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The impact of particulate matters on apoptosis in various organs: Mechanistic and therapeutic perspectives

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ABSTRACT

Ecological air contamination is the non-homogenous suspension of insoluble particles into gas or/and liquid fluids known as particulate matter (PM). It has been discovered that exposure to PM can cause serious cellular defects, followed by tissue damage known as cellular stress. Apoptosis is a homeostatic and regulated phenomenon associated with distinguished physiological actions inclusive of organ and tissue generation, aging, and development. Moreover, it has been proposed that the deregulation of apoptotic performs an active role in the occurrence of many disorders, such as autoimmune disease, neurodegenerative, and malignant, in the human population. Recent studies have shown that PMs mainly modulate multiple signaling pathways involved in apoptosis, including MAPK, PI3K/Akt, JAK/STAT, NFκB, Endoplasmic Stress, and ATM/P53, leading to apoptosis dysregulation and apoptosis-related pathological conditions. Here, the recently published data concerning the effect of PM on the apoptosis of various organs, with a particular focus on the importance of apoptosis as a component in PM-induced toxicity and human disease development, is carefully discussed. Moreover, the review also highlighted the various therapeutic approaches, including small molecules, miRNA replacement therapy, vitamins, and PDRN, for treating diseases caused by PM toxicity. Notably, researchers have considered medicinal herbs a potential treatment for PM-induced toxicity due to their fewer side effects. So, in the final section, we analyzed the performance of some natural products for inhibition and intervention of apoptosis arising from PM-induced toxicity.

1. Introduction

Environmental air pollution is one of the most destructive origins of atmosphere pollution, which directly participates in the deterioration of ecological communities. It is emanated from both natural processes and human interferences [1]. The contaminants comprise the complex blend

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of toxicant gases and pollution particulate matter (PM) [2]. The PM stands for the air-borne, small liquid or solid particles hanging in the air, which prepare a heterogeneous mixture. The mixture is composed of elemental and organic carbon, biological components (bacteria, spores, and pollens), inorganic components (trace metals, nitrates, sulfates, and ammonium), and organic compounds (polycyclic aromatic hydrocarbons; PAHs) [3,4]. According to aerodynamic particle size, PM is classified into three main subgroups, including PM10, PM 2.5, and ultrafine particles (UFPs). In recent years, due to the bursting growth in industrial activities, all three main classes of PMs have been associated with an exponential increment of environmental contamination [5]. PM is an essential subject in the human health threat. Recently, many research efforts have focused on the consequence of air contamination on the fatality rate [6–8]. In this context, Manjunatha et al. designed a study to survey the effect of existing PMs on the living ecosystem of zebrafish (Danio rerio) embryo/larvae as the disease model. Their finding suggested that PM 2.5 dramatically affects the mortality rate increment, changes the patterns of morphological variation, reduces the hatching amount, and decreases the heartbeat in zebrafish. Moreover, it induces the increment of string heart length and pericardium region. Consequently, the apoptosis leads to reduced normal intersegmental vessels (ISVs) and the motor neurons at the trunk area, and the development of the liver in zebrafish fetuses face unwanted disorders. Furthermore, scanning electron microscope analysis revealed that PM 2.5 brings on the detriment in larvae skin cell layers. Also, based on histological tests, it was reported that the larvae in the exposure to PM 2.5 suffer from some defects in neurons, liver, heart, gills, brain, and eyes. The prominent increment in cellular and sub-cellular levels of organelle dissolution also conclusively proves the undeniable effect of PM 2.5 on the occurrence of disorders in zebrafish's different organs [9]. Additionally, Li et al. designed an experiment on mice models to investigate the impact of PM10 eye drops on the performance of tears and the structure of the outer layers of the ocular. Their results suggested that PM10 triggers the apoptosis in the outer layers and the basal corneal epithelium, which results in unwanted segregation and multiplication of the ocular outer layers with a superior expression amount of K10 and decreasing in the count of goblet cells in the conjunctival fornix. Their results further disclosed that PM10 grows the amount of TNF-α, NF-κB-p65, and NF-κB in the cornea. Consequently, PM10, mainly via apoptosis induction, can change the tear film performance and have unwanted destructive effects on the formation of ocular outer layers in mice models. In this manner, PM10, mainly by activating NF-κB and TNF- α and apoptosis induction, could led to Dry eye syndrome [10]. Notably, Yuan et al. discovered that the ROS-MAPKs-apoptosis/cell cycle arrest route mainly performs in PM2.5-induced embryotoxicity by applying the rat whole embryo culture process. Their results demonstrated that exposure to PM 2.5 in concentrations equivalent to or greater than 50 μg/ml causes unexpected deficiencies in fetal development, such as reduced yolk sac dimension, crown-rump area, head length, and somite amount. Additionally, the consequence of this study further proved that the development of the fetus in the vicinity of PM2.5 with a particular concentration goes along with cell apoptosis and G0/G1 phase arrestment. Moreover, the ROS generation followed by JNK and ERK activation may be associated with PM2.5-induced apoptosis and G0/G1 phase arrest according to down-regulation of the Bcl-2/Bax protein proportion and up-regulation of p15INK4B, p16INK4A, and p21WAF1/CIP1 transcription amount. In this way, their results showed that the ROS-JNK/ERK-apoptosis and G0/G1 arrest processes accompany PM2.5-induced embryotoxicity. This procedure opens a better understanding of the PM2.5-triggered embryotoxicity molecular mechanism and provides detailed information regarding the involved pathways to improve the unwanted pregnancy consequence of PM2.5 [11]. The obtained results demonstrated that PM causes abnormalities in the growth of various tissues, such as the cardiovascular, blood veins, and lungs. These disorders are concurrent with endoplasmic reticulum (ER) stress, oxidative stress, inflammatory reactions, and apoptosis. Therefore, according to recent findings, PM-induced toxicity involves apoptosis dysregulation.

Currently, there are no effective strategies for treating PM-induced toxicity, so an urgent need is to develop efficient therapeutic strategies for alleviating PM-induced toxicity. Consequently, an extensive investigation of the molecular apoptosis procedure followed by PM-triggered toxicity would benefit prevention activities and clinical therapies for health problems caused by PM. In this manner, we discussed the mechanistic insight into apoptosis mediated by PM in the current work. We highlighted that PMs, mainly by modulating apoptosis signaling pathways, including MAPK, PI3K/Akt, JAK/STAT, NFκB, Endoplasmic Stress, and ATM/P53, exert damaging effects on multiple organs in the human body. In the final section, we will highlight that targeting apoptosis via small molecule inhibitors, miRNA replacement therapy, and herbal medicine are promising strategies for treating PM-induced toxicity.

2. Apoptosis

Apoptosis, also known as scheduled cell death, is essential in fetus growth and tissue homeostasis of multi-cellular structures. It is performed in a programmed way, accompanied by some construction changes such as cell contraction, chromatin condensation, and cytoplasmic membrane blabbing [12,13]. In general, apoptosis is done in two different ways: the first mechanism (as intrinsic route) is the mitochondria-mediated procedure, and the second is based on the receptor's death on the external layer of cells (extrinsic route). Extracellular ligands like Fas ligand (Fas-L), tumor necrosis factor (TNF), and TRAIL attach to the extracellular domain of the DR (transmembrane receptors), i.e., the type 1 TNF receptor (TNFR1), Fas (also known as CD95/Apo-1), and TRAIL receptors, respectively, to initiate the extrinsic pathway. The sequence of occurred procedure during the externally induced part of apoptosis could be determined through FasL/FasR and TNF-α/TNFR1 models. The inducement of DRs by particular death ligands (DLs) causes the development of a death-inducing signaling complex (DISC). The DISC includes DD-containing FAS-associated death protein, an adaptor molecule, procaspase-8, procaspase-10, and the cellular FLICE inhibitory proteins (c-FLIPs) [14]. To start the apoptosis, it is required that while the prodomain of caspase 8 is at the DISC, the active caspase 8 separates from DISC to initiate the cascade of caspase activation. The caspases are essential initiators of the apoptosis procedure, and their function is very closely related to their structure having different substrate preferences. Death effector domain (DED) consists caspase-8 and caspase-10 in which caspase recruitment domains (CARD) involve caspase-1, caspase-2, caspase-4, caspase-5, caspase-9, caspase-11 and caspase-12. Generally, caspases are sorted as initiator, effector, or executioner according to their location in apoptotic signaling cascades [15]. The intrinsic route, stimulated via different forces generated from outside or inside the cell, consists of oxidative tension, radiation exposure, and chemotherapeutic agents. Bax, Bak insertion in the mitochondrial membrane intervenes in the intrinsic pathway. Afterward, cytochrome c diffused from the mitochondrial intermembrane space areas toward the cytosol. Bcl-2 and Bcl-xL as anti-apoptotic proteins that prohibit the diffusion of cytochrome c. The apoptosome is obtained by incorporating cytochrome c with Apaf–1 and procaspase-9 [16]. Apoptosome is a multi-protein assembled that consists of a seven-spoke ring-shaped structure that stimulates caspase 9 after the actuation of caspase-3 signaling caspase cascade that causes the cell destruction and brings out the apoptosis [17]. The proteins associated with intrinsic routes are SMAC/DIABLO (Second mitochondrial activator of caspases/direct IAP binding protein with low PI), Caspase-9 (Cysteinyl aspartic acid-protease-9), Bcl-2 (B-cell lymphoma protein 2), Bcl-w (Bcl-2 like protein), Nox (Phorbol-12-myristate-13-acetate-induced protein 1), Aven (Cell death regulator Aven) and Myc (Oncogene Myc). The execution phase delivers the final route of apoptosis. The caspase-8, and 9 are activator caspases. In contrast, the

caspase-3, caspase-6, caspase-7, Caspase-10, CAD (Caspase-activated DNAse), and PARP (Poly (ADP-ribose) polymerase) are categorized as effector caspases. The autocleavage activates the initiator caspases and executioner caspases that finally result in the proteolyze of some substrates, which causes apoptosis. Executioner caspases initiate cytoplasmic endonuclease that leads to the apoptotic bodies through chromatin condensation and the formation of cytoplasmic blebs [18].

3. Major signaling pathway related to apoptosis

3.1. MAPK in apoptosis

Sturgill and Ray discovered a novel serine/threonine kinase in insulin-treated 3T3-L1 adipocytes more than 30 years ago. As it is responsible for facilitating the phosphorylation of microtubule-associated protein 2 (MAP-2), it was given the acronym "MAP kinase" (MAPK). In mammalians, 14 MAPK members divided into 7 subgroups have been identified, including four conventional MAPK subgroups that work in a typical three-tiered module, such as extracellular-regulated kinase (ERK1/2), C-Jun N-terminal kinase (JNK), p38 MAPK, and ERK5, and three atypical MAPK subgroups that do not follow the classical three-tiered, dual-phosphorylation signaling structure, such as ERK3/4, ERK7/8, and Nemo-like kinase (NLK) [19]. Moreover, many other studies demonstrated that MAPKs perform an important function in commuting the extra-cellular stimulants to the cell reactions, such as cell development, migration, productivity, differentiation, and death. Amongst p38, MAPK and JNK are stimulated obviously after being exposed to harsh physical, chemical, or biological situations. JNKs and p38 MAPKs are two kinases that, in exposure to extra-cellular and intracellular triggering conditions, perform a vital role in regulating cell development and death [20]. The results of many research in apoptosis propose that the JNKs and p38 MAPKs operation occurred in cell context-specific and cell type-specific mechanisms to associate the signals of transcription-dependent and transcription-independent routes. Finally, the mechanisms mentioned earlier make the caspase activation [21]. Many proteins from the Bcl-2 group with pro-and anti-apoptotic functions are subjected to the command of JNK and/or p38 MAPK cascades at the transcriptional level. Several transcription elements are controlled via JNK and P38, which cause a reduced anti-apoptotic protein expression and a prominent increment in the expression of pro-apoptotic proteins. The dimeric (homo- or heterodimer) complex composed of proteins from the ATF (activating transcription factor), Jun (c-Jun, JunB, and JunD), MAF (V-maf musculoaponeurotic fibrosarcoma), and Fos (c-Fos, FosB, Fra1, and Fra2) families are known as transcription factor AP-1 (activator protein 1), and it is a crucial JNK target. The activator protein 1 (AP-1) is responsible for the control of several cellular development and apoptosis procedures. The apoptosis procedure accompanies the AP-1 activation, but its vital role in cellular lifetime is undeniable. The intra and extracellular conditions influence the pro-apoptosis and anti-apoptosis performance of AP-1 activation [22]. Moreover, The P53 tumor suppressor protein is a well-known transcription factor controlled through JNK and P38 MAPK cascades in the apoptosis procedure. When cells are exposed to stressful situations, the p53 protein may become stabilized and activated by JNK-mediated phosphorylation. This leads to programmed cell death due to the JNK-mediated cell stress response. Similar to the c-Jun element of AP-1, p53 associates with other proteins such as p53-p73 dimers which have been found to be vital in initiating programmed cell death. After JNK activation, p53 gets phosphorylated on Thr81 in the proline-rich domain (PRD), facilitating the association of p53 and p73 in a dimer. The prepared dimer helps express many pro-apoptotic target genes such as puma and Bax. Additionally, some other transcription factors are involved in MAPK-triggered apoptosis. For example, under oxidative stress conditions, the release of the transcription factor FoxO1 is amplified under the influence of JNK-catalyzed phosphorylation, leading to cell apoptosis [23]. Notably, many researchers investigated the role of the MAPK signaling pathway in PM-induced apoptosis. In this regard, Ming et al. [24] revealed that PM2.5 exposure could exacerbate the progression of thoracic aortic aneurysm and dissection (TAAD), which could be induced by the increased apoptosis in human aortic smooth muscle cells (HASMCs) through the ERK1/2 MAPK signaling pathway. Thereby, MAPK pathways play a crucial role in PM-induced apoptosis.

3.2. PI3K/Akt in apoptosis

PI3Ks are intracellular lipid kinases that are categorized into three main groups based on their construction and selectivity. PI3Ks are crucial upstream of the PI3K/AKT signaling route [25]. Group I has a heterodimer structure and is activated by surface receptors. These lipid kinases consist of regulatory subunit P85 and catalytic subunit P110. The amino end of P85 contains two proline-rich domains and a Src Homology 3 (SH3) domain, while the carboxy end contains two SH2 regions and a non-catalytic domain that interacts with P110. When upstream signals phosphorylate PI3K/AKT, it initiates various biological processes, such as phosphorylation of downstream molecules, including actin-related protein, GSK-3β, FoxO family members, and mTOR, or forming complexes with them. The main downstream target of PI3K/AKT signaling is mTOR [26]. Moreover, it acts as an agent that controls cell metabolism by altering regular cell cycles. Likewise, the PI3K/Akt signaling pathways can regulate and prevent apoptosis by inhibiting Bcl2-antagonist of cell death bcl-2-like protein 11 (BIM), caspase-9, and forkhead box protein O1 (FoxO1) [27]. Notably, several experimental studies have demonstrated the role of PI3K/Akt signaling in PM-induced apoptosis. Recent research has revealed that PM2.5 can cause cardiomyocyte apoptosis and contribute to cardiac dysfunction through the PI3K/Akt pathway [28]. Therefore, the PI3K/Akt pathway is a potentially crucial regulator of PM-induced apoptosis.

3.3. JAK/STAT signaling pathway in apoptosis

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway is a critical component of cellular performance. Additionally, numerous other growth factors and cytokine agents have been identified as operating through the JAK/STAT signaling cascade [29]. The JAK/STAT signaling pathway contains interleukins (ILs), hormones, colony-stimulating factors, and interferons (IFNs). This pathway mediates various downstream events, including immune fitness, adipogenesis, hematopoiesis, inflammation, tissue repair, and apoptosis. The JAK/STAT signaling route is comprised of the ligand-receptor complex, JAKs, and STATs, making it an evolutionarily conserved pathway. Within this family, JAK1, JAK2, JAK3, and TYK2 are the four members of the JAK family. The STAT family also includes STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 [30]. In the JAK-mediated route, the cytokine connection of its receptor causes the dimerization of the receptor. This process is followed by phosphorylation of the receptor's cytoplasmic region. Subsequently, STAT proteins are recruited to activate the receptor in the tyrosine phosphorylation region. Finally, the STAT protein undergoes translocation and connects with DNA parts such as promoters or enhancers, resulting in the control of gene transcription. Through this process, the expression of STAT1 enhances the expression of certain apoptosis proteins, including Bcl-2, Bcl-xL, and Bcl2l1, which subsequently participate in apoptosis [31]. For instance, STAT1 triggers the preparation of apoptotic protein caspase 1, 11, and 3 and reacts with the P53 protein. Additionally, STAT1 could trigger Fas, Bcl-2, and Bcl-X gene expression. Recently, some research results demonstrated that the straight restriction of STAT3 or prevention of STAT3 dimerization via lowering Bcl-xL, Bcl-2, Survivin, and Mcl-1 levels stimulate apoptosis of breast tumor cells [32]. Notably, several studies have investigated the role of JAK/-STAT signaling in PM-induced dysregulation of apoptosis. A recent experimental study has shown that PM10 exposure could lead to cell

cycle arrest and apoptosis evasion through STAT3 activation via PKCζ and Src kinases in lung cells [33]. Thereby, PM, by modulating JAK/-STAT signaling, could lead to dysregulation of apoptosis.

3.4. NFκB in apoptosis

In 1986 Baltimore et al. discovered the nuclear factor kappa B (NFκB). The NFκB is a factor in the nucleus of B lymphocytes that are connected to the enhancer of the kappa light chain of immunoglobulin. This factor exists in their inactivated form in the cytoplasm of cells and exhibits evolutionary conservation from flies to humans [34]. As soon as it becomes active, NFκB moves to the nucleus, which controls the expression of more than 300 genes. There are several known forms of NFκB, including NFκB1 (p50/p105), NFκB2 (p52/p100), RelA (p65), RelB, and c-Rel. The finding that NFκB activation occurs during or just before cell apoptosis under stimulatory conditions led to the hypothesis that this activation is critically linked to preventing apoptosis. The activated form of NFκB preserves the cell against apoptosis by inducing survival genes such as TRAF1, TRAF2, c-IAP1, c-IAP2, IEX-IL, Bcl-xL, and BfI-1. Similarly, c-FLIP is another anti-apoptosis protein whose gene is regulated by NFκB. Although c-FLIP possesses apparent homology with pro-caspase-8, it has no catalytic activity. Overinduction of c-FLIP performs its role by blocking caspase-8 activation [35]. In particular conditions, the NFκB may increase cell death. This phenomenon is due to the induction of genes coding for the death receptor Fas or its ligand FasL [36]. Khandelwal et al. introduced a new effective nucleolar performance of RelA, which triggers apoptosis. They suggested that, besides NF-κB transcriptional performance, a viral nucleolar localization signal (NoLS)–RelA fusion protein could target RelA to the nucleolus and facilitate apoptosis. Their results showed that nucleophosmin (B23.1) is essential for both this apoptotic effect and the stress-induced nucleolar RelA's apoptotic effect. Additionally, their research findings revealed that the translocation of RelA was associated with the relocalization of NPM from the nucleolus to the cytoplasm. Finally, they demonstrated that RelA-induced accumulation of BAX in the mitochondria causes apoptosis by cytoplasmic NPM relocation [37]. Moreover, several studies investigated and demonstrated the possible role of NFκB in PM-induced apoptosis. In this regard, a recent experimental investigation disclosed that exposure to PM induces cardiomyocytes' apoptosis after myocardial infarction through NFκB activation. Therefore, NFκB activation may play a critical role in PM2.5-induced apoptosis [38].

3.5. Endoplasmic Stress in apoptosis

In the endoplasmic reticulum (ER), transmembrane proteins and those intended for secretion are created and folded [39]. Many variables influence protein folding quality, such as ATP, Ca2 + , and an oxidizing environment, which facilitate the construction of disulfide bonds. This organelle is extremely sensitive to harsh conditions that lower cellular energy, the redox state, or the number of calcium ions. Exposure to similar stressful situations decreases the protein-folding capacity of the endoplasmic reticulum. Consequently, unfolded proteins accumulate and aggregate in the endoplasmic reticulum, resulting in a condition known as ER stress [40]. In a resting state, the pro-apoptotic proteins Bax and Bak (Bax/Bak) remain inactive due to their interaction with BCL2 within the mitochondria and endoplasmic reticulum. Bim (BH3) is also restricted through its connection with cytoskeletal dynein. However, severe endoplasmic reticulum stress leads to the activation of c-Jun N-terminal kinase (JNK) and C/EBP homologous protein (CHOP), initiating the induction phase. JNK and CHOP remove the anti-apoptotic impact of BCL2; CHOP prevents BCL-2 expression, while JNK phosphorylates it. Furthermore, JNK phosphorylates Bim, causing it to be released from the cytoskeleton and become activated. These changes ultimately lead to the activation of both Bax and Bak, transmission of the signal from the ER to the mitochondria, and cell death in the execution phase. Caspases can be triggered in the endoplasmic reticulum or the apoptosome, followed by the transmission of death signals to the mitochondria and the subsequent release of cytochrome c [41]. Notably, recent studies have explored whether ER is involved in PM-induced apoptosis. In this context, Kim et al. analyzed and identified the effect of PM2.5 on keratinocyte apoptosis using RNA-sequencing (RNA-Seq) data. In their study, PM2.5-treated keratinocytes exhibited changes in cell cycle-related genes and genes involved in ER stress and intrinsic apoptosis. They concluded that by modulating ER, PM could lead to dysregulation of apoptosis in keratinocytes. Therefore, we could consider ER a vital mediator in PM-induced toxicity and apoptosis dysregulation [42].

3.6. ATM/P53 in apoptosis

When cells are exposed to genomic stress, certain signals support genomic resistance. These signaling networks activate the DNA repair machinery and trigger apoptotic cell death if DNA damage cannot be repaired. Such signals are attributed to the DNA damage response (DDR), where the tumor suppressor p53 is a primary downstream target. In response to DNA damage, p53 becomes phosphorylated by proteins such as ATM, ATR, DNA-PKcs, Chk1, Chk2, and MK2, leading to its stabilization and subsequent function as a transcription factor [43,44]. Phosphorylation at the N-terminal region next to the MDM2-binding site lowers ubiquitin-dependent degradation, causing tetramerization in the nucleus. Subsequently, p53 signaling cooperates in two cellular responses. P53 increases cell apoptosis during genotoxic stress by transactivating target genes such as NOXA, PUMA, DR5, BAK, and BAX. Additionally, p53-mediated transcriptional activation of CDKN1A, GADD45A, or RPRM improves the occurrence of stable cell cycles and provides time for the repair of genotoxic lesions [45]. Previous studies have shown that PM can induce apoptosis by modulating ATM/P53. Soberanes et al. investigated whether p53 is required for PM-induced apoptosis in human and rodent alveolar type (AT) 2 cells. They demonstrated that PM-induced apoptosis might occur via a unique p53-mitochondrial interaction relevant to lung cancer resulting from exposure to air pollution. Thus, the P53/ATM signaling pathway may be critical in PM2.5-induced apoptosis. This highlights the importance of understanding the mechanisms behind air pollution-induced diseases such as lung cancer [46] (Fig. 1).

4. Mechanistic insight into PM2.5-induced apoptosis in different organs

4.1. PM2.5-induced apoptosis in respiratory system

Recent studies showed that Fine particulate matter (PM2.5) is an essential risk factor of respiratory diseases, and the most important pathogenesis is abnormal apoptosis in airway epithelium. In this regard, recent experimental investigation disclosed that exposure to cigarette smoke solution may trigger intrinsic apoptosis of bronchial epithelial cells, and the presence of PM2.5 could exacerbate this effect. As well, the administration of the caspase inhibitor, Z-VAD FMK, may partially alleviate the apoptosis triggered by cigarette smoke solution or PM2.5-cigarette smoke solution. It was concluded that PM2.5 aggravated the caspase-dependent intrinsic apoptosis of cigarette-inflamed bronchial epithelial cells [47]. Furthermore, the study conducted by Li et al. aimed to explore the impact of Serum- and glucocorticoid-inducible kinase 1 (SGK1) on PM2.5-induced cellular apoptosis and injury within human lung alveolar epithelial A549 cells. Their initial discoveries indicated a decline in SGK1 expression within human lung alveolar epithelial (A549) cells exposed to PM2.5. In addition, their investigation demonstrated that augmenting SGK1 expression significantly reduced PM2.5-induced A549 cell apoptosis and curbed the production of ROS. Moreover, their experimentation revealed that exposure to PM2.5 had a notable impact on the ERK1/2 activation while impeding the AKT activation. Conversely, the excessive expression of SGK1 appeared to

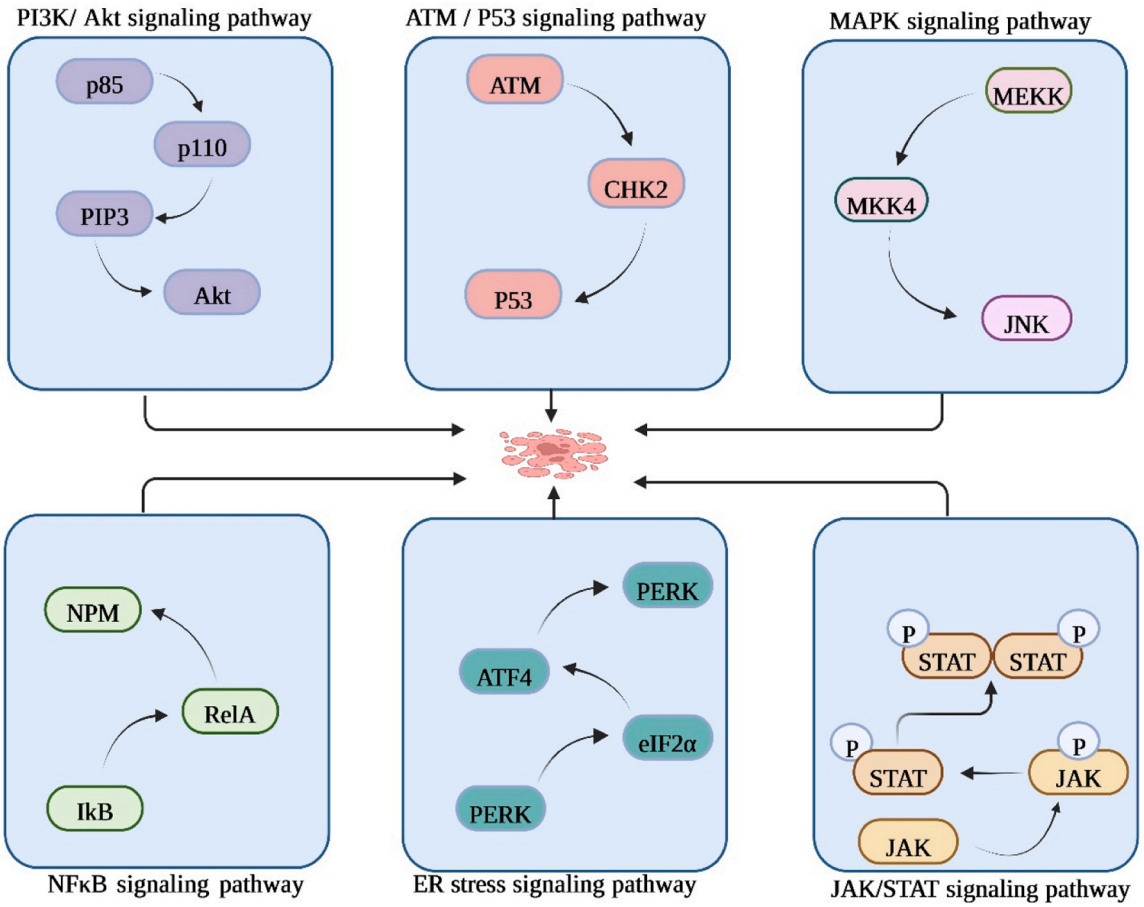

Fig. 1. Major signaling pathway involved in apoptosis.

counteract this effect. Finally, in the rescue experiment, it was observed that MK2206, which was classified as an AKT inhibitor, could mitigate the impact of SGK1 on A549 cell apoptosis. On the other hand, PD98059, categorized as an ERK1/2 inhibitor, did not exacerbate the effect any further. Taken together, their findings indicate that in human lung alveolar epithelial A549 cells, SGK1 may inhibit PM2.5-induced cell apoptosis and the generation of reactive oxygen species (ROS) through the involvement of ERK1/2 and AKT signaling pathways [48]. In another research, Liu et al. demonstrated the effect of apoptosis, oxidative tension, cytotoxicity, and cell cycle arrest activated by COF-derived PM2.5 in primary fetal alveolar type II epithelial cells (AEC II cells). Their results proved that the fume from cooking oil caused apoptosis in the endoplasmic reticulum stress route, marked by elevated levels of GRP78 and caspase-12, apoptotic markers associated with ER stress. Consequently, the COF-derived PM2.5-induced toxicity in the primary fetal AEC II cells is mediated by oxidative stress and ER stress that causes apoptosis [49]. Moreover, Deng et al. investigated the effect of PM2.5 on apoptosis in A549 cells. Their findings suggested that exposure to PM2.5 induces oxidative stress, which subsequently activates multiple cell death pathways in A549 cells. These include the tumor necrosis factor-alpha (TNF-α)-induced pathway, as evidenced by TNF-α secretion and activation of caspase-8 and − 3, and the intrinsic apoptosis pathway, as evidenced by increased expression of the pro-apoptotic protein Bax, decreased expression of the anti-apoptotic protein Bcl-2, disruption of mitochondrial membrane potential, and activation of caspase-9 and − 3. They concluded that in response to the oxidative stress caused by PM2.5, human lung epithelial A549 cells undergo both extrinsic and intrinsic apoptosis [50]. In addition, Chen et al. aimed to investigate the effects of exposure to Standard Reference Material of fine particulate matter (SRM 2786) on the apoptosis of lung bronchial epithelial cells (16HBE cells) and whether stimulating cells with SRM 2786 can hasten cell death triggered by lipopolysaccharide (LPS)-driven inflammation. They reported that SRM 2786 induces apoptosis of 16HBE cells, as evidenced by a significant decrease in the expression of Bcl-2 and an increase in the expression of Bax. Furthermore, they revealed that the percentage of apoptotic cells upon exposure to 500 μg/ml of SRM 2786 was elevated from 2.43 ± 0.21% to 43.96 ± 2.95% compared to the control group. Their subsequent functional experiments showed that lipopolysaccharide pretreatment accelerated apoptosis by increasing the production of NO and ROS, which was further exacerbated by SRM 2786 stimulation. Notably, their study showed that the levels of NO and ROS in cells exposed to LPS before treatment with 125 μg/ml of SRM 2786 were 28% and 11.6% higher than those without pretreatment. They concluded that SRM 2786 could induce apoptosis of 16HBE cells by producing free radicals. Finally, they demonstrated that an inflammatory state can exacerbate the degree of apoptosis [51]. Similarly, Xiong et al. explored the influence of fine PM on rat NR8383 cell line apoptosis and investigated the rate of apoptosis in the context of inflammation induced by lipopolysaccharide (LPS). Their results demonstrated that SRM 2786 alone causes apoptosis in a dose-dependent manner, as shown by the noticeable decrease in the expression of Bcl-2 and the parallel increase in Bax, indicating that PM may activate apoptosis through a mitochondria-mediated apoptotic mechanism. On the other hand, the increased amounts of free radicals such as NO and ROS further demonstrate the effect of oxidative stress on apoptosis. Additionally, they revealed that pre-treatment with LPS increases the apoptosis rate of NR8383 cells induced by SRM 2786. Thus, SRM 2786 activated cell apoptosis in NR8383 cells via oxidative stress, and the increased amounts of NO and ROS further support this fact. They also validated that inflammation can enhance the degree of apoptosis

[52]. Elsewhere, Reyes-Zárate et al. designed an experiment to explore the behavior of STAT3 in epithelial cells when exposed to PM10. They also studied the probable influence of STAT3 on cell survival. Their data proved that PM10 activates STAT3 through Src and PKCζ kinases and controls p21Waf1/Cip1 induction, followed by inhibited STAT3 phosphorylation, which causes cell apoptosis. As stated in the context of immunological function and apoptosis evasion in tumor growth and progression, their findings imply that exposure to PM10 may activate a survival pathway connected to STAT3 activation [33]. To further investigate the apoptosis caused by PM2.5, Zhou et al. exposed human bronchial epithelial (16-HBE) cells to various doses of PM2.5 (16–128 μg/ml) over 24 h. Their findings revealed a dose-dependent relationship between PM2.5 exposure and the induction of apoptosis, DNA strand breakage, and oxidative damage in 16-HBE cells. Additionally, the expression of P53 and P73 increased in parallel with the increment of PM2.5 in the 16-HBE cells, while the expression of p21Cip1/WAF1 demonstrated a decreasing trend. Mdm2 expression fluctuated, rising then falling, although not noticeably. Thus, according to their findings, PM2.5 may cause oxidative damage and promote apoptosis in 16-HBE cells through modulation of p53-dependent mechanisms [53]. In this manner, PM mainly by modulating apoptosis signaling pathway, particularly ROS, P53, TNF-α, and STAT3 led to respiratory system toxicity (Fig. 2).

5. PM2.5-induced apoptosis in cardiovascular system

Recent experimental investigation demonstrated that exposing to PM2.5 led to a decline in cell vitality, and even cell apoptosis within the cardiovascular system. In this context, Yang et al. determined the effect of PM2.5 on the cardiomyocyte's (AC16) cells. Their experimental results showed that when the AC16 cells were subjected to PM2.5, the LDH secretion was elevated in a dose-related behavior, although the cell viability rate decreased. Also, Malondialdehyde (MDA) synthesis and the formation of reactive oxygen species (ROS) increased, whereas glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) levels decreased (GSH-Px). Their results further suggested that PM2.5 can increase the AC16 cell's apoptosis. Additionally, they revealed that when the AC16 cells were subjected to PM2.5, the amount of protein in the Caspase-3, Caspase-9, and Bax increased. In contrast, the anti-apoptotic protein level diminishes. Thereby their research revealed that the mitochondria-mediated apoptotic pathway was partly responsible for the myocardial cytotoxicity produced by PM2.5 in the AC16 cell line, suggesting that PM2.5 may play a role in cardiac dysfunction [54]. The adverse impact of PM2.5 on myocardial after MI and the possible causes were also investigated by Li et al. Their experimental results proposed that PM2.5 disrupts cardiac performance and enlarges the infarct in the treated mouse. On the other side, they, via flow cytometry and western blotting on the Caspase 3, Bax, and BCl-2, demonstrated that being exposed to PM2.5 increases the apoptosis rate in vitro and in vivo significantly. Also, PM2.5 promoted NFκB pathway activation and augmented IL-1 and IL-6 gene expression in neonatal mouse ventricular myocytes (NMVMs) with hypoxia, which could be significantly reversed by SN-50-induced suppression of NFκB nucleus translocation. Finally, they proved that PM2.5 triggers myocardium apoptosis, causes cardiac dysfunction, and exacerbates MI by activating NFκB [38]. Furthermore, Montiel-Dávalos et al., by analyzing cell death, NFκB translocation, ROS, and nitric oxide (NO), study the influence of PM2.5 and PM10 of Mexico City on endothelial cells. Their findings evolved that PM synthesizes ROS, NO, and the translocation of NF-κB and cell apoptosis. Thus, a close presumed link between PM exposure and inflammatory and cardiovascular disorders exists. They conclude that ROS-mediated oxidative stress is a crucial mechanism by which PM induces HUVEC activation and death [55]. Elsewhere, Cao et al. experiments demonstrated the relationship between the intracellular amount of ROS, apoptosis, and mitogen-activated protein kinases (MAPKs). They conducted their experiments in the rat cardiac H9c2 cells exposed to PM2.5. Their results demonstrated that PM2.5 causes an evident decrement in the Bcl-2/Bax amount and increases the cleaved caspase-3 ratio. Additionally, their western blots experiment illustrated increased phosphorylation of MAPKs, including extracellular signal-regulated protein kinases (ERKs), c-Jun NH2-terminal kinases (JNKs), and p38 MAPK in the cells exposed to PM2.5. They also found that the p38 MAPK inhibitor SB239063

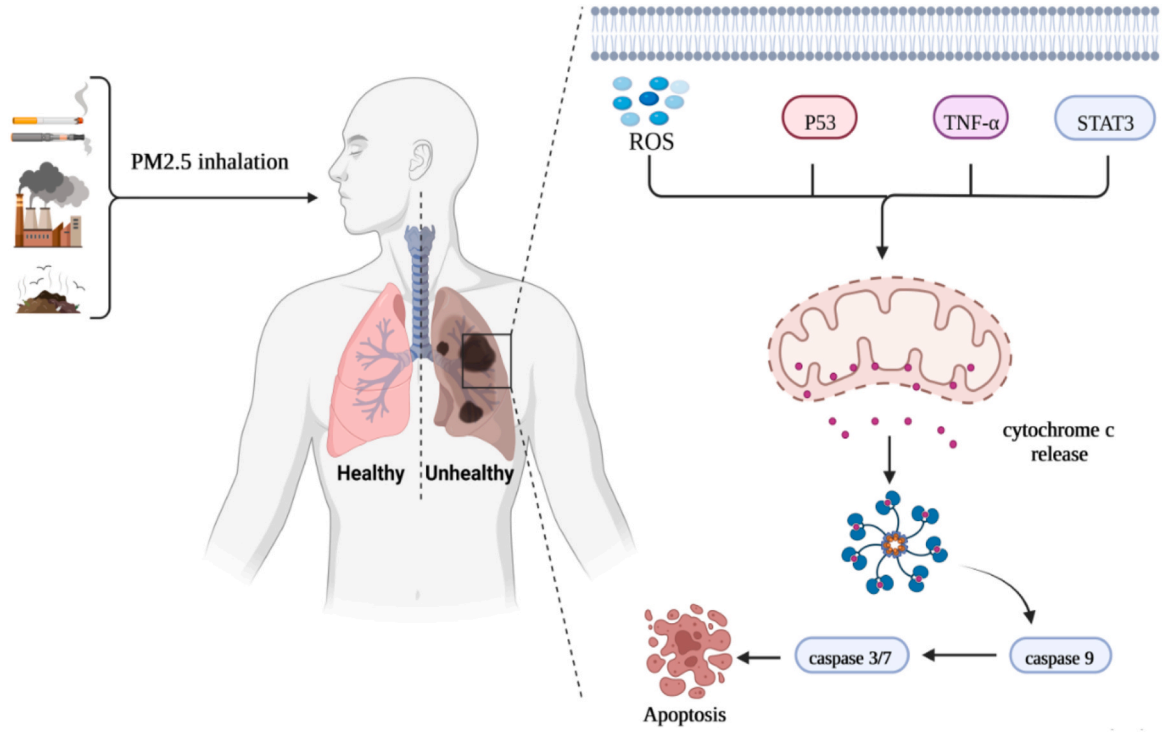

Fig. 2. Major signaling pathway involved in PM-induced toxicity in lung system.

reduced PM2.5's impact on apoptosis and the production of related proteins, whereas the ERKs inhibitor PD98059 had the opposite effect. Importantly, their results confirmed the reversed effect of PM2.5 on cell viability through ROS production and triggering the MAPK signaling pathway in H9c2 cells. Thus, they demonstrated that the MAPK signaling pathway could be considered a novel, distinctive therapeutic approach to preventing cardiac injury brought on by PM2.5 [56]. In outstanding research by Wang et al., the particulate matter (APM)-induced endothelial cell apoptosis from subcellular levels, including mitochondrial dysfunction and ER stress, was studied. Their finding suggested that PM SRM1648a causes calcium overload and oxidative stress in the EA.hy926 cells. Moreover, they revealed that some disturbance in the structure and function of the endoplasmic reticulum and mitochondria could be seen due to the particles. Such dysfunctions include mitochondrial fission and disappearance of cristae and swelling ERs, overproduction of mtROS, and substantial reduction in mitochondrial membrane potential (MMP). On the other hand, they reported that the antioxidant agents and calcium modulators could improve subcellular performance by improving subcellular function. Notably, antioxidants reduce cell stress in two distinct ways: mitochondrial and ER stress-mediated pathways. However, calcium modulators have a role in cell death that is not mediated by mitochondria. They concluded that the presence of PMs in endothelial cells disturbs the redox balance and calcium homeostasis, which causes the organelles to be damaged, and cell apoptosis [57]. In addition, Nichols et al. examined cellular apoptosis pathways in the heart after exposure to PM from local mountain-top mining (MTM). In their study, the MTM PM was administered intravenously to Sprague Dawley rats within one mile of an active MTM site, and heart tissue samples were collected for analysis. From heart tissue examination, they found that the amount of Bax/Bcl-2 in rats exposed to PMs has increased, confirming cell apoptosis. Also, in their study, Caspase-3 and − 9 activities showed an increasing manner, with no noticeable change in the caspase-8 performance. Their results demonstrated mitochondrially-driven apoptosis in the heart tissue that can be accompanied by an increase in a key transition pore constituent, cyclophilin D. In this manner; they found that heart exposure to MTM PM is associated with increased essential transition pore, which may explain the increased mitochondrially-driven apoptosis [58]. Additionally, the mechanism by which PM2.5 exposure induces acute cardiovascular events was examined by Wang et al. using high-risk cardiovascular disease patients as a model population. Their results suggested that JNK or JNK/p53 regulated Bcl-2 and Bax, subsequently increasing caspas3 expression and resulting in cardiomyocyte apoptosis following PM2.5 exposure. In their study, the hyperlipidemic rats showed more significant effects of PM2.5 on the JNK/p53 route than the normal rats. This may be why PM2.5 severely affects hyperlipidemic rats in terms of inducing inflammation and oxidative stress. As a result of PM2.5 exposure in hyperlipidemic rats, they experienced more severe inflammation and oxidative stress in their circulation, as well as a disorder of hypercoagulability and apoptosis of cardiomyocytes, which was mediated by the JNK/P53 pathways [59]. An investigation was conducted by Wang et al. using flow cytometry to determine whether PM2.5 induced apoptosis in human umbilical vein endothelial cells (HUVECs) in culture. They found that PM2.5 exposure led to increased HUVECs apoptosis in a concentration-dependent manner compared to the negative control. They also discovered a close association between the increment in the amount of PM2.5 and a noticeable rise in p53 phosphorylation, reduced Bcl-2/Bax ratio, and enhancement in activation of the downstream proteins caspase-9, − 7, − 3, and PARP. In this manner, HUVEC-induced apoptosis in response to PM2.5 primarily occurs through the p53-Bax-caspases pathway. They concluded that ambient PM2.5 exposure damages cardiovascular systems by inducing EC apoptosis. [60]. Similarly, Yin et al. designed an experiment in EC to study the relevance of PM2.5 concentration and exposure time with the COX-2/mPGES-1/PGE2 cascade activation. Based on the western blotting analysis, they observed an apparent time- and dose-dependent increase of COX-2 at protein amount. In their study, PM2.5 did not demonstrate an evident change in the COX-1 mRNA expression. In another experiment, they tested mPGES-1 expression, and a significant increase was observed. They also, via prevention of COX-2 by using a specific COX-2 inhibitor, found that NS-398 influentially prevents cell apoptosis and inflammation. In their study, PM2.5 activated the COX-2/PGES/PGE2 inflammatory pathway in vascular endothelial cells, promoting cell apoptosis and inflammation [61]. Thereby, PM mainly caused cardiovascular system damage by altering the apoptotic signaling cascade, namely ROS, P53, NFκB, and RAS/ERK (Fig. 3).

6. PM2.5-induced apoptosis in nervous system

The recent experimental investigation demonstrated that PM2.5 can induce apoptotic cell death in the nervous system, eventually leading to impaired nervous system function. In the study by Chen et al., neuronal apoptosis and synaptic injury were investigated concerning exposure to PM2.5 throughout the year. PM2.5 was found to affect the expression of apoptosis-related proteins expression (primarily Bcl-2 and Bax), activate caspase-3, and trigger neuronal death. Their study observed decreased synaptic functional protein N-methyl-D-aspartate (NMDA) receptor subunit (NR2B) and synaptic structural protein PSD-95 expression due to PM2.5 exposure. Surprisingly, PM2.5 in the winter demonstrated the highest effect on apoptosis, further confirming this phenomenon's season-related behavior. Furthermore, the impact was accompanied by a reduction in phosphorylation of both cAMP-response element binding protein (p-CREB) and extracellular signal-regulated kinase 1/2 (p-ERK1/2). In this manner, they concluded that winter PM2.5 had a substantial role in inducing neuronal and synaptic damage apoptosis across various season samples [62]. Furthermore, Zhang et al. investigate the endoplasmic reticulum (ER) stress-induced apoptosis by PM2.5 in different concentrations from 25 μg/ml to 250 μg/ml for 24 h in SH-SY5Y cells. They demonstrated that the human SH-SY5Y cells exposed to PM2.5 are subjected to an increased amount of cell apoptosis compared to the control group. Also, the expression level of GRP78 and phosphorylation of IER1α and p38 were upregulated. On the other hand, the CHOP/DR5/Caspase8/Caspase12, as the critical genes in endoplasmic reticulum stress, showed a significant increment following exposure to PM2.5. Their research indicates that PM2.5 stimulates ER stress, leading to apoptosis in SH-SY5Y cells and ultimately contributing to neurological disorders [63]. Moreover, Ji et al. studied the PM2.5 influences on the olfactory bulb (OB) of C57BL/6 mice using a real-ambient PM2.5 exposure system over four or eight weeks. They found that exposure to real-ambient PM2.5 trigger OB neuron loss, both in terms of apoptosis and ultra-microstructure analysis. In their study, real-ambient PM2.5 exposure activated microglia and increased tumor necrosis factor (TNF)-mediated signaling in the OB of mice displaying depressive-like behaviors, as shown by KEGG pathway analysis and immunofluorescence analysis. Moreover, their ex vivo biosensor experiment suggests that PM2.5 may cause systemic inflammation, increasing the inflammatory factors leading to microglia activation. Their further in-vitro co-culture models exhibited that PM2.5 stimulate the microglia cells' activation through TNFα leakage and triggers neuronal cell death employing typical caspase3 signaling. They show that PM2.5-induced microglial activation may cause neurotoxicity directly or indirectly via a systemic inflammatory response, as demonstrated by the production of tumor necrosis factor (TNF). Altogether, for early identification and potential pathogenic processes of PM2.5-induced depression, the notion that PM2.5 may impair OB may be crucial. Thereby, the primary mechanism by which PM damages the nervous system is through alteration in apoptotic signaling cascades, such as ROS, MAPK, TNF-α, and RAS/ERK [64] (Fig. 4).

7. PM2.5-induced apoptosis in reproductive system

Several experimental findings revealed that toxicants such as PM2.5

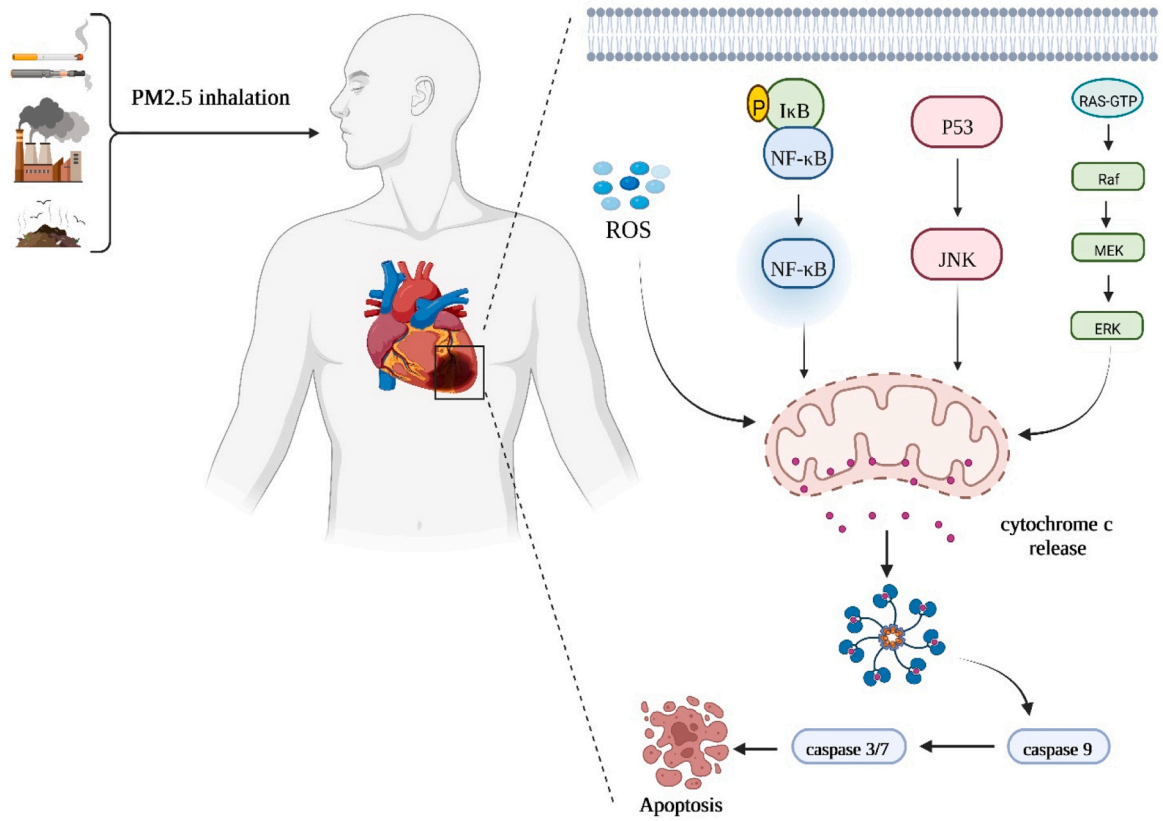

Fig. 3. Major signaling pathway involved in PM-induced toxicity in cardiovascular system.

induce reproductive dysfunction through apoptotic signaling pathways. In this regard, Liu and coworkers studied the effect of PM2.5 on spermatocyte cells' apoptosis pathway. According to their findings, PM2.5 exposure harms testicular tissue, resulting in impaired mitochondrial integrity in GC-2spd cells. PM2.5 not only causes ROS production but also activates the ATM/P53/CDK2 and mitochondrial apoptosis pathway autophagy signal pathways, triggering apoptosis in GC-2spad cells directly. In response to oxidative DNA damage, PM2.5 activates p53 through ATM signaling, leading to apoptosis via the intrinsic mitochondrial route. The researchers concluded that PM2.5 implicated in spermatogenesis dysfunction by activating the mitochondrial apoptosis pathway [65]. Elsewhere, Jo and collogues determined the poisonous influence of PM10 on the mouse oocyte maturation period. Their experiments concluded that PM10 exposure triggers the mitochondrion-derived superoxide dysfunctions and production of intracellular ROS as oocyte develops. The results of Real-time RT-PCR further proved that PM10 exposure resulted in an apparent increase in pro-apoptosis-related genes (Casp3 and Bax) as well as mitochondrial apoptosis-associated gene (Cycs) and a significant decrease in anti-apoptosis-related gene Bcl2l1. According to their results, PM10 causes some problems in oocyte and embryological growth via mitochondrial dysfunction, reactive oxygen production, and DNA destruction [66]. Moreover, Cao et al. used Sprague-Dawley (SD) rat models to examine the underlying mechanism of PM2.5-related male infertility. They observed that exposure to PM2.5 led to a rise in the levels of ROS in the rat testis, which in turn caused Sertoli cells to experience oxidative damage and, ultimately, apoptosis [67]. In addition, Zhang et al. looked at how PM2.5 affects male reproductive health from the RIPK1-mediated apoptotic signaling cascade perspective. They suggest that after exposure to PM2.5, caspase-8, RIPK1, and FAS-L expression increased parallel with the PM2.5 concentration increment. Also, their finding proposed that PM2.5 can trigger RIPK1 apoptotic signaling route in the testis tissue, which causes apoptosis. Therefore, according to these findings, PM-induced toxicity in the reproductive system is associated with an altered apoptotic signaling pathway [68].

8. PM2.5-induced apoptosis in skin

Piao et al. researched the biological processes by which PM2.5 damages the skin. DNA damage, protein carbonization, and lipid peroxidation have all been demonstrated in vitro and in vivo as results of ROS generation and oxidative stress induced by PM2.5. Mitochondrial swelling, endoplasmic reticulum stress, apoptosis, and autophagy were also observed in mouse skin tissue and HaCaT cells following PM2.5 exposure. N-acetyl cysteine attenuated PM2.5-induced cellular injury, confirming that oxidative stress was responsible for PM2.5's toxicity [69]. Moreover, Jun et al. studied how PM affects human hair follicles in vitro and hair follicular keratinocytes ex vivo. They discovered that exposure to PM boosted the generation of ROS and Duox1, an essential member of the NOX family in outer root sheath (ORS) cells. In addition, they found that treatment with PM induced a rise in the expression of MMP-1/3 in ORS cells. Their further experimentation disclosed that activation and expression of the MMP gene through keratinocyte signaling pathways are known to be under ROS-mediated matrix breakdown. Therefore, in addition to modifying biomolecules, ROS from PM can also trigger MMP activation, leading to apoptosis and inflammation in the skin, particularly in epidermal keratinocytes. In this manner, due to increased ROS levels and inflammatory cytokines produced by PM from air pollution, follicular keratinocytes may undergo apoptosis, resulting in hair loss. Their results show that PM-induced toxicity in the skin is due primarily to dysregulated apoptotic signaling pathways [70].

9. PM2.5-induced apoptosis in Ocular system

Yang et al. designed an experiment to investigate the influence of the

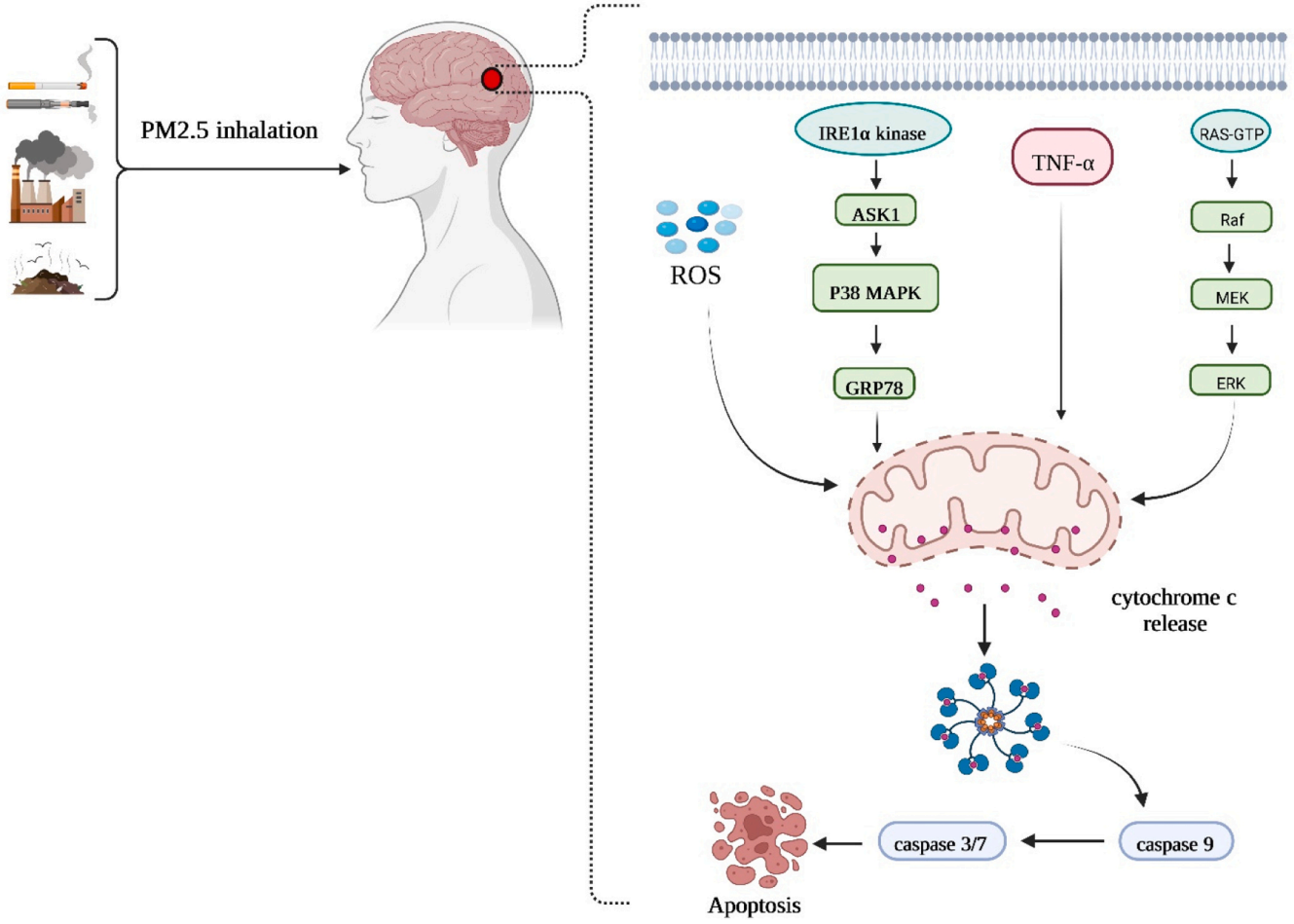

Fig. 4. Major signaling pathway involved in PM-induced toxicity in brain system.

PM (SRM 2786) treatment on the C57BL/6 mice ocular surfaces and culture Human corneal epithelium (HCE). Fine suspension of PM was administered to C57BL/6 mice for as long as 6 months in their research. Their results proved that fine PM causes injuries in the mouse eye. During treatment, the time and the applied dose of PM were also influential in the damages. They observed that parallel with the developing damage to the corneal epithelium, the break-up time of tear films and secretion reduced. Also, the apoptosis of conjunctival goblet cells and the conjunctival epithelial cells hypoplasia increased. Moreover, in both the conjunctiva and cornea of animals treated with fine PM, IL-23, IL-22, IL-18, and MCP-1 levels were upregulated. Furthermore, in HCE cells exposed to fine PM for 12 h and 24 h, there was an increase in apoptosis and ROS production in a time- and dose-dependent manner. In addition to demonstrating cytotoxicity against HCE cells, their research also indicated that exposure to fine PM suspension resulted in alterations to the ocular surface that were clinically comparable to those seen in dry eyes. These findings demonstrate that the dysregulated apoptotic signaling pathway is primarily responsible for PM-induced toxicity in the visual system [71].

10. PM2.5-induced apoptosis in kidney system

Huang et al. investigated the toxicity of PM2.5 on the proximal tubule epithelial cells (HK-2 cells). Their experiments showed that PM2.5 cause an elevated oxygen species generation and increased apoptosis in the proximal tubule epithelial cells. In addition, they observed an elevated expression of Nrf2, HO-1, and NQO1 and a decreased expression of Keap1, which confirmed that the antioxidant route is activated by PM2.5 exposure. Moreover, exposure to PM2.5 has also been demonstrated to activate apoptotic pathways, as shown by an upregulation of pro-apoptotic proteins caspase-8, caspase-3, and Bax and downregulation of anti-apoptotic proteins Bcl-2. They determined that PM2.5 caused harm to HK-2 cells through the antioxidant and apoptotic pathways. Consequently, these findings indicate that PM-induced kidney injury is primarily attributed to dysregulated apoptotic signaling pathways [72].

11. PM2.5-induced apoptosis in immune system

According to Liu et al., the study aimed to examine the toxic influence of PM2.5 and possibly the mechanisms by which they impacted the macrophage foam cell generation induced by oxidized low-density lipoprotein (ox-LDL). There was a decline in cell viability and an increase in LDH levels, both indicators of cytotoxicity, in macrophage foam cells exposed to PM2.5. In addition, after being exposed to PM2.5, macrophage foam cells showed severe damage to their mitochondria, including swelling, rupturing of the cristae, and mitochondria disappearance. Their study further showed that PM2.5 augmented the apoptotic rate by increasing Caspase-3, Bax, Caspase-9, and Cyt C proteins and the downregulation of Bcl-2, representing the activation of mitochondria-mediated apoptosis. Thereby, their results raise the possibility that PM2.5 exacerbates lipid buildup, mitochondrial dysfunction, and apoptosis in macrophage foam cells, contributing to atherosclerosis development. In this manner, PM2.5 exposure is associated with increased immune system cell apoptosis, which could lead to immune system-related disorders [73] (Fig. 5).

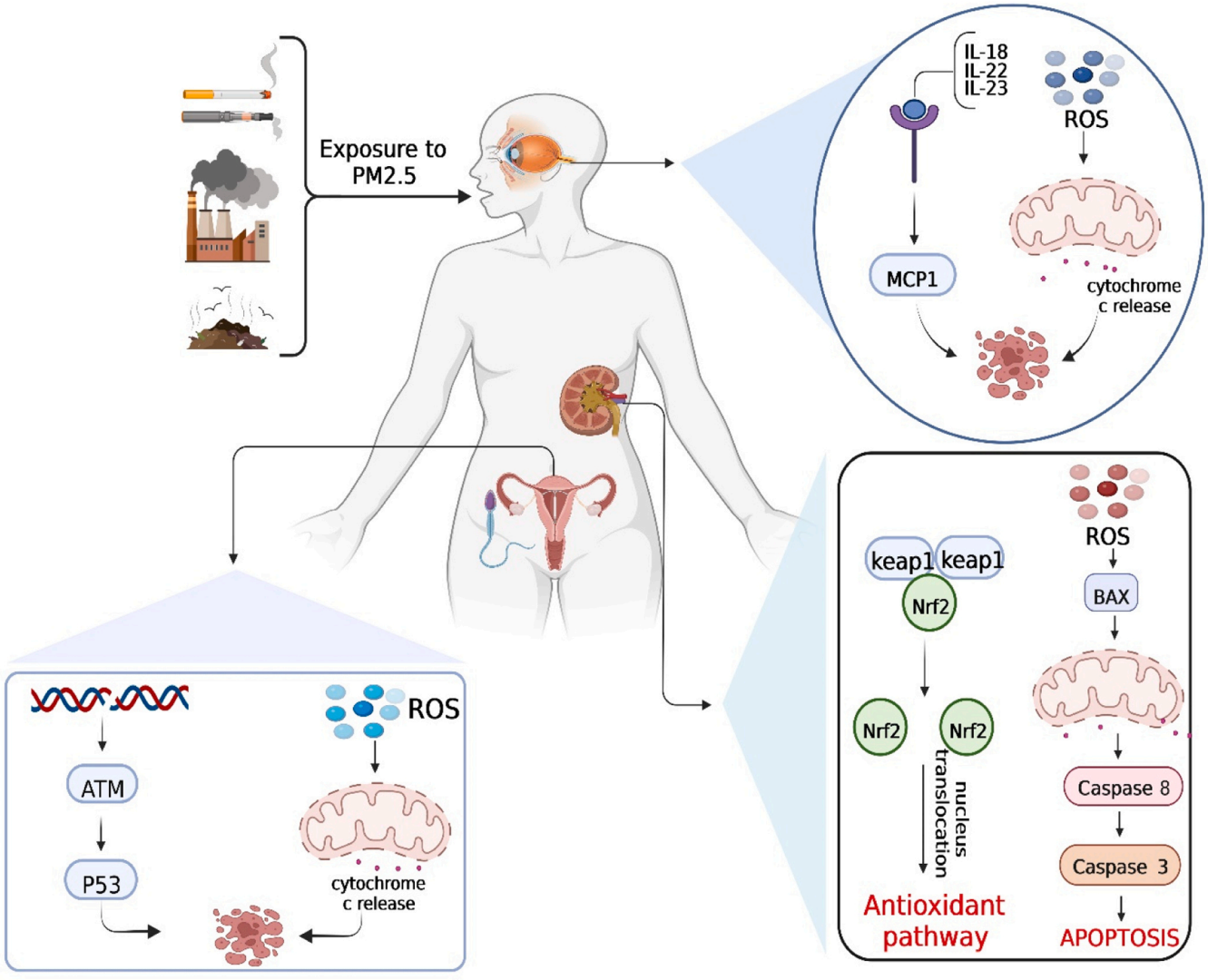

Fig. 5. Major signaling pathway involved in PM-induced toxicity in different organs such as ocular, kidney, and reproductive system.

12. Targeting apoptosis could alleviate PM-induced toxicity

Apoptosis or programmed cell death, serves numerous critical functions in mammals. During the initial stages of development, cell death plays a key role in the formation of fingers and toes by eliminating any excess cells. During the process of neuronal development, cell death plays a crucial role in removing neurons that are no longer necessary once they have established synaptic contacts at their final targets [74]. Apoptosis is also responsible for maintaining tissue homeostasis by eliminating damaged or spent cells, as well as shaping the immune system through the removal of harmful cells. Anomalies in apoptosis have become a major field of interest to researchers and could result in dysregulated inflammatory response and tissue injury. Some diseases pertain to deficiency of apoptosis while others pertain to its redundancy [75]. A growing number of evidences demonstrated that PM could upregulate apoptosis-related genes and pathways to induce apoptosis. This raises the possibility that targeting apoptosis related genes and signaling pathways could be exploited as an alternative strategy to combat PM-induced toxicity. This highlights the possibility of repurposing apoptosis blocking drugs to treat PM-induced toxicity with the economic benefits of accelerating the path from bench to bedside. Thereby, there are currently several compounds that have reached the stage of experimental evaluation that target specific apoptotic regulators. The following section provides an overview of these strategies and agents.

13. Targeting apoptosis in PM-induced toxicity via small molecules

In terms of targeted drugs, there are generally two broad classifications: small molecules and macromolecules (e.g., monoclonal antibodies). In comparison to macromolecule drugs, small-molecule targeted drugs offer certain advantages in terms of pharmacokinetic (PK) properties, cost-effectiveness, patient adherence, as well as the storage and transportation of drugs. Despite challenged by macromolecule drugs represented by monoclonal antibodies in recent years, small-molecule targeted drugs still gain great development. Over the past decade, there have been remarkable advances in identifying and creating new small-molecule inhibitors that target apoptosis pathways to treat a variety of diseases. As a result of these efforts, certain compounds are now undergoing clinical development. In this regard, ABT-199/venetoclax is a highly effective class of small molecule BCL-2 inhibitors that shows high response rate in hematological malignancies [76]. The recent experimental investigation also revealed that ABT-199 could ameliorate toxicity induced by environmental toxicants. In this regard, Geng et al. conducted research to determine the pathological characteristics of lung inflammation brought on by PM and to test the hypothesis that Bcl-2 is critical to developing and maintaining this

inflammation. Their study provides an effective model of PM-induced lung inflammation over time. The in vivo data demonstrated a rise in inflammatory cell numbers. Inflammatory cells were found to be more viable due to increased anti-apoptosis protein Bcl-2 expression. Mice with Bcl-2 overexpression were found to have a diminished ability to eliminate PM-induced inflammatory cells following PM administration. Finally, by causing inflammatory cells to apoptosis, the researchers could reduce inflammatory reactions brought on PM via administering a selective Bcl-2 inhibitor, ABT-199, as a local treatment. As a result, ABT-199 could be used to manage and treat lung inflammation brought on by environmental causes [77].

14. MiRNA replacement therapy for PM2.5-induced toxicity

MicroRNAs have been identified as vital endogenous gene expression modifiers in every tissue [78–81]. These small RNAs are non-coding and have ~22-nt length endogenously-initiated small RNA molecules that are effective in post-transcriptionally and repressing mRNAs translation or modification of cleavage of target mRNAs [82–85]. Notably, a recent investigation disclosed that miRNAs function as a critical player in PM-induced toxicity [86]. Li and coworkers surveyed the key miRNA regulating apoptotic pathways in exposure to PM2.5. They demonstrated that environmental stressors influence the expression profile of microRNAs. Li et al. aimed to employ human A549 cells as a model of target lung cells to determine which biological pathways and processes are controlled by miRNAs and contribute to the ambient PM2.5 inhalation-induced toxicity. MiRNA microarrays were used to profile the changes in miRNAs following PM2.5 treatment. Their results revealed that miRNA-1306 and miRNA-1228 are deregulated, and the primary biological pathways include apoptosis, which conducts a considerable amount of apoptotic portions of A549 cells. Their results further disclosed that PM2.5-triggered A549 apoptosis is started by mitochondrial dysfunction, and the miR-1228 performs a protective role toward apoptosis following treatment with PM2.5. Thus, the authors concluded that mitochondria dysfunction is the root cause of PM2.5-induced apoptosis in A549 cells and that miR-1228 * might function as a protective agent in A549 cells from apoptosis [87]. Furthermore, a study by Li et al. examined miR-486's protecting role in preventing cell injury caused by PM2.5. Their experiments revealed that following PM2.5 treatment, the miR-486 is expressed lower than usual, and the miR-486 mimic treatment decreases (ROS) production and cell apoptosis. Moreover, they discovered that miR-486 regulates the protein amounts of PTEN and FOXO1 negatively, and miR-486 mimics decreased the Bax/Bcl2 ratio. Also, it was shown that PTEN and FOXO1 intervene in the miR-486 protection role when the human lung alveolar epithelial A549 cells are exposed to PM2.5. Their results proposed that the administration of miR-486 can be considered a helpful route against cell injuries triggered by PM2.5. In this manner, the application of miRNA replacement therapy to combat PM2.5-induced toxicity is worth [88]. These findings demonstrated that miRNA profile modulation could be beneficial for diagnosis and a potential therapeutic agent against toxicity induced by environmental toxicants such as PM. However, despite the impressive potential of miRNAs, significant obstacles hinder their use as therapeutic agents. One of the key challenges lies in the delivery of miRNA-targeting agents, which is critical for achieving their intended effects within cells and tissues. Achieving effective delivery with high specificity and efficacy remains a significant problem. Other limitations include limited in vivo stability, tissue distribution, and untoward side effects. Although either viral vectors or nonviral delivery systems such as liposomes could overcome these challenges, both liposomes and viral vectors may be toxic and/or immunogenic, restricting their clinical application. Liposomes are utilized to deliver small interference RNAs (siRNA). However, synthetic systems such as liposomes yield relatively lower than viral vectors [89]. Altogether, it is likely that miRNAs will be used as therapeutic agents against toxicity induced by environmental toxicants such as PM in the near feature.

15. Other therapeutic agents for PM2.5-induced toxicity

15.1. Targeting apoptosis via FGF10

Fibroblast growth factor 10 (FGF10), an essential component of the FGF family, was first isolated from rat embryos and is crucial for proper embryonic development. Numerous investigations have substantiated the various biochemical and physiological features of FGF10, including regulating appropriate organogenesis and preserving tissue homeostasis. Notably, the administration of FGF10 has been observed to confer neuroprotective benefits in neonatal rats with hypoxic-ischemic (HI) brain injuries. These protective effects stem from FGF10's ability to shield the neurovascular unit (NVU) from HI-induced damage, as evidenced by its capacity to reduce neuronal cell apoptosis, mitigate disruptions in the blood-brain barrier, and suppress gliosis [90]. Therefore, FGF10 could function as an apoptosis-based therapeutic agent in various diseases. Further, FGF10 could also serve as a protective factor against environmental toxicants-induced toxicity. In this regard, the effects of FGF10 on lung inflammation and damage and any possible therapeutic advantages were studied by Liu et al. using in vivo and in vitro models. It turned out that FGF10 reduced the accumulation of inflammatory cells and apoptosis in vivo. Interestingly, FGF10 levels in the bronchoalveolar lavage fluid (BALF) were significantly higher in the PM group. Furthermore, it was shown that PM-induced elevation in IL-8, IL-6, PGE2, TNF-α, and in BALF and cell supernatant were significantly attenuated by pretreatment with FGF10. According to their data, FGF10 prevents activation of inflammatory response and apoptosis induced by PM in the airways. In this manner, FGF10 is exploitable to prevent and manage airway inflammation caused by PM [91].

15.2. Targeting apoptosis via PDRN

Polydeoxyribonucleotide (PDRN) comprises a blend of deoxyribonucleotide polymers with varying lengths, ranging between 50 and 2000 base pairs. In addition, it contains nucleosides derived from salmon trout (Oncorhynchus mykiss) sperm that undergo a rigorous purification and sterilization process to ensure a significant proportion of DNA and the absence of active proteins or peptides [92]. The anti-inflammatory effect of PDRN and ability to suppress apoptotic cell death imply its therapeutic potential in multiple diseases. In this regard, the mechanism of PDRN treatment for liver damage has been investigated recently. The administration of PDRN in the CCl4-induced ALI animal model resulted in the suppression of inflammation and apoptosis. The co-administration of the adenosine A2A receptor antagonist 3,7-dimethyl-1-propargylxanthine (DMPX) with PDRN also resulted in the disappearance of its anti-inflammatory and anti-apoptotic effects. Thereby, the utilization of PDRN as a therapeutic agent for acute liver damage holds promise in achieving favorable outcomes [93]. Importantly, it was found that PDRN could be used as a therapeutic agent in environmental toxicology. In this context, in an experiment conducted by Hwang et al., the therapeutic effects of PDRN in the human NCI-H358 cells in exposure to PM10 were explored. The results revealed that treating with PDRN diminishes the PM10-induced inflammatory cytokines activation. Also, an increased level of Bcl-2 and lowered Bax and Bid amount was observed in the PDRN-treated group. Moreover, the prevention effect of PDRN treatment on caspase-9, Apaf-1, and caspase-3 was verified. According to their research, PDRN is a potent antiapoptotic agent, mediated by decreasing caspase-3, caspase-9, and Apaf-, which are downstream signals that regulate apoptosis. It has been suggested that PDRN therapy reduces inflammation by shielding apoptotic factors and inflammatory cytokines from injuries brought on by PM10 [94].

15.3. Targeting apoptosis via vitamins

The vitamins' safety, efficacy, and low price compared with other therapeutic agents make them an excellent choice for preventing and

treating toxicities. Recently, vitamins have been used as antioxidant agents in different studies to prevent or treat toxicities in the various body systems induced by diverse toxicants such as PMs. In this regard, in a survey conducted by Gai et al., vitamin C, aspirin, ozone, and vitamin E were examined for potential protective influences on fertility in female mice exposed to PM2.5. They observed that exposure to PM2.5 decreased AMH levels but that the impact could be mitigated by vitamin E, aspirin, vitamin C, and ozone. They also observed increased TNF- α, IL-6, caspase-3, Bax/Bcl-2, and 8-OHdG expression in the PM2.5 group compared to the control group. In contrast, they found that TNF- α, IL-6, caspase-3, Bax/Bcl-2, and 8-OHdG expression significantly decreased in the PM2.5 + ozone, PM2.5 + aspirin, PM2.5 + Vitamin E, and PM2.5 + Vitamin C groups. Thereby, its preventive properties likely stem from its capacity to mitigate the inflammatory and oxidative stress brought on by PM2.5, which in turn, apoptotic regulation proteins suppressed and, eventually, the rate of ovarian apoptosis lowered. Thereby, vitamins, mainly by modulating apoptosis, could be a successful therapeutic agent against PM2.5-induced toxicity [95].

16. Could herbal medicine alleviate particulate matter-induced toxicity?

As a massive source of natural materials, plants offer many outstanding chemical and structural characteristics that have made them exciting materials to remedy many diseases. Thanks to the low-cost, eco-friendly, plentiful, and renewable structure of plants, they have attracted increasing attention in different fields of science. More than 80% of the global population prefers medications derived from plants for their health care. Meanwhile, more than 50% of medicine is from natural sources or their derivatives, and 74% percent of the most critical drugs contain active plant ingredients. According to previous research studies, some plant extracts and natural products can reduce PM-caused toxicity. In this context, Nguyen et al. looked at how Astragali Radix (AR) and its active component, formononetin (FMT), affected keratinocytes' ability to produce a sound barrier following being exposed to diesel particulate matter (PM). In HaCaT cells, they discovered that PM boosted BAX and p53 expression and induced the cleavage of caspase 3 and PARP, while AR and FMT therapy suppressed these effects. Following reconstructing human skin in 3D, they histologically analyzed the model. They disclosed that AR and FMT upregulated the expression of Ki67 in the 3D human skin model, whereas that of cleaved caspase 3 was downregulated. Moreover, they found that FMT and AR substantially prevented ERK phosphorylation in PM-stimulated HaCaT cells but not p38 MAPK or JNK phosphorylation. Accordingly, by modulating keratinocyte proliferation and apoptosis, they concluded that both FMT and AR play a pivotal role in alleviating PM-induced epidermal barrier abnormalities and eventually function as antipollution agents [96]. Altogether, the modulation of apoptosis by plant extracts may make them effective anti-pollution agents and reduce the toxicity of particulate matter (PM). In the following section, we focus on herbal extracts that target apoptosis and exert potent anti-PM activity.

16.1. Euphorbia supina extracts

Euphorbia supina Rafin (ESR) extract is a Korean weed used as a traditional medicine in treating various diseases, such as hepatitis, skin inflammation, and bronchitis. The extract of this plant (ESR-Ex) with anti-oxidative activities encompasses terpenes, flavonoids, and tannins [97]. It was proposed by Shin et al. that this extract performs a protective role from apoptosis caused by diesel particulate matter (DPM) via the prevention of NOX activation in keratinocytes. They showed that this prevention occurs by blocking aryl hydrocarbon receptor (AhR) activation-mediated transcription of neutrophil cytosolic factor 1 (NCF1)/p47phox, a subunit of NOX blockage. They concluded that as a result of ESR-Ex inhibiting AhR activation-mediated NOX activation, KC is protected from DPM-induced apoptosis, and it further protects KC by boosting sphingomyelinase and hydrolysis of sphingomyelin, therefore blocking an apoptotic lipid mediator (ceramide production). In this manner, ESR-Ex may reduce the risk of developing lung cancer, asthma, cardiovascular disease, and COPD, all associated with cigarette smoke and air pollution exposure [98].

16.2. Eckol extract

Ecklonia species, which are marine brown algae with a wide distribution, have been found to contain large amounts of Eckol, a precursor substance of the dibenzo-1,4-dioxin class of phlorotannins. Due to the compound's medicinal qualities and health benefits, extensive study has taken place over the past three decades, leading to the discovery of compounds with biological activity in macro algae [99]. In this regard, Eckol was tested by Zhen et al. to demonstrate how it protects human HaCaT keratinocytes from PM2.5 damage. They found that PM2.5 raises apoptotic protein levels and promotes MAPK signaling, while Eckol does the opposite, blocking MAPK signaling and preventing apoptosis. They further disclosed that Eckol works by inhibiting MAPK, which prevents PM2.5 from inducing cell apoptosis. In this manner, Eckol reduces ROS generation in skin HaCaT cells to prevent apoptosis induced by PM2.5 [100].

16.3. Fisetin extract

Fisetin Extract is an abundant flavonoid in some vegetables and fruits such as strawberries, onions, and grapes. Compared to many other polyphenols and plant-based antioxidants, this extract has outstanding biological characteristics such as anti-carcinogenic, anti-inflammatory, and antioxidant features [101]. Research conducted by Molagoda et al. focused on the anti-apoptosis characteristics of Fisetin extract in HaCaT keratinocytes. Their results proposed that this extract prevents the generation of ROS and intervenes in apoptotic protein expression. They discovered that apoptosis activation by PM2.5 has linked to the activation of the endoplasmic reticulum (ER) stress response, which was mediated by the protein kinase R-like ER kinase (PERK)-eukaryotic initiation factor 2 (eIF2α)-transcription factor activator 4 (ATF4)-C-CAAT-enhancer-binding protein (C/EBP) homologous protein (CHOP) axis. Additionally, PM2.5 treatment leads to significant upregulation of Ca2 + levels in cytosol. They have discovered that Fisetin lowers cytosolic Ca2 + levels and prevents the protein production associated with ER stress, such as CHOP, phospho-eIF2, 78 kDa glucose-regulated protein (GRP78), and ATF4. As a result of these findings, Fisetin is thought to reduce ER stress and ROS generation, thereby preventing apoptosis brought on by PM2.5. As a consequence, Fisetin may provide protection for keratinocytes apoptosis brought on by PM2.5 [102].

16.4. Purpurogallin

In a recent study, purpurogallin (PG) had antioxidant, anti-inflammatory, and anticancer properties. It is derived from oak nutgalls, a natural source of phenols. Zhen et al. investigated PG's cytoprotective and antioxidant activities against UVB- and/or PM2.5-induced oxidative stress in HaCaT cells and elucidated the mechanisms behind these benefits. In their study, treatment with PG was found to reduce the levels of cleaved PARP, Bax, cleaved caspase-3, and cleaved caspase-9, whereas Bcl-2 levels were increased, and the number of apoptotic bodies was reduced. As an extra benefit, they discovered that PG inhibited caspase activation, thereby preventing apoptosis by regulating the levels of proteins associated with apoptosis. In addition, there was evidence of the expression of the proteins related to MAPK signaling pathways, such as JNK, P38, and ERK. UVB irradiation increased the phosphorylation of p38, ERK, and JNK, while PG pretreatment decreased the phosphorylation of these proteins. Based on these results, PG may be helpful in skin protection against PM2.5 and UVB irradiation [103].

16.5. Rhynchosia nulubilis

There is a large consumption of soybeans (Glycine max) in Asia, as well as fermented soybean sauces made from soybeans. Due to its anti-inflammatory and antioxidant characteristics, Rhynchosia Nulubilis (black soybean; RN) has been historically used to prevent chronic respiratory illness. The beneficial health effects of soybeans can be attributed to various bioactive components, including soyasaponins, polysaccharides, proteins, isoflavones, and pro-anthocyanidins [104]. Lee et al. investigated whether an extract of germinating RN fermented in LAB may protect against PM-induced oxidative stress and cell death in the A549 type II alveolar epithelial cell line. They demonstrated that the fermentation of GR with L. pentosus SC65 (GR-SC65) effectively inhibited apoptosis and intracellular ROS induced by PM. As well, in their study, apoptosis-related signaling proteins (activated-caspase-3, BAX, activated-PARP, activated-caspase-9) were observed to be suppressed, and an anti-apoptosis (BCL2) protein boosted in concentration when GR-SC65 was present. They discovered that GR-SC65 might be used to treat and prevent lung damage brought on by PM [105].

16.6. Diphlorethohydroxycarmalol

Known for its abundance of bioactive compounds, including diphlorethohydroxycarmalol (DPHC), Ishige okamurae is brown marine algae that are edible and rich in phlorotannins. Evidence shows that this marine algae have a wide range of therapeutic properties, including antidiabetic, anticancer, antibacterial antioxidant, antihypertensive, anti-inflammatory, and anticoagulant effects [106,107]. Zhen et al. tested DPHC's protective effect against skin damage induced by PM2.5 and described how it works in vitro and in vivo. In their study, human keratinocytes treated with DPHC are protected from autophagy, endoplasmic reticulum stress, and DNA damage following exposure to PM2.5, and reduces the reactive oxygen species production induced by PM2.5. In addition, PM2.5 has been revealed to induce apoptosis and the expression of MAPK protein; however, these modifications could be reduced by mitigating the effects of PM2.5 with DPHC. They also found that MAPK signaling was involved in modifying PM2.5-induced skin damage after investigating the molecular mechanisms behind these activities using MAPK inhibitors. Given these results, DPHC shows promise as a topical drug capable of protecting skin against PM2.5 [108].

16.7. Blueberry anthocyanin-enriched extracts (BAE)

It has been demonstrated that anthocyanins, found in berries including blueberry, barberry, bilberry, and cranberry, as well as in grapes and other pigmented plants, could limit the adverse effects of cyclophosphamide on the cardiovascular system. Wang et al. assessed the BAE influence on cardiovascular injuries induced by PM2.5 and the mechanisms responsible for this phenomenon. According to their findings, BAE, especially when administrated at 1.0 g/kg, improved ECG and reduced cytokine levels in rats exposed to PM2.5. During the experimental investigation, superoxide dismutase activity, Interleukin 10, and Bcl-2 protein expression all rose in heart tissue. In contrast, the levels of angiotensin II, interleukin 6, endothelin 1, and malondialdehyde declined, and Bax protein expression did. In this manner, it has been shown that BAE can protect against the damage caused by PM2.5 to the cardiovascular system if administered at certain levels [109].

16.8. Procyanidins

It has been discovered that green tea, grape seeds, hawthorn, and ginkgo contain flavonoid phytochemicals Procyanidins (PC). It is thought that PC's powerful antioxidative capabilities, which limit free radical formation, scavenge free radicals, and balance the body's redox system, plays a significant role in preventing CVD. A study conducted by Zhang et al. investigated PC's protective properties on vascular smooth muscle cells (VSMCs) apoptosis induced by PM2.5 and the mechanisms underlying these effects. They discovered that PC supplementation reduced oxidative stress and vascular apoptosis by upregulating nuclear factor erythroid 2-related factor 2 (Nrf2) and its downstream antioxidant genes, including heme oxygenase 1 and NAD (P) H dehydrogenase (quinine) 1. They, via in vitro experimentation, found that PM2.5, in a dose-dependent manner, caused cytotoxicity in VSMCs. That PC prevented this cytotoxicity through Nrf2 signal pathway activation, decreasing oxidative stress and eventually lowering apoptosis. Their results showed that PC inhibits VSMCs apoptosis brought on by PM2.5 by activating the Nrf2 signaling pathway. In this manner, the supplementation of PC is an exciting approach to prevent and treat PM2.5-induced vascular damage based on the protective effects of PC observed in VSMCs. However, further studies will be required to determine whether PM2.5 has detrimental effects on the environment and whether PC has protective effects [110].

16.9. Thalictrum minus L

The thalictrum genus is widely distributed in Africa, Europe, and Asia and, owing to its biological properties, such as antiviral, antifungal, and anti-inflammatory, has been used as a remedy for gingivitis, dysentery, ad enteritis in several medical systems. In many parts of the world, including Europe, Mongolia, Iran, and Syria, Thalictrum minus L. (TML) is one of the most popular therapeutic plants. In this context, as well as treating lung inflammation and fungal infections in Mongolia, the extract of TML has been used in Iran to treat bedsores. Badamja et al. looked at how effectively TML worked against acute lung injury (ALI) induced by PM and what could be the underlying processes. During TML treatment, p-AMPK-Nrf2 expression was significantly elevated, but KEAP expression was suppressed, and cyclooxygenase-2 (COX2) and NLRP3/caspase-1 activation were blocked. Apoptosis proteins were also evaluated in terms of their levels of expression. In their study, when the PM was applied, the levels of proapoptotic Bax and cleaved caspase-3 increased, whereas the levels of antiapoptotic Bcl-2 decreased. They also found that among the TML group, the Bax to Bcl2 ratio and the level of cleaved caspase-3 expression both decreased. They further disclosed that TML suppressed inflammatory cytokines and apoptotic pathways to attenuate PM-induced ALI. In this manner, TML, as complementary traditional medicine, can be used as a novel treatment for ALI caused by PM due to its chemical components and mode of action [111].

16.10. Peucedanum japonicum Thunb. Leaf extract

Traditional uses of Peucedanum japonicum Thunb. (Family Apiaceae) (PJE) includes use as a vegetable in the East Asian region. Still, it is also made into medicines for treating colds, headaches, neuralgia, rheumatoid arthritis, and other inflammation-related conditions. Various chemical compounds have been reported in P. japonicum, including steroid glycosides, phenolic compounds, coumarins, inositols, chromones, and polyacetylenes (PJE). Furthermore, besides its anti-inflammatory properties, P. japonicum has antiallergic, antioxidant, antiplatelet, and anti-obesity properties [112]. In a study by Kang et al. on ocular surface injury induced by PM, the leaf extract of PJE was evaluated for its effects on wound healing. Their research indicates that PJE prevents apoptosis from happening during the healing process of PM-induced corneal lesions. Their findings help us understand how PJE may be used to treat PM-related corneal damage [112].(Fig. 6).

17. Conclusion

Any substance potentially harming vegetation, animals, humans, or other materials is considered an air pollutant. Anthropogenic activities cause most environmental air pollution, though several physical activities can release different environmental pollutants (fire, volcanoes, etc.). As a result of a wide range of natural and artificial processes,

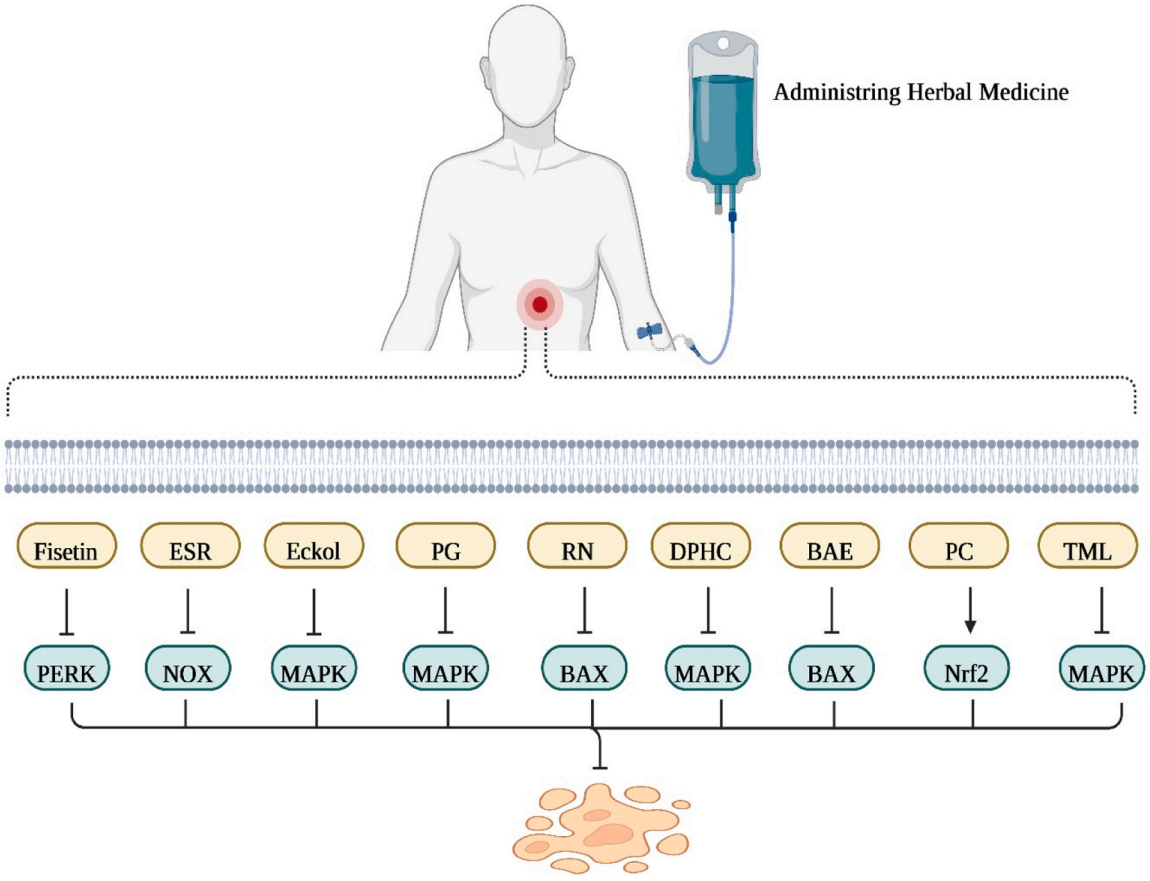

Fig. 6. some herbal extract involved in apoptosis inhibition.

hazardous substances can be released into the environment, which can negatively impact people's and the environment's health. The term PM is used to refer to a class of air pollutants that are composed of complex and variable mixtures of particles. They can vary in size and composition and are produced due to various natural and human activities. Several different systems and organs are affected by PM, both acutely and chronically. PM has been found to affect human health primarily through apoptosis in recent experimental studies. Recent research demonstrated that numerous signaling pathways could regulate apoptosis, including MAPK, PI3K/Akt, JAK/STAT, NFκB, Endoplasmic Stress, and ATM/P53. A growing body of evidence shows that PM, mainly by modulating apoptosis, contributes to physiological damage to various organs, including the lung, skin, cardiovascular system, kidneys, and reproductive organs. Understanding the molecular mechanisms that regulate apoptosis and how PM induces apoptosis in different organs also provides novel opportunities for treating PM-induced toxicity. Here, we demonstrated that targeting apoptosis via miR-486 administration, PDRN, vitamins, and FGG10 could be exploited to prevent and manage PM-induced toxicity. Besides, we highlighted that natural compounds, including plant-derived compounds including Fisetin, ESR, Eckol, PG, RN, and BAE, mainly targeting apoptosis, could protect or decrease PM-induced toxicity on different organs. Overall, we infer that targeting apoptosis mechanisms could be a promising therapy that will continue to evolve as a first-line defense against PM-induced toxicity in clinical practice.

Ethics approval and consent to participate

Not applicable.

CRediT authorship contribution statement

Seyed Mohsen Aghaei-Zarch, Amir Hosein Sanjari Nia, Fatemehsadat Aghaei-Zarch, Mehrdad Talebi, Hassan Rasoulzadeh, Jalaledin Ghanavi: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Masomeh Nasiri Moghadam, Sajad Najafi, Saeid Bagheri-Mohammadi, Fatemehsadat Mousavi-nasab, Ali Toolabi, Morteza Nouri**: Designing the tables and figures, Writing – review & editing. MT, MNM, JG, SBM, AT, HR, SN, SMAZ, FAZ and MN collected and analyzed the literature, drafted the figures and wrote the paper; SMAZ, HR, MNM, MT, AHSN, FM and JG conceived and gave the final approval of the submitted version. All authors have read and agreed to the published version of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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