



Impact of Particulate Matter 2.5 in Acne Vulgaris: A Literature Review

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ABSTRACT

Air pollution is the contamination of any chemical, physical or biological agent that alters the characteristics of the atmosphere. The main environmental pollutants consist of nitrogen dioxide (NO₂), sulfur dioxide (SO₂), carbon monoxide (CO), heavy metals, particulate matter (PM)₁₀ and PM_{2.5}. Particulate matter is a heterogeneous mixture of small particles and liquids consisting of organic chemicals, acids, metals, soil or dust particles. Hair has a diameter of 50-70 μm, while PM₁₀ is 2.5-10 μm and PM_{2.5} is < 2.5 μm. Air pollution can induce or aggravate skin diseases including acne vulgaris. Particulate matter_{2.5} triggers skin inflammation and stimulates inflammatory acne lesions through lipid peroxidation and Aryl hydrocarbon receptor (AhR) signaling. Interleukin (IL)-1α and IL-8 are elevated in inflammatory lesions of acne compared to normal skin, showing their role in the exacerbation of acne. The main preventive and therapeutic strategies against air pollution-induced skin damage consist of preventing the penetration of air pollutants through the skin and hair follicles, removing pollutants, improving skin barrier function, increasing skin hydration, and reducing inflammation, as well as preventing collagen and elastin degradation.

1. Introduction

Air pollution is defined as environmental contamination by any chemical, physical, or biological agent that alters the characteristics of the atmosphere.¹ Air pollution is estimated to be the leading cause of 3.3 million premature deaths on the whole Asia. The United States Environmental Protection Agency states that the major environmental pollutants are nitrogen dioxide (NO₂), sulphur dioxide (SO₂), carbon monoxide (CO), heavy metals, particulate matter 10 (PM₁₀), and particulate matter 2.5 (PM_{2.5}). Particulate matter (PM) is a major pollutant caused by industrial and transportation activities, particularly in the urban areas.² Particulate matter is a heterogeneous mixture of small particles and liquids consisting of organic chemicals, acids, metals, soils, or dust particles.³ Air pollution in

Indonesia, especially in Palembang, has reached dangerous level. In fact, Palembang has become one of the worst-polluted cities in Indonesia.*

Several studies have shown a definite correlation between the air pollution and cardiovascular and respiratory diseases. Air pollution also causes an oxidative stress to the skin and may also trigger inflammation, such as psoriasis, atopic dermatitis, and acne vulgaris.³ Exposure to air pollutants may also lead to the inflammatory acne.²

Acne vulgaris (AV) is a disorder of the pilosebaceous unit that mainly occurs in adolescents. The AV may manifest as pleomorphic lesions, comedones, papules, pustules, nodules, and cysts of the varying severity. Acne vulgaris is one of the three most common skin diseases, especially in adolescents and young adults (12-25 years), with a

prevalence ranging around 85%.⁴ The global AV prevalence ranges at around 9.38% for any given age. The country and age differences affect the prevalence of AV, with an estimated 35-100% of young adults suffered from the AV.⁵ Sitohang (2019) in Indonesia showed that AV is more prevalent among women aged around 20 years.⁶ The new cases of AV at the Dermatology, Venereology and Esthetics Medicine (DVE) Outpatient Clinic in our institution was 222 cases between 2019–2022 alone.**

Acne vulgaris is classified as a non-life-threatening disease, although the AV may cause severe psychological and social impacts. Anxiety, decreased self-confidence, and symptoms of depression are commonly found in severe AV cases, particularly when the post-acne scar tissue and post-inflammatory hyperpigmentation occurs.^{2,4} This literature review is aimed to better understand the impact of PM_{2,5} on AV and its management.

Air pollution

Air pollution is known to cause serious health problems in humans.⁷ Air pollutants are divided into indoor and outdoor air pollutions. Indoor air pollutant is caused by indoor contaminants that are formed during the fire, such as cooking, smoking, lighting candles, and burning wood. Indoor air pollution mainly occurs due to poor ventilation of the room resulting in an accumulation of the contaminants in the room air. The most common sources of pollution are human activities, e.g. transportation and industry. The atmospheric sulfur and nitrogen products from mountain eruptions or forest fires is also known to be one of the natural sources of air pollution.⁸ Air pollutants of global

concern include PM, polycyclic aromatic hydrocarbons (PAHs), benzene, ozone (O₃) and other gases such as CO, NO₂, SO₂, heavy metals, and volatile organic compounds (VOC).^{3,9}

Particulate matter (PM)

Particulate matter is one of the most dangerous pollutants, consisting from the mixture of small particles from other sources and liquid organic chemicals, acids, metals, and soil or dust particles. Smaller particulate matter has longer half-life in the atmosphere, resulting in suspended PM and eventual spread to the distant locations. Particulate matter also has the ability to damage ecosystems, including to forests and crops, as well as absorbing water.¹⁰ Urbanization and rapid industrial development lead to the universal increase of the PM concentration in the air.¹¹

Particulate matter may trigger oxidative stress in living organisms.⁷ High risk of death from PM is associated with the stroke, ischemic heart disease, chronic obstructive lung disease, and lung cancer.¹² The PM₁₀ may also cause autophagy in several organs and trigger the development of respiratory diseases.¹³ In addition to causing disorders in respiratory and heart systems, PMs may induce skin cancer, inflammatory skin disease, pigmentation abnormalities, and acne.³

Particulate matter is classified based on its diameter, ranging from 2.5-10 µm (PM₁₀) to ≤ 2.5 µm (PM_{2.5}).³ The PM_{2.5}, with a diameter of ≤ 2,5 µm, has a relatively large surface area with high toxin absorption capacity.¹³ The PM_{2.5} is also known to be highly reactive to the skin and can interfere with melanocyte functions in the basal stratum.¹⁴

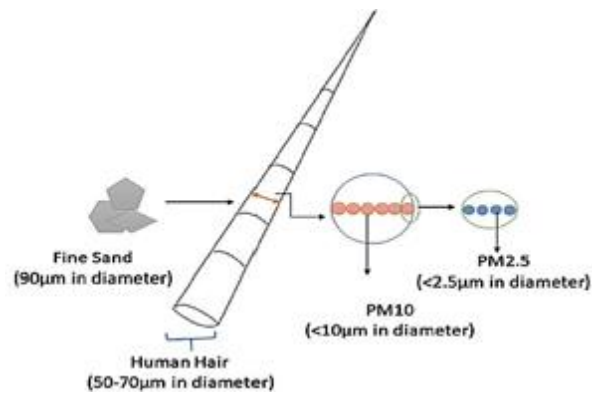


Figure 1. Comparison of PM sizes¹⁵

*Particulate Matter 2.5 data from BMKG in September 2023

**Data of DVE-RSMH Palembang outpatient visit care Januari 2019-Desember 2022

*Particulate Matter2.5 data from BMKG

The World Health Organization (WHO) recommends a maximum PM₁₀ concentration of 15 µg/m³ and PM_{2.5} concentration of 5 µg/m³.¹⁶ The Meteorological, Climatological and Geophysical Agency (Indonesian BMKG) divides the air quality based on PM_{2.5} levels into five categories: good (aerial PM_{2.5} concentration between 0–15.5 µg/m³), medium (aerial PM_{2.5} concentration between 15.6–55.4 µg/m³), unhealthy (aerial PM_{2.5} concentration between 55.5–150.4 µg/m³), highly unhealthy (aerial PM_{2.5} concentration between 150.5–250.4 µg/m³), and hazardous (when the aerial PM_{2.5} concentration is above 250.4 µg/m³).^{*} Particulate matter and O₃ can also directly interfere with the production of vitamin D. The ultraviolet B (UVB) absorption disorders caused by PMs and O₃ are increasingly becoming an important health concern. The skin itself is not only important producer of the vitamin D₃, but also acts as the target organ of vitamin D₃ during the formation of skin and hair follicles.³

Impact of pm on the skin

Air pollution, especially PMs, can induce or exacerbate skin pathological conditions, including premature skin aging, skin cancer (melanoma, squamous cell carcinoma and basal cell carcinoma), inflammatory skin diseases (e.g. atopic dermatitis),

acne, alopecia, skin pigmentation defects (e.g. vitiligo, melasma, post-inflammatory pigment alteration), and itching disorders.³ Fuks (2019) also showed the correlation between 5 years of O₃ exposure and the occurrence of extrinsic skin aging.⁹

Aryl hydrocarbon receptors (AhRs) are found in skin cells and are essential for the integrity of the skin and the skin immune system.⁷ Particulate matters can activate AhRs, triggering the production of inflammatory cytokines (interleukin-6 (IL-6, IL-8, IL-1α, and IL-1β) while also simultaneously immunosuppress the keratinocytes and fibroblasts.³ Particulate matters and O₃ can cause upregulation of the cyclooxygenase-2 (COX-2) and activation of keratinocytes and fibroblastic NF-κβ through the AhR-related pathway. Particulate matters can also stimulate phosphorylation through the ERK/MAPK and JNK pathways in the presence of the ROS. Cyclooxygenases-2, IL-1α, and IL-1β can interfere with the matrix metalloprotein-1 (MMP-1) regulation resulting in neocollagenesis disorders. Cigarette smoke and other air pollutants can also interfere with the biosynthesis of collagen types III, IV, and VIII, as well as to trigger abnormal elastin fiber synthesis, causing wrinkles and premature skin aging.³

*Particulate Matter2.5 data from BMKG

Although AhR is known for its negative effects,

AhR also has protective functions in the form of increased skin repair, inflammation, antioxidants, and anti-cancer properties. The positive and negative

responses of the AhR depends on the triggering events.³(Figure 2).

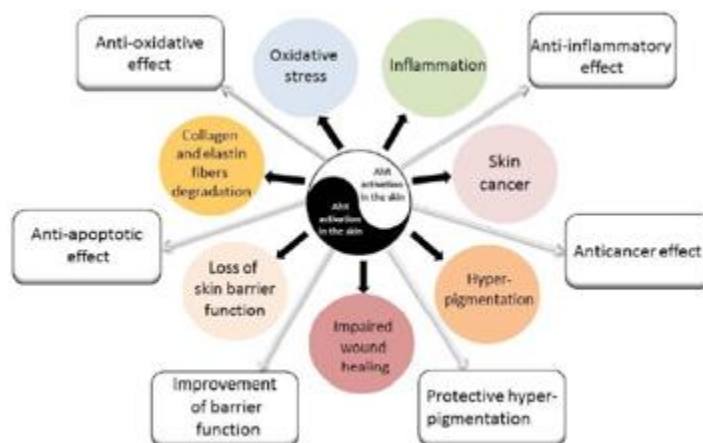


Figure 2. AhR signal path activation and skin response to PM has a negative effect (black arrow line) and a positive effect (white arrows line)³

Acne vulgaris is a complex and multifactorial inflammatory disease. Recent researches have described the cellular and molecular mechanisms involved in AV.⁴ The pathogenesis of acne involves epidermal follicle hyperproliferation, sebum production, *Corynebacterium acnes* infection, inflammatory reactions, and immune responses.¹⁷ Each of these processes is interrelated and is under the influence of hormones and the immune system.⁴

Epidermal follicle hyperproliferation in AV occurs as a result of initial changes in the polybasic follicles as a change in the keratinization pattern in the follicles. The corneal stratum cells of the infra infundibulum become more desmosomes, tonofilaments, keratohyalin grains, and lipids, but contain fewer lamellar grains so that the corneum stratum is thicker and attached to the early formation of the micro comedone (Figure 3).¹⁸

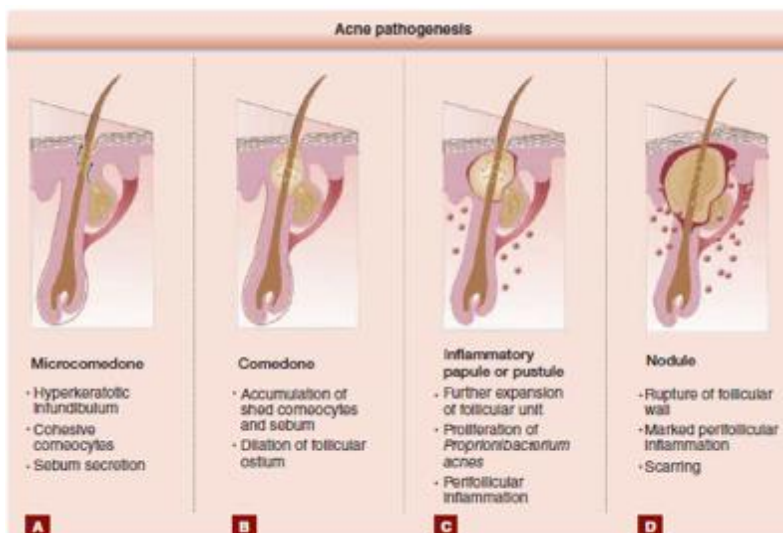


Figure 3. Pathogenesis of Acne Vulgaris⁴

The micro comedo continues to grow with the presence of keratin, sebum, and bacteria. The distended comedo causes a rupture of the follicle wall releasing keratin, sebum, and bacteria into the surrounding dermis, causes an inflammatory response. The CD4⁺ lymphocytes are also found around the pilosebaceous unit, while the CD8⁺ cells are found in the blood vessels within 24 hours of the comedo rupture. One or two days after the comedo rupture, the neutrophils become the predominant cell in the ruptured micro comedo.¹⁷ While the rupture is important for the inflammation, the inflammation of the skin can also occur before the comedo is formed.¹⁹ Biopsies taken from comedo-free acne-prone skin showed an increase of the skin inflammation when compared to the normal skin. It suggests that inflammation may precede the formation of comedones.⁴

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Corynebacterium acnes is a Gram-positive anaerobic, micro-aerophilic bacterium found in sebaceous follicles and is the dominant bacteria in sebaceous glands, covering almost 90% of the transcripts of the 16S bacteria. *Staphylococcus*

epidermidis is also present in the follicle but commonly found near the surface, suggesting that these bacteria do not contribute to the internal inflammation. Colonization of the *C. acnes* increases significantly during puberty, coinciding with the period when AV usually occurs. Adolescents suffering from AV may harbor 100 times as many *C. acnes* bacteria on their skin as compared to the healthy population. However, there is no consistent data linking the number of *C. acnes* organisms inside the sebaceous follicles with the severity of AV.⁴

The cellular differentiation and pro-inflammatory cytokine and chemokine responses vary depending on the *C. acnes* strain that dominates the follicle. Ribotypes *C. acnes* associated with AV induce T helper responses 1 (Th1) and Th17, which contribute to AV inflammation, but ribotype *C. acnes* related to healthy skin induces high levels of IL-10, which is believed to regulate and inhibit inflammatory responses.¹⁸ *Corynebacterium acnes* may also induce metalloproteinase (MMPs) 1 and 9 and tissue inhibitors of metalloproteinase (TIMP)-1, the main regulator for MMP-9 and MMP-1. In addition, all-trans retinoid acid (ATRA) decreases MMP and increases TIMP-1, suggesting one-way ATRA can reduce the acne scars by modulating MMP and TIMP expression, shifting from the matrix degradation phenotypes to matrix preservation phenotypes.^{4,17}

Acne vulgaris can be classified into mild, moderate, and severe subtypes. Mild AV consists of non-inflammatory (comedo) lesions, several inflammatory lesions (papulopustular), or both. Medium vulgar acne consists of more inflamed lesions, sometimes accompanied by nodules, and mild scar tissue. Severe acne vulgaris is defined by the widespread inflammatory lesion, without or with nodules, or moderate AV that has not healed with treatment for 6 months, or AV with any type of lesion that causes serious psychological disorders. The Indonesian Acne Expert Meeting (IAEM) based its AV classification to Lehmann criteria.²⁰

Table 1. Recommendations for IAEM grade acne according to Lehmann²⁰

| Severity | Lesion Type | | | Total number of lesion |
|----------|-------------|---------------------|-------|------------------------|
| | Comedo | Inflammatory lesion | | |
| | | Pustule | Cysts | |
| Mild | < 20 | < 15 | 0 | < 30 |
| Moderate | 20 - 100 | 15 - 50 | < 5 | 30-125 |
| Severe | > 100 | > 50 | > 5 | > 125 |

The Lehmann criteria is a classification system used to categorize acne vulgaris into the mild, moderate, and severe types based on the number and type of lesions present on the skin.

Mild AV: comedones (blackheads and whiteheads) existence with few papules and pustules. Mild AV is

classified as Grade I, Moderate AV: several papules, pustules, as well as several nodules and cysts existence. Acne vulgaris is being classified in Grade II, Severe AV: nodular and cystic lesions dominate accompanied by widespread scar tissue. (Figure 4).²⁰



Figure 4. AV severity, light AV (A), moderate AV (B), severe AV (C)*

*Documentation of DVE Department, Srirwijaya University

Induction of Acne by PM2.5

Both PM_{2.5} and NO₂ exposure on the skin are significantly associated with the number of AV lesions and increased sebum production. Increased SO₂ concentrations indicate a negative relationship with AV. age, sex and long exposure to air pollutants are risk factors for AV in adult and adolescent patients.³

In general, air pollution triggers an oxidative stress response to the skin.²¹ This can affect health and can be exacerbated by exposure to ultraviolet (UV) rays.³ Oxidative stress causes lipid peroxidase, protein carbonylation, and genomic and mitochondrial DNA (mtDNA) oxidation damage. The primary product of oxygen stress caused by air

contamination is the highly reactive 4-hydroxynonenal aldehyde compound (4HNE) formed from the non-enzymatic peroxydase ω -6 polyunsaturated fatty acids (PUFAs) in membranes such as linoleic acid, which is important for the Skin. 4-hydroxynonenal aldehyde can be formed directly at O₃ exposure by oxidizing PUFA present on the upper layers of the skin and indirectly after PM and cigarette smoke contamination.³

Environmental stressors such as O₃, UVA exposure, PM_{2.5} and cigarette smoke can trigger lipid peroxidase processes, resulting in increased comedogenic molecular production and skin dysfunction (Figure 5).³

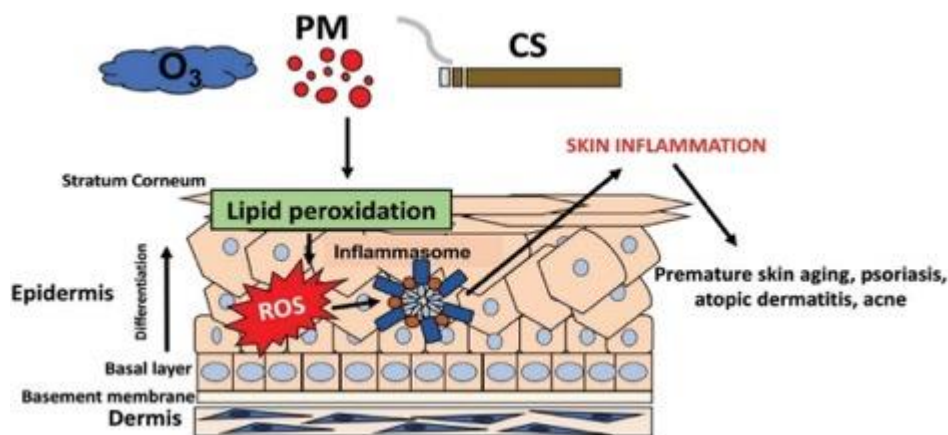


Figure 5. PM 2.5 mechanism induces acne vulgaris¹⁹

Inflammasome is a cytosolic multiprotein oligomeric complex of the natural immune system. Activation of this inflammation complex will lead to the release of numerous inflammatory cytokines. Inflammasomes have been associated with several skin disorders, including the AV. Several inflammasomes are commonly known, including node-like receptors (NLRs) and Aim2-like receptors (e.g. NLRP1, NLRP3, NLRC4, and AIM2) in many immune cells, but can also be found in keratinocytes. The activation of NLRP3 by ROS has been associated with the exacerbation of the AV.¹⁹ The PM_{2.5}, O₃, cigarette smoke, NO₂, and UV rays can increase transepidermal water loss (TEWL) and interfere with the normal functioning of the skin as well as with the skin's integrity, causing the exacerbation AV and other dermatological conditions. Exposing keratinocytes to PM_{2.5} downregulates the terminal marker genes, including filaggrin (FLG). The filaggrin protein contributes to the formation of corneum layers of the skin. The downregulation of FLG also disrupts the integrity of the skin and increase the risk of *C. acne* colonization resulting in the inflammation on the skin.²²

The higher concentration of inflammatory cytokines (e.g. IL-1 α and IL-8) in inflamed AV lesions than in normal skin proves significant role of the cytokines in the AV pathogenesis. Colonization of *C. acne* in areas with high sebum may trigger

inflammation of the pilosebaceous unit, the hallmark feature of the AV.³ Abolhasani (2021) suggested that there is a link between air pollution and AV incidents.⁹ Liu et al. also indicates that the increase of PM_{2.5}, PM₁₀, and NO₂ in the air is associated with the increased visits due to AV to health facilities. A study in China also found that increased exposure to PM (PM_{2.5} and PM₁₀) and NO₂ was significantly linked to more severe AV lesions and increased sebum production (hyperseborrhea). Sebum is produced by sebaceous glands and consisted of a mixture of triglycerides, wax esters, and squalene. The sebum secretion provides the suitable environment for normal lipophilic skin flora, such as *C. acnes*, *Staphylococci* spp. and *Malassezia* spp. to proliferate.³ Exposing epidermal lipid layer to air pollutants may result in the increased oxidation of the squalene and reduced the concentration of the linoleic acid, resulting in enhanced comedogenesis.⁹ Inhabitants of Shanghai and Mexico City suffering from the high levels of air pollutants also suffers from hyperseborrhea and dysseborrhea.³

Treatment of Acne Vulgaris

The primary preventive and therapeutic strategies for air pollution-related skin damage should include the control of exposure to the air pollutants and their penetration through the skin and hair follicles, removing contaminants, improving skin protection,

increasing the skin hydration, reducing inflammation utilizing antioxidants properties, and preventing the collagen and elastin degradation.³ Yusnenian's study recommends air pollution control over areas with high level of pollutants to protect public health.¹¹ The use of water cleaners and improvements of indoor ventilation may help controlling indoor air pollution.⁸ Protecting the skin through the protective clothing, frequent washing to remove the pollutants, and the application of protective creams may help to maintain and restore the function of the skin.³ Maintaining the facial hygiene during the AV therapy

is of a well-known importance. Excessive cleaning or the use of alkaline soaps results in increased skin pH, interfering the function of natural protective lipids, and increasing the risk of irritation due to exposure to the numerous topical AV therapies. Newer synthetic detergents able to cleanse the skin with minimal interference to the normal skin pH should be used. Cleansers containing benzoyl peroxide, salicylic acid, or sulfur are more effective for the hard-to-reach areas, such as the skin on the back.⁴

Treatments of air pollution-related AV is similar to the treatment of AV in general (Table 2).

Table 2 Algorithm of Acne vulgaris Therapy²⁴

| Grade/Therapy | Mild | Moderate | Severe |
|-----------------------------|---------------------------------------|---------------------------------------|---|
| Topical, first line | RA, SA, BPO/pustule of pregnant woman | RA, BPO, AB BPO of pregnant woman | AB BPO of pregnant woman |
| Oral | | Dox E of pregnant woman | Azitro, Quinolon E of pregnant woman |
| Topical, second line | AA BPO of pregnant woman | AA, SA, TAIL BPO of pregnant woman | AA, SA, TAIL BPO of pregnant woman |
| Oral | | Others Ab | F: Aan M: IsotO |
| Topical, third line | RA+BPO, AB> BPO of pregnant woman | RA+BPO, AB> BPO of pregnant woman | AA, SA, TAIL BPO of pregnant woman |
| Oral | | Others Ab | F: isotret GCS/CSS (AF) |
| Adjuvant | KIE, SC, SP, LL, K (PPX, SS) | | |
| Maintenance | KIE, SC, RA<0,01-0,025%, K(PPX) | | |

Adjuvant antioxidants for the air pollution-related AV might be beneficial through the reduction of the free radicals. An antioxidant-rich diet, e.g. fruit, vegetables, olive oil, and fish are thus recommended.²² Plant extracts and other natural ingredients with high antioxidant properties may protect against oxidative damage caused by air pollution on the skin.³ The use of moisturizers in conjunction with topical antioxidants (e.g. vitamins A, niacinamide, vitamin C, and vitamin E) may also prevent AV exacerbation.²²

The AhR modulator is a new prevention and alternative strategy for the air pollution-related AV.

Tapinarof is a natural non-steroidal anti-inflammatory drug with AhR modulator properties is currently in clinical trials. Tapinarof can specifically bind and activate AhR in the skin, lowering the inflammation on the skin. The use of topical tapinarof in 1% cream preparation in mice resulted in the reduction of the cytokines, epidermal thickening, and erythema.^{3,25}

5. Conclusion

The air pollution is globally steadily increasing. The air pollution has become a major risk factor contributing to various health disorders, including

skin disorders. Inflammatory skin diseases, such as AV, increase is affected by the increasing pollutants, particularly PM. Particulate matters trigger oxidative stress resulting in the lipid peroxidation. This reaction produces ROS on the skin which in turn activates inflammasomes. This complex activation will cause the release of inflammatory cytokines that can predate or aggravate AV. Particulate matters also decrease the expression of FLG gene resulting in increased TEWL. Oxidative stress also forms 4HNE compounds, highly reactive compound interfering the linoleic acid formation and the development of the AV. Increased sebum production become one of the risk factors of AV. Prevention strategies should be emphasized to treat the PM2.5-related AV.

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