways in lungs including chemokine signaling, HIF-1 signaling, inflammatory TNF-α, IL-17 signaling and cytokine-cytokine receptor interaction; in liver, $PM_{2.5}$ alters the expressions of numerous genes involved in metabolic signaling pathways including AMPK signaling, JAK-Stat signaling, cytokine-cytokine receptor and PPAR signaling [26]. Similarly, exposure of human and mouse macrophages to $PM_{2.5}$ (400-500 μg/ml) causes generation of oxidative stress (ROS), activation of inflammatory NF-κB signaling, secretion of inflammatory cytokines IL-1β, TNF-α and impaired phagocytosis, and thus disrupt inflammatory cell clearance by macrophages [27].

Furthermore, RNA seq analysis of RNA extracted from control and $PM_{2.5}$ (500 µg/ml for 24h)-exposed PMA-primed THP-1 human macrophages reveal that expression of 1213 genes involved in different cellular pathways are deregulated by $PM_{2.5}$ including upregulation of IL-17, NF-κB, TNF-α, and PPAR-γ signaling pathways and downregulation of PI3K/AKT and cytokine-receptor interaction pathways [27]. Similarly, a short-term exposure (72h) to $PM_{2.5}$ (200µg/mouse) causes elevated levels of inflammatory markers Mac3, pStat3 and Vcam1 and apoptotic marker cleaved caspase 3 in murine lung and heart tissues [28]. Furthermore, the RNA seq analysis of RNA extracted from controls and $PM_{2.5}$ (200 µg/mouse) instilled (72h) murine lungs, and gene ontology analysis revealed that $PM_{2.5}$ significantly upregulated inflammatory pathway as shown by deregulation of many inflammatory genes including Nlrp3, IL-1β, TNFrsf8, 9, 11a, 12a, 1b, and NF-κB2. Interestingly, many downregulated genes in response to $PM_{2.5}$ participate in metabolism (Ghosh AK et al. unpublished data). Collectively, these results on the impacts of air pollutant $PM_{2.5}$ on global gene expression profiling under different experimental milieus reveal that many common signaling pathways are deregulated by $PM_{2.5}$ exposure including significant activation of inflammatory and oxidative stress pathways.

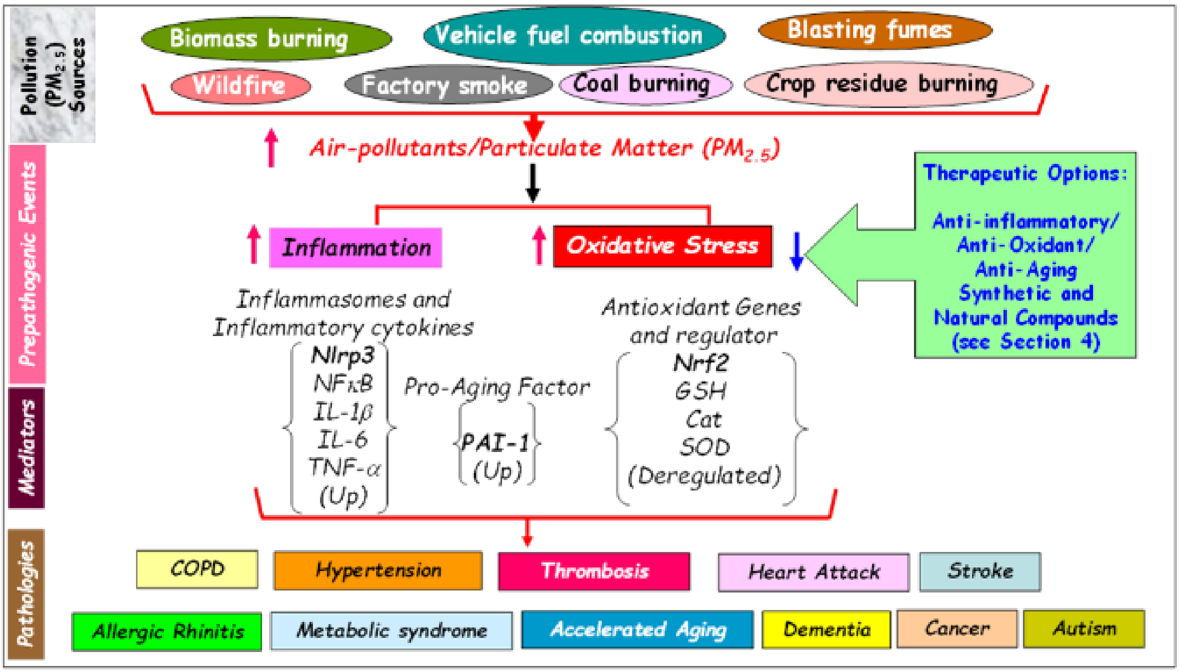


**Figure 1** Schematic illustration showing the sources of air pollutant $PM_{25}$ and the contribution of $PM_{2.5}$-induced inflammation and oxidative stress in organismal pathologies and accelerated biological aging. The potentiality of several synthetic and natural compounds (Table 1 and 2) as therapeutic agent for amelioration of $PM_{2.5}$-induced inflammation, oxidative stress and pathogenic signaling are presented as described under section #4

### 3.2. $PM_{2.5}$-induced inflammation, oxidative stress, and allergic rhinitis.

It is well known that people with allergic rhinitis (AR) are more sensitive to air-pollutants. The impact of $PM_{2.5}$ in allergic airway inflammation has been studied using ovalbumin-induced AR mouse model [29]. Exposure of ovalbumin-induced AR mice to $PM_{2.5}$ (100 µg/mouse) causes augmented inflammation due to increased levels of inflammatory cytokines IL-4, IL-5, and IL-13 that eventually increases oxidative stress as evidenced by increased levels of malondialdehyde (MDA) synthesis. Furthermore, $PM_{2.5}$ exposure inhibits the level of Nrf2, the key regulator of antioxidant genes, in AR mice showing lack of protection of lungs from $PM_{2.5}$-induced oxidative stress [29]. This is consistent with the observation that $PM_{2.5}$ (50µg/ml) reduces the levels of Nrf2 in cardiac fibroblasts [28]. A recent study showed that $PM_{2.5}$ (100 µg/mouse/day/for 30 days) significantly induces the infiltration of eosinophils in bronchoalveolar lavage fluid and inflammatory cells in the lung tissues of ovalbumin (OVA)-induced combined allergic rhinitis and asthma syndrome (CARAS) mouse model [30]. While the levels of transcription factor GATA4, and Th2 and Th17 cytokines IL-4, IL-5, IL-13, and IL-17 are significantly increased compared to control, the levels of Th1 cytokines like IL-12 and IFN-γ are significantly decreased in nasal lavage fluid and broncho alveolar lavage fluid derived from CARAS/$PM_{2.5}$ mice compared to CARAS and control. Additionally, exposure to $PM_{2.5}$ leads to activation of NF-κB signaling in CARAS mouse model. These results confirm that $PM_{2.5}$ aggravates allergic inflammation by increasing the secretion of inflammatory cytokines [30]. In addition, the role of TLR2/TLR4 and MyD88 in $PM_{2.5}$-induced (100 µg/mouse/4 times in 2 weeks interval) worst inflammatory reaction in OVA-induced mouse model of asthma has been examined. While $PM_{2.5}$ exposure exacerbates

OVA-induced lung inflammation or eosinophilia in wildtype mice as shown by increased levels of neutrophils, macrophages, and upregulation of IL-1β, IL-5, IL-12, IL-13, chemokine KC in lungs, $PM_{2.5}$ fails to increase inflammation in TLR2 or TLR4 or MyD88 deficient mice [31]. Comparable results were obtained by Wang and colleagues [32] in an asthma mouse model exposed to $PM_{2.5}$. Collectively, these results suggest that exposure to $PM_{2.5}$ aggravates allergic reaction where both inflammatory and oxidative stress pathways contribute to aggravated pulmonary symptoms in mouse model of AR and Asthma.

### 3.3. $PM_{2.5}$-induced inflammation, oxidative stress, and fibrogenesis.

$PM_{2.5}$ exposure-induced inflammation and oxidative stress ignite matrix remodeling in the heart and lungs. Exposure to $PM_{2.5}$ (100 μg/mouse/every 3rd day for total 9 days) induces the levels of secreted IL-17A, IL-1β and TNF-α by γδT and Th17 cells those lead to a massive inflammation and lung injury. Further, $PM_{2.5}$ stimulates the levels of TGF-β1, Smad-dependent TGF-β profibrogenic responses including myofibroblast differentiation, excessive collagen synthesis and fibrogenesis [33]. Further, the $PM_{2.5}$-activated profibrogenic pathway is diminished in IL-17A null murine lung tissues compared to wildtype mice indicating IL-17A aggravates $PM_{2.5}$-induced inflammation and lung fibrogenesis [33]. Similarly, exposure to $PM_{2.5}$ increases lung injury, decreases lung functions including lung vital capacity and airway resistance through induction of inflammation and oxidative stress in mice and mouse bronchial epithelium cells as evidenced by elevated levels of IL-1β, IL-16, PI3K/mTOR signaling pathways [34]. Importantly, exposure to low, medium, and high doses of $PM_{2.5}$ (3 mg, 8 mg, 13 mg/kg body weight/once per week for 4 weeks) induces worst inflammation and lung injury as shown by increased expression of ACP, CRP, VEGF, and IL-6 in broncho alveolar lavage fluid compared to control rats. Additionally, the protein levels of VEGF, JAK2, Stat3 and matrix protein collagen are significantly elevated in $PM_{2.5}$-treated rat lung tissues compared to controls [35]. These results suggest that $PM_{2.5}$-induced PI3K/mTOR and JAK/Stat3 signaling pathways may contribute to massive lung inflammation and fibrogenesis. Interestingly, exposures of mice to printing room generated $PM_{2.5}$ (5μg, 10μg or 15μg/g BW on day 1 and 3) significantly increased malondialdehyde (MDA) activity, increased expression of inflammatory cytokines like IL-1β, TNF-α, and IL-6 and decreased expression of antioxidant SOD on day 4 of exposure. In addition, primary profibrogenic signaling mediator TGF-β-induced pERK1-MAPK activity is also increased by $PM_{2.5}$ indicating exposure for a significant amount of time to print room-generated $PM_{2.5}$ is a major risk factor for increased lung oxidative stress, inflammation, pyroptosis and pulmonary fibrosis [36].

Exposure to $PM_{2.5}$ (50μg/mouse/every 3 days/total 6 times) causes increased infiltration of inflammatory cells and lung injury including peri-bronchial fibrosis and airway wall thickening in mice [27]. Exposure to $PM_{2.5}$ (4mg/kg daily for 5days) also significantly increases the levels of CXCL1, IL-6 and IL-18. The levels of Nlrp3/NF-κB and Akt signaling are significantly elevated in hearts of $PM_{2.5}$ exposed mice. Therefore, Nlrp3/NFκB-induced inflammation may contribute to $PM_{2.5}$-induced cardiac pathologies including fibrogenesis [37]. As HDAC3 plays a key role in regulation of inflammatory genes and control inflammation in response to external stresses, the significance of HDAC3 in $PM_{2.5}$-induced inflammation-related symptoms in mice has been examined [38]. While $PM_{2.5}$ inhalation (101.5+/- 2.3 μg/^m3, flow rate: 75L/min for 6h/day/5 time per week) induces the Smad-dependent TGF-β signaling in wildtype mice, this profibrogenic signaling is further activated in lungs derived from $PM_{2.5}$-exposed HDAC3 deficient mice [38]. Therefore, specific activation of HDAC3 may be a viable approach to control the extent of $PM_{2.5}$-induced lung inflammation and fibrosis. Exposure to concentrated $PM_{2.5}$ (671.87μg/m^3 for 8 or 16 weeks, 6 h/day) also imparts its negative influence on the cardiac structure and function as shown by cardiac hypertrophy, fibrosis, and abnormal cardiac systolic function. $PM_{2.5}$ induces inflammation through activation of PI3K/Akt/FOXO1 signaling pathways that contribute to cardiac hypertrophy and fibrogenesis "in mice" [39]. Furthermore, the offspring from mice exposed to $PM_{2.5}$ during gestation period develop cardiac hypertrophy that is associated with increased levels of acetyltransferase p300, acetylated H3K9 and cardiac transcriptional regulators Gata4 and Mef2c [40]. Therefore, prenatal, or postnatal exposure to environmental pollutant $PM_{2.5}$ induces cardiac inflammation, cellular apoptosis, fibrogenesis and abnormal cardiac structure and function.

### 3.4. $PM_{2.5}$-induced inflammation, oxidative stress, metabolic syndrome, and accelerated aging.

Exposure to $PM_{2.5}$ is associated with accelerated aging and metabolic disorders [9,10,41]. Using *Drosophila* as a model for longevity study, Wang, and colleagues [42] showed that exposure to concentrated $PM_{2.5}$ (80 μg/m^3) reduces *Drosophila* lifespan in both males and females compared to *Drosophila* exposed to filtered air (PM2.5:4 μg/m^3) (50% survival 20-21 days vs 40 days for filtered air exposed flies). Interestingly, males are more sensitive to $PM_{2.5}$ than females [42]. It is important to note that $PM_{2.5}$ driven *Drosophila* mortality is also associated with increased oxidative stress as evidenced by increased expression of SOD1, Catalase, Thor and Duox as an adaptive responses to $PM_{2.5}$-induced stress; and inflammation as shown by elevated expression of Jak, Jnk and NF-κB in *Drosophila* whole body. Additionally, DCFH oxidation is significantly increased in whole body lysates from concentrated $PM_{2.5}$-exposed flies compared to filtered air exposed flies indicating $PM_{2.5}$ induces systemic oxidative stress. Exposure of *Drosophila* for 15 days to concentrated $PM_{2.5}$ (6h/day, 5days/week, average concentration of $PM_{2.5}$ :17μg and 24 μg/m^3/24h) also induces abnormal metabolism including deregulated insulin signaling and insulin resistance as evidenced by elevated levels of glucose and trehalose and increased expression of Ilp2 and Ilp5 transcripts in *Drosophila* [42]. Therefore, the results of this *in vivo* study confirmed the negative impact of $PM_{2.5}$-induced inflammation and oxidative stress on organismal metabolism and longevity.

As shortening of telomere length is a bonafide marker of chronological and accelerated aging, the impact of air-pollution exposure on cord blood and placental telomere length in 641 newborns has been investigated [9]. Upon measuring the telomere length in cord blood buffy coat and placental tissues, this study showed that mothers exposed to higher levels of $PM_{2.5}$ (5 μg/m^3 increase during entire pregnancy period) gave birth to newborns with significantly shorter telomere length, an indicator of shorter lifespan [9]. Hence, this study further indicates that prenatal exposure to increased levels of air pollutants is associated with accelerated biological aging process. Further, a recent study on the effects of $PM_{2.5}$ on *Caenorhabditis elegans* lifespan define that exposure to low dose (94 μg/ml) and high dose (119 μg/ml) of water-soluble component of $PM_{2.5}$ (WS-$PM_{2.5}$) significantly shortened the lifespan of *C. elegans*. $PM_{2.5}$ imparts adverse effects on healthspan as evidenced by reduced rate of head thrashing and pharyngeal pumping and decreased body length compared to control animal without $PM_{2.5}$ exposure under heat stress environment. RNA seq analysis revealed that the adverse effects of $PM_{2.5}$ on nematode lifespan and healthspan are associated with deregulation in insulin/IGF-1 signaling and fat metabolism [10]. Collectively, the results of these *in vivo* studies clearly indicate the deleterious effects of $PM_{2.5}$ exposure on organismal lifespan and healthspan. Further research is needed to determine the molecular basis underlying the negative effects of $PM_{2.5}$ on mammalian lifespan and healthspan using suitable mammalian models.

It is evident from the above-discussed studies that for each investigation, different experimental milieu in terms of sources, concentration, heterogeneity in the composition of particulate matter, time of collection, period of exposure to $PM_{2.5}$, cell lines and animal models are used. However, despite the experimental heterogeneity, the results of all the studies provide clear and convincing evidence that $PM_{2.5}$ induces massive inflammation and oxidative stresses, the root causes of all air pollutant-induced multi-organ pathologies and accelerated aging process.

## 4. Efficacies of natural and synthetic compounds in alleviation of $PM_{2.5}$-induced inflammation, oxidative stress, and diseases.

In this section, the recent findings on the efficacies of different synthetic and natural compounds in amelioration of $PM_{2.5}$-induced sustained oxidative stress, inflammation and associated pathologies using animal and cellular models are discussed.

### 4.1. Lessons from studies using animal models and synthetic compounds.

The potential of different synthetic molecules to alleviate $PM_{2.5}$-induced inflammation, oxidative stress, and associated pathologies have been evaluated in preclinical settings [**Table 1**]. A wealth of research demonstrates that an imbalance in the level of plasminogen activator inhibitor-1 (PAI-1), the most potent inhibitor of serine proteases uPA/t-PA, is associated with a wide variety of diseases including cardiovascular, pulmonary, metabolism and accelerated aging, and upregulated by the exposure to $PM_{2.5}$ [43-49]. Recently, the efficacy of a drug-like small molecule inhibitor *TM5614* targeting PAI-1 in amelioration of $PM_{2.5}$-induced pulmonary and cardiac pathologies has been evaluated [28]. A short-term exposure (24 h) of mice to $PM_{2.5}$ (50 μg/mouse) increases the levels of circulatory PAI-1, inflammatory cytokine IL-6 and thrombin, a coagulation factor involved in vascular thrombosis. Interestingly, $PM_{2.5}$ did not increase the levels of circulatory PAI-1, thrombin, and IL-6 in mice pretreated with PAI-1 inhibitor *TM5614* (10mg/kg/day). Importantly, PAI-1 specific inhibitor *TM5614* diminishes short-term (72h) $PM_{2.5}$ exposure (200 μg/mouse/once)-induced inflammatory markers Mac3, pStat3 and Vcam1, and apoptotic marker cleaved caspase 3 in lung and cardiac tissues [28]. Analysis of RNA seq data reveals while $PM_{2.5}$ (200 μg/mouse once in 72 h) induces the inflammatory factors including Nlrp3, IL-1β, NF-κB2, TNFrsf11a, TNFrsf12a, pretreatment of mice with *TM5614* (10 mg/kg/day) prevents induction of these inflammation mediators (Ghosh et al. unpublished data). After long-term exposure to $PM_{2.5}$ (100 μg/mouse/week for 4 weeks), mice develop lung and heart vascular thrombosis. Most importantly, pretreatment with *TM5614* significantly decreases $PM_{2.5}$-induced vascular thrombosis in lungs and hearts [28]. Therefore, air pollutant $PM_{2.5}$-induced inflammation, apoptosis and vascular thrombosis can be controlled by promising drug-like small molecule *TM5614* targeting PAI-1, a pro-thrombotic and pro-aging factor. Future preclinical study using large animal cohort is required to proceed for clinical trials of this drug for the treatment of air-pollutant-induced pathologies.

Exposure to $PM_{2.5}$ (120 μg/ml for 14 days) causes massive lung inflammation and lung injury like alveolar structure disruption in mice. Importantly, $PM_{2.5}$ augments the levels of inflammatory cytokines like TNF-α, IL-6, and IL-1β, inflammasome Nlrp3 and apoptotic caspase pathway both in mouse and 16HBE cell (20 μg/ml/24h) models. Significantly, $PM_{2.5}$ exposer-induced lung inflammation and pyroptosis are blocked by the pretreatment of mice with Nlrp3-specific inhibitor *MCC950* (2.5 mg/kg) suggesting targeting Nlrp3 with small molecule inhibitor is a practical approach to control $PM_{2.5}$-induced persistent inflammation and pyroptosis-driven lung pathologies [50]. Furthermore, exposure of 16HBE cells to $PM_{2.5}$ (10-40 μg/ml) causes elevated IL-1β expression, increased small GTPase Rac1 and increased inflammation. However, pretreatment of 16HBE for 30 min with Rac1 inhibitor *NSC23766* suppresses $PM_{2.5}$-induced IL-1β secretion. This study also showed that pharmacological inhibition of Rac1 with *NSC23766* (1mg/kg for 9 days; 30 min pretreatment before $PM_{2.5}$ exposure) blocks $PM_{2.5}$ (100 μg/every 3rd day for 9 days)-induced increased IL-1β secretion, infiltration of neutrophils and macrophages in murine lungs [51]. Therefore, Rac1 may be a druggable target for therapy of $PM_{2.5}$-induced increased inflammation and associated lung diseases. As data are limited, further preclinical studies are needed to confirm the beneficial effects of these synthetic compounds in amelioration of $PM_{2.5}$-induced massive inflammation, oxidative stress, and pathologies.

**Table 1** The list of synthetic compounds used in amelioration of pollution $PM_{2.5}$-induced cellular abnormality and organismal pathologies in preclinical setup. The list includes only the compounds which are discussed in this article. Inflamm: Inflammation; OS: Oxidative stress; Pyrop :Pyroptosis CM: Cardiomyocytes.

| Synthetic Compounds | Targets | Animals/ Cells | Reduced $PM_{2.5}$-induced prepathogenic events | Ref. # |
|---|---|---|---|---|
| 1. *TM5614* | PAI-1 | Mice | Inflamm. (Lungs, Heart) | 28 |
| 2. *MCC950* | Nlrp3 | Mice/16HBE | Inflamm. (Lungs, Cells) | 50 |
| 3. *NSC23766* | Rac1 | Mice/16HBE | Inflamm. (Lungs, Cells) | 51 |
| 4. *GSK 13788* | Nox1/4 | EAhy.926 | Inflamm., OS (Cells) | 71 |
| 5. *Ropivacaine* | $Na^+$ Channel | BEAS-2B | Inflamm., OS (Cells) | 72 |
| 6. *Z-VAD-FMK* | Caspase | 16HBE | Inflamm., Pyrop. (Cells) | 19 |
| 7. *VX-765* | Caspase | 16HBE | Inflamm., Pyrop. (Cells) | 19 |
| 8. *Vitamin D3* | Vit D Receptor | 16HBE/CM | Inflamm., Pyrop.,OS (Cells) | 73,74 |
| 9. *TAK242* | TLR4 | RAW264.7 | Inflamm. (Cells) | 75 |
| 10. *Polymyxin B* | Endotoxin | RAW264.7 | Inflamm. (Cells) | 76 |
| 11. *Bay 11-7085* | NF-kB | RAW264.7 | Inflamm. (Cells) | 76 |
| 12. *NAC* | ROS | RAW264.7 | OS (Cells) | 76 |

### 4.2. Lessons from studies using animal models and natural compounds.

Here, the efficacies of several natural compounds in alleviation of $PM_{2.5}$-induced pathologies ignited by $PM_{2.5}$-induced inflammation and oxidative stresses are discussed [**Table 2**]. As *Salvianolic acid B (SalB)* is a known strong anti-oxidative and anti-inflammatory natural agent [52], a recent study evaluated the efficacy of *SalB* (0.3 mg/kg, 0.9 mg/kg and 1.8mg/kg) inhalation on $PM_{2.5}$ (10 μg daily for 5 days)-induced inflammation and oxidative stress in mice [53]. Treatment with SalB significantly reduces $PM_{2.5}$-induced infiltration of neutrophil and macrophage, expression levels of IL-1β, TNF-α, KC, TGF- β, TLR4, MyD88, TRAP6 and Nlrp3 in a dose-dependent manner and thus alleviates inflammation in the lung tissues. Importantly, treatment of $PM_{2.5}$-exposed mice with *SalB* rescued $PM_{2.5}$-induced suppression of antioxidant genes SOD, CAT, GSH and GSH-Px in mouse lungs [53]. These results clearly suggest *SalB* is highly effective in alleviation of $PM_{2.5}$-induced inflammation, oxidative stress and thus abnormal lung structure and function.

The therapeutic efficacy of steroidal alkaloid *Sipeimine*, an anti-inflammatory and anti-asthmatic agent, has been evaluated in amelioration of $PM_{2.5}$-induced lung inflammation and injury [54]. Pretreatment of mice with *Sipeimine* (30 mg/kg/day/for 3 days) blocks $PM_{2.5}$ (7.5 mg/kg/day for 2days)-induced lung inflammation, pulmonary edema, and injury through suppression of inflammatory cytokines TNF-α, IL-1β and oxidative stress through reversal of $PM_{2.5}$-induced increased MDA and decreased GSH. Importantly, *Sipeimine* blocks $PM_{2.5}$-induced inhibition of Nrf2, the primary regulator of antioxidant genes, and thus diminishes oxidative stress [54]. These results implicate the therapeutic potential of *Sipeimine* for the treatment of $PM_{2.5}$-induced lung pathologies through inhibition of inflammation and oxidative stress. Additionally, pretreatment of Sprague-Dawley rats with *Sipeimine* (15 mg/kg-30 mg/kg) for 3 days significantly decreases $PM_{2.5}$ (7.5mg/kg)-induced lung injury-related damage that is accompanied by reduced levels of inflammatory IL-1β, IL-18, TNF-α, Nlrp3 and apoptotic caspase. The anti-inflammatory effect of *Sipeimine* has been further supported by the observation that the beneficial effect of *Sipeimine* is blocked by pretreatment with Nlrp3 activator nigericin [55]. Thus, *Sipeimine* effectively ameliorates $PM_{2.5}$-induced inflammation, oxidative stress, pyroptosis and lung injury in both rodent models.

Similarly, the therapeutic efficacy of *Astragaloside IV (AS-IV),* a plant product from *Astragalus membranaceous* with anti-oxidative and anti-inflammatory properties, in amelioration of $PM_{2.5}$-induced massive lung pathologies has been studied in a rat model [56,57]. Pretreatment of rats with *AS-IV* (50-100 mg/kg/day/for 3 days) improved $PM_{2.5}$ (7.5 mg/kg/day)-induced lung injury as shown by the decreased inflammatory signaling molecules IL-6, TNF-α, CRP, TLR4 and NFκB pathways and oxidative stress in lungs [56,57]. *AS-IV* inhibits $PM_{2.5}$-induced PI3K/mTOR pathway and NF-kB translocation in NR8383 rat macrophages. Furthermore, *AS-IV* blocks $PM_{2.5}$-induced suppression of antioxidant genes SOD and CAT [57]. Importantly, pretreatment of mice with *AS-IV* (50-100 mg/kg) also reduces $PM_{2.5}$ (7.5 mg/kg/twice, 0, 24h followed by harvest at 36h)-induced inflammation, oxidative stress and pyroptosis through Nlrp3 pathway because pretreatment with Nlrp3 activator nigericin diminishes beneficial effect of *AS-IV* on $PM_{2.5}$-induced lung pathologies [58]. Therefore, the bioactive herbal substance *AS-IV* has therapeutic potential in amelioration of $PM_{2.5}$-induced inflammation and oxidative stress-driven lung pathologies. Thus, *AS-IV* may be a future potential drug to control $PM_{2.5}$-induced lung injury and Nlrp3 is a potent druggable target for therapy.

The efficacy of *Tussilagone (TLS),* a natural compound derived from flower bud, in amelioration of $PM_{2.5}$-induced lung pathologies has been evaluated [59]. Treatment of mice with *TLS* (20mg/kg/every 3 days) blunts $PM_{2.5}$ (20mg/kg/4h inhalation/day for 6 days)-induced ROS production or oxidative stress, lung inflammation as shown by reduced levels of IL-1 β, IL-6, IL-12, and TNF-α and injury through downregulation of $PM_{2.5}$-induced HIF-1α and NF-κB signaling. In addition, pretreatment of human lung epithelial cells (A549) with *TLS* (25 μg/ml) reduces $PM_{2.5}$ (30 μg, 100 μg, 300 μg/ml for 4 days)-induced apoptosis markers like cleaved caspase 3 and LDH activity, and inflammatory cytokines IL-1β, IL-6, and TNF-α [59]. Collectively, these results indicate the therapeutic potential of *TLS* for the treatment of air pollution-induced lung inflammation, pyroptosis and oxidative stress. The therapeutic efficacy of *Deng-Shi-Qing-Mai-Tang (DSQMT),* a Chinese herbal formula, on $PM_{2.5}$-induced lung injury has been assessed [60]. Treatment with *DSQMT* (3 ml of 0.72, 1.45, 2.90 g/ml) significantly decreases the inflammatory cytokines IL-1β, IL-6, and TNF-α and pathologies like damaged lung tissues and higher lung permeability index in rats exposed to $PM_{2.5}$ (50 μg/rat/week for 8 weeks). Additionally, *DSQMT* (20% of medicated serum 1.45g/ml) decreases the $PM_{2.5}$ (0.5mg/ml)-induced increased expression of many factors involved in inflammation including IL-1β, IL-6 and TNF-α in rat alveolar macrophages, NR8383 [60]. Thus, this study implicated *DSQMT* as a potential natural compound to control air pollution-induced lung injury through modulation of $PM_{2.5}$-induced inflammatory responses. As *Schisandrae Fructus* fruit is known to possesses the anti-inflammatory and antioxidant activities, the therapeutic efficacy of *Schisandrae fructus ethanol extract (SF)* (200 μg and 400 μg/ml pretreated for 1h) on $PM_{2.5}$ (50 μg/ml for 24h)-induced inflammatory and oxidative stress developed in RAW264.7 macrophages and post fertilized (day3) zebrafish larvae has been evaluated [61]. Significantly, *SF* reduces the expression of $PM_{2.5}$-induced inflammatory cytokines IL-6 and IL-1β, NO and COX2 through disruption of nuclear translocation of NF-κB from cytoplasm to nucleus and impaired NF-κB signaling. Pretreatment with *SF* also blocks $PM_{2.5}$-induced ROS activity in macrophages and zebrafish larvae as shown by ROS fluorescence intensity [61]. Therefore, *SF* with anti-inflammatory as well as antioxidant properties is an excellent choice for the treatment of oxidative stress- and inflammation-induced tissue damages. Future *in vivo* studies are needed to explore the therapeutic efficacy of *SF* in amelioration of $PM_{2.5}$-induced massive inflammation and oxidative stress in mammalian models.

*Bergapten* (5-methoxysporalen), a bergamont essential oil, possesses antioxidant and anti-inflammatory properties. While exposure to $PM_{2.5}$ (100 μg/mouse for 30 days) aggravates OVA-induced combined allergic rhinitis and asthma syndrome (CARAS) with massive lung inflammation and lung injury in mice, treatment of mice with *Bergapten* (3,10,30 mg/kg) induces OVA-specific IgG2A and decreases the level of IgE and IgG1 in serum. Most importantly, *Bergapten* reduces the inflammation in nasal mucosa and lungs through induction of Th1 cytokine IL-12, IFN-γ and reduction of Th2 cytokines IL-4, IL-5, and IL-13 [62]. These results indicate that *Bergapten* is a potential natural therapeutic agent to treat CARAS and $PM_{2.5}$-induced worst lung pathologies. Similarly, the efficacy of *Rosavidin*, a phenylpropanoid compound having multiple biological activities extracted from the *Rhodiola crenulata* plant, in amelioration of $PM_{2.5}$-induced lung pathology has been examined in a rat model [63]. Pretreatment of rats with *Rosavidin* (50-100 mg/kg/day for 3 days) diminishes $PM_{2.5}$ (7.5mg/kg twice in 36h at 0h and 24h)-induced inflammation and ameliorates lung pathologies in rats through inhibition of inflammatory and apoptotic regulators including IL-1β, Nlrp3 inflammasome, and caspase. This study further demonstrated that Nlrp3 specific activator nigericin blunts *Rosavidin*-mediated amelioration of $PM_{2.5}$-induced lung pathologies [63]. Therefore, *Rosavidin* has potential to be a remedy to controlling $PM_{2.5}$-induced inflammation and pyroptosis-driven lung pathologies. It is well documented that exposure to $PM_{2.5}$ causes worst lung pathologies in COPD patients [64,65]. *Bufei Yishen formula (ECC-BYF),* a Chinese herbal medicinal formula, efficiently improves COPD in a rat model that was developed by repeated cigarette smoke inhalation (2 times daily, 30 min each time for 8 weeks and intranasal instillation of pneumonia bacteria once for every 5 days). Whole body exposure of COPD rats to $PM_{2.5}$ for another 8 weeks (average daily conc. of $PM_{2.5}$ 739.97μg/m^3; 4h/day for 8 weeks) leads to excessive lung inflammation, lung tissue remodeling and decreased lung function in this rat model of COPD. However, $PM_{2.5}$ failed to induce inflammation, oxidative stress, pyroptosis and excessive collagen deposition in the lungs of *ECC-BYF*-treated COPD rat model [66]. These results clearly indicate the therapeutic efficacy of *ECC-BYF* for the treatment of $PM_{2.5}$-induced worst lung inflammation, pyroptosis and lung injury in COPD in a preclinical setting.

As *Juglanin* is a plant product with anti-inflammatory and anti-oxidative properties, the therapeutic efficacy of *Juglanin* on $PM_{2.5}$-induced inflammation, oxidative stress, and liver injury has been assessed [67]. Interestingly, *Juglanin* (40mg/kg/day, via gavage 6h prior to $PM_{2.5}$ exposure) reduces $PM_{2.5}$ (151.1 +/- 2.5 μg/m^3, 6 h /day, 5 times/week for 24 weeks)-induced liver injury in mice through activation of antioxidant gene regulator Nrf2, and suppressor of IKKe (SIKE), a known negative regulator of inflammatory signaling. It is important to note that Nrf2 and SIKE KO mice are more susceptible to $PM_{2.5}$-induced oxidative stress/ROS generation as shown by higher level of MDA, lower level of SOD, and increased inflammation as shown by higher IL-1β, IL-6, TNF-α, and liver injury as shown by higher ALT and AST compared to wildtype mice. These *in vivo* observations on the beneficial effects of *Juglanin* on $PM_{2.5}$-induced liver injury have also been replicated *in vitro* using human liver cell line LO2 [67]. Together, this study suggests the significant involvement of Nrf2 and SIKE pathways in $PM_{2.5}$-induced liver injury and most importantly, *Juglanin* is a potential therapeutic agent to controlling $PM_{2.5}$-induced inflammation, oxidative stress, and liver pathologies. A recent study also showed that Nrf2 protects $PM_{2.5}$ (20mg/kg)-induced lung injury through its regulation of iron-dependent cellular death or ferroptosis. This is supported by the observation that ferroptosis and lung injury in response to $PM_{2.5}$ are more severe in Nrf2-deficient mouse lung tissue and cellular model [68]. Similarly, *Tectoridin* (50-100 mg/kg), a bioactive molecule, also ameliorates $PM_{2.5}$ (20mg/kg for 7 days)-induced lung injury in mice as revealed by decreased morphological damage, necrosis, edema and inflammation with decreased IL-6 and TNF-α through stimulation of antioxidant gene regulator Nrf2 and antioxidant genes like GSH and GPX4. In addition, pretreatment of BEAS-2B cells with *Tectoridin* (25, 50 and 100 μM for 1 h) reduces $PM_{2.5}$ (400 μg/ml for 24h)-induced ROS generation through activation of Nrf2, GSH and inhibition of $PM_{2.5}$-induced inflammatory MDA [68]. These results suggest that *Tectoridin* has potential to controlling $PM_{2.5}$-induced oxidative stress, ferroptosis, and lung pathologies. It is known that exercise-induced myokine, *Irisin*, a polypeptide derived from muscle and adipose tissues, is a potent anti-inflammatory agent that diminishes metabolic syndrome [69]. Interestingly, pretreatment of mice with recombinant *Irisin* (250 μg/kg) significantly diminishes the $PM_{2.5}$ (8mg/kg for 24h)-induced increased level of inflammatory cytokines IL-1β, IL-18, TNF-α and mediators of inflammation including NF-κB, and Nlrp3 inflammasome [70]. Therefore, *Irisin* is an effective myokine in amelioration of $PM_{2.5}$-induced lung pathologies through suppression of inflammatory pathways.

Collectively, the results from these studies in this section indicate that irrespective of the unique characteristics of each natural compound and doses used, all the tested compounds are efficacious in diminishing $PM_{2.5}$-induced pathologies through suppression of massive inflammation and oxidative stress, the prepathogenic events. However, further long-term *in vivo,* and *in vitro* studies are essential to understand in-depth the underlying molecular mechanisms by which these natural compounds directly target specific molecule in cells and govern the factors/mediators involved in inflammation, pyroptosis and oxidative stress.

### 4.3. Lessons from studies using cellular models and synthetic compounds.

The focus of this section is to discuss the major findings on the efficacies of several synthetic compounds in amelioration of $PM_{2.5}$-induced cellular abnormalities including activation of oxidative stress and inflammatory pathways using cellular models [**Table 1**].

Fine particulate matter ($PM_{2.5}$)-induced detrimental effects on endothelial cells, the first cellular barrier of the cardiovascular system, have been well studied. To investigate the contribution of oxidative stress and inflammation on $PM_{2.5}$-induced endothelial injury, the effect of $PM_{2.5}$ on EA.hy926 endothelial cells was examined [71]. $PM_{2.5}$ exposure (50 μg/ml for 24h) induces NOX1/4, superoxide, $H_2O_2$, ET1 and decreases NO pathway. Furthermore, $PM_{2.5}$ causes an imbalance in the ratio of t-PA to PAI-1 due to significantly increased expression of PAI-1 and decreased expression of t-PA. Exposure to $PM_{2.5}$ also augments the expression levels of inflammatory cytokines including IL-1β and IL-18 in this cell line, indicating $PM_{2.5}$ exposure contributes to endothelial dysfunction. Importantly, pretreatment of EAhy.926 cells with NOX1/4 inhibitor (*GSK 13783*) (5uM) diminishes $PM_{2.5}$-induced oxidative stress and inflammation and thus ameliorates $PM_{2.5}$-induced endothelial dysfunction [71]. Hence, NOX1/4 may be a druggable target to reduce air pollutant $PM_{2.5}$-induced endothelial dysfunction and associated cardiovascular diseases. The pharmacological effect of *Ropivacaine*, a widely used local anesthetic, on $PM_{2.5}$-induced acute lung injury has been explored in cultured lung cells [72]. Exposure to $PM_{2.5}$ (100μg/ml) induces the inflammatory and oxidative stress in lung cells BEAS-2B as shown by increased expression of inflammatory cytokines IL-6, IL-8, IL-1β, TNF-α and oxidative stress-related MDA, and decreased expression of GSH. However, pretreatment of BEAS-2B cells with *Ropivacaine* (1 μM, 10 μM, 100 μM) reduces

$PM_{2.5}$-induced inflammatory pathway, oxidative stress, and cell death through downregulation of inflammasome Nlrp3 and apoptotic caspase pathways [72], indicating *Ropivacaine* has potential to reduce $PM_{2.5}$-induced inflammation, oxidative stress, and thus may be effective in diminishing lung injury-associated pathologies. Similarly, pretreatment of human bronchial epithelial cells (16HBE) with Caspase inhibitors *Z-VAD-FMK* and *VX-765* block wood smoke-derived $PM_{2.5}$ (5, 10, 20 μg/ml)-induced inflammation and pyroptosis of 16HBE cells as evidenced by decreased levels of LDH activity, caspase, inflammatory cytokines IL-1β and IL-18, the downstream targets of Nlrp3 [19]. These results show the potential of these synthetic caspase inhibitors to block wildfire/wood smoke-induced massive inflammation and pyroptosis.

**Table 2** The list of natural compounds used in amelioration of air pollution $PM_{2.5}$-induced cellular abnormality and organismal pathologies in preclinical setup. The list includes only the natural compounds which are discussed in this article. Inflamm: Inflammation: OS: Oxidative stress; Pyrop: Pyroptosis; Ferrop: Feroptosis.

| Natural Compounds | Animals/Cells | Reduced PM2.5-induced prepathogenic events | Ref. # |
|---|---|---|---|
| 1. *SalB* | Mice | Inflamm., OS (Lungs) | 53 |
| 2. *Sipeimine* | Mice/Rats | Inflamm., OS, Pyrop. (Lungs) | 54,55 |
| 3. *AS-IV* | Mice/Rats/NR8383 | Inflamm., OS (Lungs, Cells) | 56,57,58 |
| 4. *TLS* | Mice/A549 | Inflamm., OS, Pyrop (Lungs, Cells) | 59 |
| *5. DSQMT* | Rats/NR8383 | Inflamm. (Lungs, Cells) | 60 |
| *6. SF* | Zebrafish/RAW264.7 | Inflamm., OS (Whole Body, Cells) | 61 |
| 7. *Bergapten* | Mice | Inflamm. (Lungs) | 62 |
| 8. *Rosavidin* | Rats | Inflamm., pyrop. (Lungs) | 63 |
| 9. *ECC-BYF* | Rats | Inflamm., OS, Pyrop. (Lungs) | 66 |
| 10. *Juglanin* | Mice/LO2 | Inflamm., OS (Liver, Cells) | 67 |
| 11. *Tectoridin* | Mice/BEAS-2B | Inflamm., OS, Ferrop(Lungs, Cells) | 68 |
| 12 *Irisin* | Mice | Inflamm. (Lungs) | 70 |
| 13. *ATX* | BV2 | Inflamm., OS (Cells) | 79 |
| 14. *OP-D* | MLE-12 | Inflamm. (Cells) | 80 |
| 15. *Coelonin* | RAW264.7/J774A.1 | Inflamm., OS, Pyrop. (Cells) | 83 |

As *Vitamin $D_3$* possesses anti-inflammatory activity, the therapeutic potential of *VitD3* in $PM_{2.5}$-induced inflammation has been assessed in human bronchial epithelial cells (16HBE) [73]. $PM_{2.5}$ (200μg/ml for 48h)-treated 16HBE cells produce elevated levels of ROS and MDA, and the secretion of inflammatory mediators IL-6, IL-18, NF-κB and Nlrp3 inflammasome. However, pretreatment of 16HBE with *VitD3* (1nM) for 24h decreases the $PM_{2.5}$-induced ROS generation, and expression of MDA, IL-6, IL-8, NF-κB and Nlrp3, indicating *VitD3* is effective in inhibition of $PM_{2.5}$-induced inflammatory and oxidative stress responses [73]. Similarly, pretreatment of rat neonatal cardiomyocytes with *VitD3* (10^-8 mol/L) significantly reduce the cooking oil fumes-derived $PM_{2.5}$ (50 μg/ml)-induced ROS production, inflammation and pyroptosis through suppression of inflammatory signaling pathways JAK/Stat1 and NF-κB. Further, *VitD3* also prevents $PM_{2.5}$-induced inhibition of antioxidant SOD and GSH in cardiomyocytes [74]. Collectively, these results indicate that *VitD3* protects heart and lung cells from $PM_{2.5}$-induced inflammation, oxidative stress, and associated pathologies. Another study [75] showed that while the expression levels of inflammatory TLR4, NF-κB and COX2 are significantly increased in $PM_{2.5}$ (250 μg/ml for 24-72 h)-treated RAW264.7 macrophages, pretreatment with TLR4-inhibitor *TAK242* (5-20 μM) significantly inhibits $PM_{2.5}$-induced pro-inflammatory signaling molecules IL-6, MCP1 and TNF-α [75]. Therefore, TLR4-specific inhibitor has potential to controlling $PM_{2.5}$-induced inflammation. Similarly, the levels of inflammatory markers IL-1β, COX2 and oxidative stress marker Hmox1 are also significantly elevated in $PM_{2.5}$-exposed (30 μg/ml for 3h) mouse macrophages. While $PM_{2.5}$-induced inflammatory responses are decreased in RAW264.7 macrophages either by pretreatment with endotoxin neutralizer *polymyxin B* (0.2 mg/ml) or NF-kB inhibitor *Bay 11-7085* (10 μM), the oxidative stress responses are decreased by antioxidant *n-acetyl cysteine (NAC)* (10mM) [76]. Collectively, the results of these *in vitro* studies provide clear evidence that different synthetic compounds targeting different molecules can effectively block $PM_{2.5}$-induced inflammation and oxidative stress pathways in different cellular models.

### 4.4. Lessons from studies using cellular models and natural compounds.

In this section, the major findings on the efficacies of several natural compounds in amelioration of $PM_{2.5}$-induced cellular abnormalities are discussed [**Table 2**]. It is known that exposure to $PM_{2.5}$ not only affects lungs and cardiovascular system but also affects brain and cognitive functions. Air pollutant $PM_{2.5}$ can reach to the brain and contributes to accelerated neurological syndromes including Alzheimer's disease [77,78]. As carotenoid, *Astaxanthin (ATX)* is a known anti-inflammatory and neuroprotective agent, the efficacy of *ATX* on $PM_{2.5}$-induced inflammation and neurotoxicity has been evaluated and demonstrated that $PM_{2.5}$ stimulates the levels of ROS/oxidative stress, inflammatory mediators IL-1β, IL-6, TNF-α, TLR2/4, and COX2 and stress-induced protein HO-1 in BV-2 microglial cells. Most importantly, $PM_{2.5}$ (50 μg/ml/24h) failed to induce the inflammatory markers in rat glial cells pretreated with *ATX* (1, 10 μg/ml) for 4 h. *ATX* also prevents $PM_{2.5}$-induced inhibition of IL-10 and Arg-1. Hence, *ATX* is effective in prevention of $PM_{2.5}$-induced inflammation- and oxidative stress-associated neurological disorders [79]. The plant product *Ophiopogonin D* (*OP-D*) is also an anti-inflammatory agent. Pretreatment of mouse lung epithelial cells MLE-12 with *OP-D* (10-80 μM) for 1h inhibits $PM_{2.5}$ (15 μg/cm^2 for 24h)-induced inflammation as shown by the decreased levels of IL-1β, IL-6, IL-8, and TNF-α. The *OP-D* exerts its anti-inflammatory effect through downregulation of NFκB signaling and activation of AMPK activity as pretreatment of cells with AMPK inhibitor (Compound C, 10 μM) blocks anti-inflammatory activity of *OP-D* [80]. As the dihydrophenanthrene *Coelonin*, derived from the flowering plant *Bletilla striata,* is a known anti-inflammatory agent [81,82], its therapeutic efficacy in amelioration of $PM_{2.5}$-induced inflammation has been evaluated [83]. Pretreatment with *Coelonin* (1.25, 2.5 or 5 μg/ml for 2h) ameliorates $PM_{2.5}$ (200μ/ml for 18h)-induced inflammation, oxidative stress and pyroptosis of RAW264.7 and J774A.1 macrophages through suppression of Nlrp3 inflammasome, IL-6, TNF-α, TLR4, COX2, and NF-κB signaling [83]. These results suggest that different natural compounds are effective in diminishing $PM_{2.5}$-induced massive inflammation, oxidative stress, and pyroptosis.

Therefore, the results of all these cell biology studies suggest that pharmacological modulation of inflammatory mediators or oxidative stress regulators are ideal therapeutic approaches to controlling air-pollutant $PM_{2.5}$-induced disease development. However, more in-depth preclinical studies using proper models are necessary to reproduce the efficacies of these natural and synthetic compounds in $PM_{2.5}$-induced cellular abnormalities and pathologies. It is also important to identify the direct cellular target of each natural compound and the downstream signaling pathway controlling inflammation and oxidative stress.

## 5. Conclusion

Air pollution is one of the major risk factors to human health and shortening of healthspan worldwide. In search of remedies for the air pollution driven stress-induced health risk, many investigations have been undertaken worldwide as discussed in this article. A careful analysis of all these preclinical studies on air pollutant $PM_{2.5}$ and its impact on organismal health unequivocally proved the pivotal contribution of $PM_{2.5}$-induced inflammation and oxidative stress in initiation and progression of a wide variety of pathologies and accelerated aging process. Hence, the development of drug-like small molecules targeting $PM_{2.5}$-deregulated pathogenic factors will be a promising approach for amelioration of $PM_{2.5}$-induced oxidative stress, inflammation, and associated pathologies. Meta-analysis of related published data set on air-pollution deregulated molecules, cellular and biological processes may be helpful to identify unique and common pathogenic factor(s). Based on the observations made by different studies, albeit limited, under different experimental milieus as has been discussed earlier in this article, it is noticeable that while the expression level of Nrf2, the master regulator of antioxidant genes, is decreased, the levels of inflammasome Nlrp3 and pro-aging factor PAI-1 are significantly elevated in response to air pollutant $PM_{2.5}$ exposures. Therefore, development of natural or synthetic drugs either, as an activator targeting Nrf2 or repressor/inhibitor targeting Nlrp3 or PAI-1 will be a feasible approach to abate air pollution-induced initiation of multiorgan pathologies [see **Figure 1**]. Further, it is crucial to evaluate the efficacies of the above-discussed natural and synthetic compounds in diminishing $PM_{2.5}$-induced oxidative stress, inflammation, and pyroptosis by large cohort study in an unbiased preclinical setting. To rule out the possible harmful effects, it is also crucial to determine the toxicity of each synthetic as well as natural compound after long-term use in control and $PM_{2.5}$-exposed animal models. The identification of the most efficacious and non-toxic safe compound for the clinical trial and its success will save billions of people worldwide from air pollution $PM_{2.5}$-induced devastating diseases, and thus will increase the healthspan.

## Compliance with ethical standards

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*Disclosure of Conflict of Interest*

The author declares no conflict of interest.

## References


[1] Orru, H.; Ebi, K.L.; Forsberg, B. The Interplay of Climate Change and Air Pollution on Health. Curr. Environ. Health. Rep. 2017, 4, 504-513.

[2] Steven, S.; Frenis, K.; Oelze, M.; Kalinovic, S.; Kuntic, M.; Bayo Jimenez, M.T.; Vujacic-Mirski, K.; Helmstädter, J.; Kröller-Schön, S.; Münzel, T.; Daiber, A. Vascular Inflammation and Oxidative Stress: Major Triggers for Cardiovascular Disease. Oxid. Med. Cell. Longev. 2019, 2019, 7092151.

[3] Du, Y.; Xu, X.; Chu, M.; Guo, Y.; Wang, J. Air particulate matter and cardiovascular disease: the epidemiological, biomedical, and clinical evidence. J. Thorac. Dis. 2016, 8, E8-E19.

[4] Brook, R.D.; Rajagopalan, S.; Pope, C.A. 3rd; Brook, J.R; Bhatnagar, A.; Diez-Roux, A.V.; Holguin, F.; Hong, Y.; Luepker, R.V.; Mittleman, M.A.; Peters, A.; Siscovick, D.; Smith, S.C. Jr; Whitsel, L.; Kaufman, J.D. American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation. 2010, 121, 2331-2378.

[5] Grande, G.; Ljungman, P.L.S.; Eneroth, K.; Bellander, T.; Rizzuto, D. Association Between Cardiovascular Disease and Long-term Exposure to Air Pollution With the Risk of Dementia. JAMA Neurol. 2020, 77, 801-809

[6] Simkhovich, B.Z.; Kleinman, M.T.; Kloner, R.A. Particulate air pollution and coronary heart disease. Curr. Opin. Cardiol. 2009, 24, 604-609.

[7] Franchini, M.; Mannucci, P.M. Thrombogenicity and cardiovascular effects of ambient air pollution. Blood. 2011, 118, 2405-2412.

[8] Dutheil, F.; Comptour, A.; Morlon, R.; Mermillod, M.; Pereira, B.; Baker, J.S.; Charkhabi, M.; Clinchamps, M.; Bourdel, N. Autism spectrum disorder and air pollution: A systematic review and meta-analysis. Environ. Pollut. 2021, 278, 116856.

[9] Martens, D.S.; Cox, B.; Janssen, B.G.; Clemente, D.B.P.; Gasparrini, A.; Vanpoucke, C.; Lefebvre, W.; Roels, H.A.; Plusquin, M.; Nawrot, T.S. Prenatal Air Pollution and Newborns' Predisposition to Accelerated Biological Aging. JAMA Pediatr. 2017,171, 1160-1167.

[10] Zhang, W.; Li, Z.; Li, G.; Kong, L.; Jing, H.; Zhang, N.; Ning, J.; Gao, S.; Zhang, Y.; Wang, X.; Tao, J. PM2.5 induce lifespan reduction, insulin/IGF-1 signaling pathway disruption and lipid metabolism disorder in Caenorhabditis elegans. Front. Public. Health. 2023,11,1055175.

[11] Kaur, R.; Pandey, P. Air Pollution, Climate Change, and Human Health in Indian Cities: A Brief Review. Front. Sustain. Cities, 2021, 3,705131.

[12] Wu, C.L.; Wang, H.W.; Cai, W.J.; He, H.D.; Ni, A.N.; Peng, Z.R. Impact of the COVID-19 lockdown on roadside traffic-related air pollution in Shanghai, China. Build. Environ. 2021, 194, 107718.

[13] Marwah, M.; Agrawala, P.K. COVID-19 lockdown and environmental pollution: an Indian multi-state investigation. Environ. Monit. Assess. 2022, 194, 49.

[14] Mariussen, E.; Fjellsbø, L.; Frømyr T.R.; Johnsen, I.V.; Karsrud, T.E.; Voie, Ø.A. Toxic effects of gunshot fumes from different ammunitions for small arms on lung cells exposed at the air liquid interface. Toxicol. In Vitro. 2021, 72,105095.

[15] Kim, Y.H.; Vance, S.A.; Aurell, J.; Holder, A.L.; Pancras, J.P.; Gullett, B.; Gavett, S.H.; McNesby, K.L.; Gilmour, M.I. Chemistry and lung toxicity of particulate matter emitted from firearms. Sci. Rep. 2022, 12, 20722.

[16] Zheng, X.Y.; Tong, L.; Shen, D.; Yu, J.E.; Hu, Z.Q.; Li, Y.J.; Zhang, L.J.; Xue, E.F.; Tang, H.F. Airborne Bacteria Enriched PM2.5 Enhances the Inflammation in an Allergic Adolescent Mouse Model Induced by Ovalbumin. Inflammation. 2020, 43, 32-43.

[17] Krall, J.R.; Mulholland, J.A.; Russell, A.G.; Balachandran, S.; Winquist, A.; Tolbert, P.E.; Waller, L.A.; Sarnat, S.E. Associations between Source-Specific Fine Particulate Matter and Emergency Department Visits for Respiratory Disease in Four U.S. Cities. Environ. Health Perspect. 2017, 125, 97-103.

[18] Farina, F; Sancini, G; Mantecca, P; Gallinotti, D; Camatini, M; Palestini, P. The acute toxic effects of particulate matter in mouse lung are related to size and season of collection. Toxicol. Lett. 2011, 202, 209-217.

[19] Fu, X.; Hong, W.; Li, S.; Chen, Z.; Zhou, W.; Dai, J.; Deng, X.; Zhou, H.; Li, B.; Ran, P. Wood smoke particulate matter (WSPM2.5) induces pyroptosis through both Caspase-1/IL-1β/IL-18 and ATP/P2Y-dependent mechanisms in human bronchial epithelial cells. Chemosphere. 2022, 307, 135726.

[20] Merk, R.; Heßelbach, K.; Osipova, A.; Popadić, D.; Schmidt-Heck, W.; Kim, G.J.; Günther, S.; Piñeres, A.G.; Merfort, I.; Humar, M. Particulate Matter ($PM_{2.5}$) from Biomass Combustion Induces an Anti-Oxidative Response and Cancer Drug Resistance in Human Bronchial Epithelial BEAS-2B Cells. Int. J. Environ. Res. Public Health. 2020, 17, 8193.

[21] Nemmar, A.; Vanbilloen, H.; Hoylaerts, M.F.; Hoet, P.H.; Verbruggen, A.; Nemery, B. Passage of intratracheally instilled ultrafine particles from the lung into the systemic circulation in hamster. Am. J. Respir. Crit. Care. Med. 2001, 164, 1665-1668.

[22] Robertson, S; Miller MR. Ambient air pollution and thrombosis. Part. Fibre. Toxicol. 2018, 15, 1.

[23] Wu, X.; Pan, B.; Liu, L.; Zhao, W.; Zhu, J.; Huang, X.; Tian, J. In utero exposure to PM2.5 during gestation caused adult cardiac hypertrophy through histone acetylation modification. J. Cell. Biochem. 2019, 120, 4375-4384.

[24] Nelin, T.D.; Joseph, A.M.; Gorr, M.W.; Wold, L.E. Direct and indirect effects of particulate matter on the cardiovascular system. Toxicol. Lett. 2012, 208, 293-299.

[25] Zhou, Z.; Liu, Y.; Duan, F.; Qin, M.; Wu, F.; Sheng, W.; Yang, L.; Liu, J.; He, K. Transcriptomic Analyses of the Biological Effects of Airborne PM2.5 Exposure on Human Bronchial Epithelial Cells. PLoS One. 2015, 10, e0138267.

[26] 26. Jeong, S.; Park, S.A.; Park, I.; Kim, P.; Cho, N.H.; Hyun, J.W.; Hyun, Y.M. PM2.5 Exposure in the Respiratory System Induces Distinct Inflammatory Signaling in the Lung and the Liver of Mice. J. Immunol. Res. 2019, 2019, 3486841.

[27] Zhao, C.; Pu, W.; Niu, M.; Wazir, J.; Song, S.; Wei, L.; Li, L.; Su, Z.; Wang, H. Respiratory exposure to PM2.5 soluble extract induced chronic lung injury by disturbing the phagocytosis function of macrophage. Environ. Sci. Pollut. Res. Int. 2022, 29,13983-13997.

[28] Ghosh, A.K.; Soberanes, S.; Lux, E.; Shang, M.; Aillon, R.P.; Eren, M.; Budinger, G.R.S.; Miyata, T.; Vaughan, D.E. Pharmacological inhibition of PAI-1 alleviates cardiopulmonary pathologies induced by exposure to air pollutants $PM_{2.5}$. Environ. Pollut. 2021, 287, 117283.

[29] Piao, C.H.; Fan, Y.; Nguyen, T.V.; Shin, H.S.; Kim, H.T.; Song, C.H.; Chai, O.H. PM2.5 Exacerbates Oxidative Stress and Inflammatory Response through the Nrf2/NF-κB Signaling Pathway in OVA-Induced Allergic Rhinitis Mouse Model. Int. J. Mol. Sci. 2021, 22, 8173.

[30] Piao, C.H.; Fan, Y.; Nguyen, T.V.; Song, C.H.; Kim, H.T.; Chai, O.H. PM2.5 exposure regulates Th1/Th2/Th17 cytokine production through NF-κB signaling in combined allergic rhinitis and asthma syndrome. Int. Immunopharmacol. 2023, 119, 110254.

[31] He, M.; Ichinose, T.; Yoshida, Y.; Arashidani, K.; Yoshida, S.; Takano, H.; Sun, G.; Shibamoto, T. Urban PM2.5 exacerbates allergic inflammation in the murine lung via a TLR2/TLR4/MyD88-signaling pathway. Sci Rep. 2017, 7, 11027.

[32] Wang, L.; Cui, Y.; Liu, H.; Wu, J.; Li, J.; Liu, X. PM2.5 aggravates airway inflammation in asthmatic mice: activating NF-κB via MyD88 signaling pathway. Int J Environ Health Res. 2023, 33, 563-574.

[33] Cong, L.H.; Li, T.; Wang, H.; Wu, Y.N.; Wang, S.P.; Zhao, Y.Y.; Zhang, G.Q.; Duan, J. IL-17A-producing T cells exacerbate fine particulate matter-induced lung inflammation and fibrosis by inhibiting PI3K/Akt/mTOR-mediated autophagy. J. Cell. Mol. Med. 2020, 24, 8532-8544.

[34] Han, X.; Zhuang, Y. PM2.5 induces autophagy-mediated cell apoptosis via PI3K/AKT/mTOR signaling pathway in mice bronchial epithelium cells. Exp. Ther. Med. 2021, 21, 1.

[35] Yue, W.; Chen, X.; He, S.; Li, N.; Zhang, L.; Chen, J. Exposure interval to ambient fine particulate matter (PM2.5) collected in Southwest China induced pulmonary damage through the Janus tyrosine protein kinase-2/signal transducer and activator of transcription-3 signaling pathway both in vivo and in vitro. J. Appl. Toxicol. 2021, 41, 2042-2054.

[36] Zou, C.; Yang, H.; Cui, L.; Cao, X.; Huang, H.; Chen, T. Potential hazardous effects of printing room PM2.5 exposure include promotion of lung inflammation and subsequent injury. Mol. Med. Rep. 2020, 22, 3213-3224.

[37] Jin, Y.; Wu, Z.; Wang, N.; Duan, S.; Wu, Y.; Wang, J.; Wu, W.; Feng, F. Association of EGF Receptor and NLRs signaling with Cardiac Inflammation and Fibrosis in Mice Exposed to Fine Particulate Matter. J. Biochem. Mol. Toxicol. 2016, 30, 429-437.

[38] Gu, L.Z.; Sun, H.; Chen, J.H. Histone deacetylases 3 deletion restrains PM2.5-induced mice lung injury by regulating NF-κB and TGF-β/Smad2/3 signaling pathways. Biomed. Pharmacother. 2017, 85, 756-762.

[39] Su, X.; Tian, J.; Li, B.; Zhou, L.; Kang, H.; Pei, Z.; Zhang, M.; Li, C.; Wu, M.; Wang, Q.; Han, B.; Chu, C.; Pang, Y.; Ning, J.; Zhang, B.; Niu, Y.; Zhang, R. Ambient PM2.5 caused cardiac dysfunction through FoxO1-targeted cardiac hypertrophy and macrophage-activated fibrosis in mice. Chemosphere. 2020, 247, 125881.

[40] Wu, X.; Pan, B.; Liu, L.; Zhao, W.; Zhu, J.; Huang, X.; Tian, J. In utero exposure to PM2.5 during gestation caused adult cardiac hypertrophy through histone acetylation modification. J. Cell. Biochem, 2019, 120, 4375-4384.

[41] Xu, M.X.; Zhu, Y.F.; Chang, H.F.; Liang, Y. Nanoceria restrains PM2.5-induced metabolic disorder and hypothalamus inflammation by inhibition of astrocytes activation related NF-κB pathway in Nrf2 deficient mice. Free Radic. Biol. Med. 2016, 99, 259-272.

[42] Wang, X.; Chen, M.; Zhong, M.; Hu, Z.; Qiu, L.; Rajagopalan, S.; Fossett, N.G.; Chen, L.C.; Ying, Z. Exposure to Concentrated Ambient PM2.5 Shortens Lifespan and Induces Inflammation-Associated Signaling and Oxidative Stress in Drosophila. Toxicol Sci. 2017, 156, 199-207.

[43] Vaughan, D.E.; Rai, R.; Khan, S.S.; Eren, M.; Ghosh, A.K. Plasminogen Activator Inhibitor-1 Is a Marker and a Mediator of Senescence. Arterioscler. Thromb. Vasc. Biol. 2017, 37, 1446-1452.

[44] Ghosh, A.K.; Bradham, W.S.; Gleaves, L.A.; De Taeye, B.; Murphy, S.B.; Covington, J.W.; Vaughan, D.E. Genetic deficiency of plasminogen activator inhibitor-1 promotes cardiac fibrosis in aged mice: involvement of constitutive transforming growth factor-beta signaling and endothelial-to-mesenchymal transition. Circulation. 2010, 122, 1200-1209.

[45] Ghosh, A.K.; Vaughan, D.E. PAI-1 in tissue fibrosis. J Cell Physiol. 2012, 227, 493-507.

[46] Upadhyay, S.; Ganguly, K.; Stoeger, T.; Semmler-Bhenke, M.; Takenaka, S.; Kreyling, W.G.; Pitz, M.; Reitmeir, P.; Peters, A.; Eickelberg, O.; Wichmann, H.E.; Schulz, H. Cardiovascular and inflammatory effects of intratracheally instilled ambient dust from Augsburg, Germany, in spontaneously hypertensive rats (SHRs). Part. Fibre. Toxicol. 2010, 7, 27.

[47] Budinger, G.R.; McKell, J.L.; Urich, D.; Foiles, N.; Weiss, I.; Chiarella, S.E.; Gonzalez, A.; Soberanes, S.; Ghio, A.J.; Nigdelioglu, R.; Mutlu, E.A.; Radigan, K.A.; Green, D.; Kwaan, H.C.; Mutlu, G.M. Particulate matter-induced lung inflammation increases systemic levels of PAI-1 and activates coagulation through distinct mechanisms. PLoS One. 2011, 6, e18525.

[48] Ghosh, A.K.; Rai, R.; Park, K.E.; Eren, M.; Miyata, T.; Wilsbacher, L.D.; Vaughan, D.E. A small molecule inhibitor of PAI-1 protects against doxorubicin-induced cellular senescence. Oncotarget. 2016, 7, 72443-72457.

[49] Ghosh, A.K.; Kalousdian, A.A.; Shang, M.; Lux, E.; Eren, M.; Keating, A.; Wilsbacher, L.D.; Vaughan, D.E. Cardiomyocyte PAI-1 influences the cardiac transcriptome and limits the extent of cardiac fibrosis in response to left ventricular pressure overload. Cell. Signal. 2023, 104, 110555.

[50] Jia, H.; Liu, Y.; Guo, D.; He, W.; Zhao, L.; Xia, S. PM2.5-induced pulmonary inflammation via activation of the NLRP3/caspase-1 signaling pathway. Environ. Toxicol. 2021, 36, 298-307.

[51] Zhang, S.; Zhang, W.; Zeng, X.; Zhao, W.; Wang, Z.; Dong, X.; Jia, Y.; Shen, J.; Chen, R.; Lin, X. Inhibition of Rac1 activity alleviates PM2.5-induced pulmonary inflammation via the AKT signaling pathway. Toxicol. Lett. 2019, 310, 61-69.

[52] Xiao, Z.; Liu, W.; Mu, Y.P.; Zhang, H.; Wang, X.N.; Zhao, C.Q.; Chen, J.M.; Liu, P. Pharmacological Effects of Salvianolic Acid B Against Oxidative Damage. Front. Pharmacol. 2020, 11, 572373.

[53] Guan, Y.; Li, L.; Kan, L.; Xie, Q. Inhalation of Salvianolic Acid B Prevents Fine Particulate Matter-Induced Acute Airway Inflammation and Oxidative Stress by Downregulating the LTR4/MyD88/ NLRP3 Pathway. Oxid Med Cell Longev. 2022, 2022, 5044356.

[54] Wang, Y.; Shen, Z.; Zhao, S.; Huang, D.; Wang, X.; Wu, Y.; Pei, C.; Shi, S.; Jia, N.; He, Y.; Wang, Z. Sipeimine ameliorates PM2.5-induced lung injury by inhibiting ferroptosis via the PI3K/Akt/Nrf2 pathway: A network pharmacology approach. Ecotoxicol. Environ. Saf. 2022, 239, 113615.

[55] Huang, D.; Shen, Z.; Zhao, S.; Pei, C.; Jia, N.; Wang, Y.; Wu, Y.; Wang, X.; Shi, S.; He, Y.; Wang, Z.; Wang, F. Sipeimine attenuates PM2.5-induced lung toxicity via suppression of NLRP3 inflammasome-mediated pyroptosis through activation of the PI3K/AKT pathway. Chem. Biol. Interact. 2023, 376, 110448.

[56] Wu, Y.; Xiao, W.; Pei, C.; Wang, M.; Wang, X.; Huang, D.; Wang, F.; Wang, Z. Astragaloside IV alleviates PM2.5-induced lung injury in rats by modulating TLR4/MyD88/NF-κB signalling pathway. Int. Immunopharmacol. 2021, 91, 107290.

[57] Pei, C.; Wang, F.; Huang, D.; Shi, S.; Wang, X.; Wang, Y.; Li, S.; Wu, Y.; Wang, Z. Astragaloside IV Protects from PM2.5-Induced Lung Injury by Regulating Autophagy via Inhibition of PI3K/Akt/mTOR Signaling in vivo and in vitro. J. Inflamm. Res. 2021, 14, 4707-4721.

[58] Huang, D.; Shi, S.; Wang, Y.; Wang, X.; Shen, Z.; Wang, M.; Pei, C.; Wu, Y.; He, Y.; Wang, Z. Astragaloside IV alleviates PM2.5-caused lung toxicity by inhibiting inflammasome-mediated pyroptosis via NLRP3/caspase-1 axis inhibition in mice. Biomed. Pharmacother. 2022, 150, 112978.

[59] Lin, H.; Chen, M.; Gao, Y.; Wang, Z.; Jin F. Tussilagone protects acute lung injury from PM2.5 via alleviating Hif-1α/NF-κB-mediated inflammatory response. Environ. Toxicol. 2022, 37, 1198-1210.

[60] Zhou, Y.; Liu, J.; Jiang, C.; Chen, J.; Feng, X.; Chen, W.; Zhang, J.; Dong, H.; Zhang, W. A traditional herbal formula, Deng-Shi-Qing-Mai-Tang, regulates TLR4/NF-κB signaling pathway to reduce inflammatory response in PM2.5-induced lung injury. Phytomedicine. 2021, 91, 153665.

[61] Lee, H.; Park, C.; Kwon, D.H.; Hwangbo, H.; Kim, S.Y.; Kim, M.Y.; Ji, S.Y.; Kim, D.H.; Jeong, J.W.; Kim, G.Y.; Hwang, H.J.; Choi, Y.H. Schisandrae Fructus ethanol extract attenuates particulate matter 2.5-induced inflammatory and oxidative responses by blocking the activation of the ROS-dependent NF-κB signaling pathway. Nutr. Res. Pract. 2021, 15, 686-702.

[62] Jiang, Y.; Nguyen, T.V.; Jin, J.; Yu, Z.N.; Song, C.H.; Chai, O.H. Bergapten ameliorates combined allergic rhinitis and asthma syndrome after PM2.5 exposure by balancing Treg/Th17 expression and suppressing STAT3 and MAPK activation in a mouse model. Biomed. Pharmacother. 2023, 164, 114959.

[63] Huang, D.; Jia, N.; Pei, C.; Shen, Z.; Zhao, S.; Wang, Y.; Wu, Y.; Shi, S.; Li, S.; Wang, Z. Rosavidin protects against PM2.5-induced lung toxicity via inhibition of NLRP3 inflammasome-mediated pyroptosis by activating the PI3K/AKT pathway. Biochem. Pharmacol. 2023, 213, 115623.

[64] Guo, X.; Lin, Y.; Lin, Y.; Zhong, Y.; Yu, H.; Huang, Y.; Yang, J.; Cai, Y.; Liu, F.; Li, Y.; Zhang, Q.Q.; Dai, J. PM2.5 induces pulmonary microvascular injury in COPD via METTL16-mediated m6A modification. Environ. Pollut. 2022, 303, 119115.

[65] Fan, X.; Dong, T.; Yan, K.; Ci, X.; Peng, L. PM2.5 increases susceptibility to acute exacerbation of COPD via NOX4/Nrf2 redox imbalance-mediated mitophagy. Redox Biol. 2023, 59, 102587.

[66] Li, J.; Wang, J.; Li, Y.; Zhao, P.; Tian, Y.; Liu, X.; He, H.; Jia, R. Effective-component compatibility of Bufei Yishen formula protects COPD rats against PM2.5-induced oxidative stress via miR-155/FOXO3a pathway. Ecotoxicol Environ Saf. 2021, 228, 112918.

[67] Ge, C.; Tan, J.; Zhong, S.; Lai, L.; Chen, G.; Zhao, J.; Yi, C.; Wang, L.; Zhou, L.; Tang, T.; Yang, Q.; Lou, D.; Li, Q.; Wu, Y.; Hu, L.; Kuang, G.; Liu, X.; Wang, B.; Xu, M. Nrf2 mitigates prolonged PM2.5 exposure-triggered liver inflammation by positively regulating SIKE activity: Protection by Juglanin. Redox Biol. 2020, 36, 101645.

[68] Dong, T.; Fan, X.; Zheng, N.; Yan, K.; Hou, T.; Peng, L.; Ci, X. Activation of Nrf2 signalling pathway by tectoridin protects against ferroptosis in particulate matter-induced lung injury. Br. J. Pharmacol. 2023, 180, 2532-2549.

[69] Slate-Romano, J.J.; Yano, N.; Zhao, T.C. Irisin reduces inflammatory signaling pathways in inflammation-mediated metabolic syndrome. Mol. Cell. Endocrinol. 2022, 552, 111676.

[70] Jiao, R.; Han, Z.; Ma, J.; Wu, S.; Wang, Z.; Zhou, G.; Liu, X.; Li, J.; Yan, X.; Meng, A. Irisin attenuates fine particulate matter induced acute lung injury by regulating Nod2/NF-κB signaling pathway. Immunobiology. 2023, 228, 152358.

[71] Zou, L.; Xiong, L.; Wu, T.; Wei, T.; Liu, N.; Bai, C.; Huang, X.; Hu, Y.; Xue, Y.; Zhang, T.; Tang, M. NADPH oxidases regulate endothelial inflammatory injury induced by $PM_{2.5}$ via AKT/eNOS/NO axis. J. Appl. Toxicol. 2022, 42, 738-749.

[72] Zuo, R.; Li, X.Y.; He, Y.G. Ropivacaine has the potential to relieve PM2.5-induced acute lung injury. Exp. Ther. Med. 2022, 24, 549.

[73] Xin, L.; Che, B.; Zhai, B.; Luo, Q.; Zhang, C.; Wang, J.; Wang, S.; Fan, G.; Liu, Z.; Feng, J.; Zhang, Z. 1,25-Dihydroxy Vitamin $D_3$ Attenuates the Oxidative Stress-Mediated Inflammation Induced by $PM_{2.5}$ via the p38/NF-κB/NLRP3 Pathway. Inflammation. 2019, 42, 702-713.

[74] Luo, C.M.; Feng, J.; Zhang, J.; Gao, C.; Cao, J.Y.; Zhou, G.L.; Jiang, Y.J.; Jin, X.Q.; Yang, M.S.; Pan, J.Y.; Wang, A.L. 1,25-Vitamin D3 protects against cooking oil fumes-derived PM2.5-induced cell damage through its anti-inflammatory effects in cardiomyocytes. Ecotoxicol. Environ. Saf. 2019, 79, 249-256.

[75] Fu, H.; Liu, X.; Li, W.; Zu, Y.; Zhou, F.; Shou, Q.; Ding, Z. PM2.5 Exposure Induces Inflammatory Response in Macrophages via the TLR4/COX-2/NF-κB Pathway. Inflammation. 2020, 43, 1948-1958.

[76] Bekki, K.; Ito, T.; Yoshida, Y.; He, C.; Arashidani, K.; He, M.; Sun, G.; Zeng, Y.; Sone, H.; Kunugita, N.; Ichinose, T. PM2.5 collected in China causes inflammatory and oxidative stress responses in macrophages through the multiple pathways. Environ. Toxicol. Pharmacol. 2016, 45, 362-369.

[77] Shou, Y.; Huang, Y.; Zhu, X.; Liu, C.; Hu, Y.; Wang, H. A review of the possible associations between ambient PM2.5 exposures and the development of Alzheimer's disease. Ecotoxicol. Environ. Saf. 2019, 174, 344-352.

[78] Thiankhaw, K.; Chattipakorn, N.; Chattipakorn, S.C. PM2.5 exposure in association with AD-related neuropathology and cognitive outcomes. Environ. Pollut. 2022, 292, 118320.

[79] Kim, R.E.; Shin, C.Y.; Han, S.H.; Kwon, K.J. Astaxanthin Suppresses PM2.5-Induced Neuro-inflammation by Regulating Akt Phosphorylation in BV-2 Microglial Cells. Int. J. Mol. Sci. 2020, 21, 7227.

[80] Wang, Y.; Li, D.; Song, L.; Ding, H. Ophiopogonin D attenuates PM2.5-induced inflammation via suppressing the AMPK/NF-κB pathway in mouse pulmonary epithelial cells. Exp. Ther. Med. 2020, 20, 139.

[81] Jiang, F.; Li, M.; Wang, H.; Ding, B.; Zhang, C.; Ding, Z.; Yu, X.; Lv, G. Coelonin, an Anti-Inflammation Active Component of Bletilla striata and Its Potential Mechanism. *Int. J. Mol. Sci*. 2019, 20, 4422.

[82] Lv, S.S.; Fu, Y.; Chen, J.; Jiao, Y.; Chen S.Q. Six phenanthrenes from the roots of Cymbidium faberi Rolfe and their biological activities. Nat. Prod. Res. 2022, 36, 1170-1181.

[83] Bao, X.D.; Zu, Y.Y.; Wang, B.X.; Li, M.Y.; Jiang, F.S.; Qian, C.D.; Zhou, F.M.; Ding, Z.S. Coelonin protects against PM2.5-induced macrophage damage via suppressing TLR4/NF-κB/COX-2 signaling pathway and NLRP3 inflammasome activation in vitro. Environ Toxicol. 2023, 38, 1196-1210