Natural products as promising therapeutics for fine particulate matter-induced skin damage: review of pre-clinical studies on skin inflammation and barrier dysfunction (#110893)

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- Methods described with sufficient detail & information to replicate.
- Is the Survey Methodology consistent with a comprehensive, unbiased coverage of the subject? If not, what is missing?
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Natural products as promising therapeutics for fine particulate matter-induced skin damage: review of pre-clinical studies on skin inflammation and barrier dysfunction

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Particulate matter smaller than 2.5 μm (PM2.5) is a major air pollutant associated with an increased risk of health problems, including skin diseases. This study reviews the potential of natural products as therapeutic agents to alleviate PM2.5-induced skin damage. The skin, the first barrier and largest organ, is primarily damaged by PM2.5 through various pathways. Several studies have shown that PM2.5 upregulates inflammatory responses by increasing excessive reactive oxygen species (ROS) and various inflammatory cytokines, leading to PM2.5-induced skin damage. The ROS/MAPK and COX2/PGE2 inflammatory pathways are achieved through free radical scavenging and phase II detoxification. In this review, we explain the mechanisms of action of natural products and examine their functions in protecting against environmental skin diseases. In addition, this review suggests the effective dosages of natural products for future clinical applications. The article may be useful for dermatologists, molecular biologists and scientists, clinicians and anyone involved in preventive health care and alternative medicine. Available scientific literature published between 1999 and 2024 was searched using PubMed and Google Scholar search engines. Several keywords related to the topic were used. Only 41 of the papers screened were selected for this review as these were the most relevant publications on the topic of the preventive benefits of natural products and specific pathways targeting PM2.5-induced skin damage. All relevant research that met the criteria was included in this review and exclusion criteria were also defined. Only full original articles and English-language studies were considered. The review found that natural products, including phenolic/polyphenolic compounds and flavonoids, act as anti-inflammatory and antioxidant agents that support skin protection, including protection against oxidative stress, inhibition of enzymes that promote free radical formation,

enhancement of antioxidant enzyme activity, and overall reduction of ROS formation. Interestingly, several natural products have demonstrated efficacy in reducing intracellular ROS, oxidative stress, mitochondrial dysfunction, autophagy and apoptosis caused by PM2.5. In addition, phytochemicals support the restoration of the skin wound healing process and muscle contraction impaired by environmental pollutants, including PM2.5 and UV radiation. This review presented promising agents to protect against environmental health problems by highlighting their mechanisms of action, particularly through antioxidant and anti-inflammatory compounds such as sulforaphane, hesperidin, quercetin, catechin, diphloroethohydroxycarmalol, resveratrol and ginsenosides, which are interesting candidates for nutraceuticals and have the potential to reduce dependence on drugs. However, the low stability and bioavailability of natural products remains a major challenge that warrants further research and development.

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Abstract

Particulate matter smaller than 2.5 μm (PM2.5) is a major air pollutant associated with an increased risk of health problems, including skin diseases. This study reviews the potential of natural products as therapeutic agents to alleviate PM2.5-induced skin damage. The skin, the first barrier and largest organ, is primarily damaged by PM2.5 through various pathways. Several studies have shown that PM2.5 upregulates inflammatory responses by increasing excessive reactive oxygen species (ROS) and various inflammatory cytokines, leading to PM2.5-induced skin damage. The ROS/MAPK and COX2/PGE2 inflammatory pathways are achieved through free radical scavenging and phase II detoxification. In this review, we explain the mechanisms of action of natural products and examine their functions in protecting against environmental skin diseases. In addition, this review suggests the effective dosages of natural products for future clinical applications. The article may be useful for dermatologists, molecular biologists and scientists, clinicians and anyone involved in preventive health care and alternative medicine. Available scientific literature published between 1999 and 2024 was searched using PubMed and Google Scholar search engines. Several keywords related to the topic were used. Only 41 of the papers screened were selected for this review as these were the most relevant publications on the topic of the preventive benefits of natural products and specific pathways targeting PM2.5-induced skin damage. All relevant research that met the criteria was included in this review and exclusion criteria were also defined. Only full original articles and English-language studies were considered. The review found that natural products, including phenolic/polyphenolic compounds and flavonoids, act as anti-inflammatory and antioxidant agents that support skin protection, including protection against oxidative stress, inhibition of enzymes that promote free radical formation, enhancement of antioxidant enzyme activity, and overall reduction of ROS formation. Interestingly, several natural products have demonstrated efficacy in reducing intracellular ROS, oxidative stress, mitochondrial dysfunction, autophagy and apoptosis caused by PM2.5. In addition, phytochemicals support the restoration of the skin wound healing process and muscle contraction impaired by environmental pollutants, including PM2.5 and UV radiation. This review presented promising agents to protect against environmental health problems by highlighting their mechanisms of action, particularly through antioxidant and anti-inflammatory compounds such as sulforaphane, hesperidin, quercetin, catechin, diphloroethohydroxycarmalol, resveratrol and ginsenosides, which are interesting candidates for

nutraceuticals and have the potential to reduce dependence on drugs. However, the low stability and bioavailability of natural products remains a major challenge that warrants further research and development.

Keywords: Antioxidant; particulate matter 2.5 (PM2.5); natural products; skin damage; inflammation; skin barrier dysfunction

Introduction

Particulate matter less than 2.5 micrometers in size (PM2.5) *(Thangavel et al. 2022)*, a particle composed of inorganic ions, carbonaceous compounds and mineral dust (*McDuffie et al. 2021*), has increased in recent years due to the combustion of biomass (*Suriyawong et al. 2023*), and fuels (*Vohra et al. 2021*). PM 2.5 has been found to be associated with an increased risk of various diseases, including respiratory damage (*Huang et al. 2021*), cardiovascular disease *(Krittanawong et al. 2023*), chronic kidney disease *(Xu et al. 2022*), intellectual development disorders *(Chang et al. 2023; McGuinn et al. 2020*), and Alzheimer's disease (F*u et al. 2022; Yang et al. 2022*).

Skin becomes a primary protective barrier of the human body from external pollution, adversely impacted by PM2.5 through diverse pathways and mechanisms. PM2.5 generates reactive oxygen species (ROS) that cause oxidative stress, which impairs cell viability, induces DNA damage and lipid peroxidation, and alters protein carbonylation, which in turn triggers endoplasmic reticulum (ER) stress, mitochondrial swelling, autophagy and cell apoptosis in both HaCaT cells and mouse skin tissue (*Piao et al. 2018; Zhen et al. 2019*). PM2.5 has been extensively studied for its role in disrupting the epidermal skin barrier through AhR- and Th17 cell-mediated inflammatory pathways (*Kim et al. 2023*). Polycyclic aromatic hydrocarbons (PAHs) in particulate matter play a role in AhR-mediated skin damage by activating several downstream pathways involving upregulation of CYP1A1 and the AhR/Nox2/p47phox pathway. Exposure to PM2.5 causes ERK/p38-dependent signaling as well as NF-κB- and JNK-dependent activation of activator protein 1 (AP-1) transcription factors. In addition, the enhancement of c-Src activity by AhR activation leads to EGFR activation and downstream MAPK signaling (*Diao et al. 2021*). Previous research demonstrated that PM2.5 exposure leads to a significant increase in chemokines, including the chemokine C-X-C motif ligand 1 (CXCL1) and interleukin 8 (IL-8), triggering neutrophil chemotaxis and upregulating inflammatory responses in the skin (*Kono et al. 2023*). The development of allergic diseases, such as atopic dermatitis, is associated with PM2.5-induced TNF-α, which contributes to a deficiency of filaggrin (FLG) in the skin, leading to further impairment of the skin barrier function (*Kim et al. 2021*). Exposure of HaCaT keratinocytes to PM2.5 has been shown to modulate the activity of apoptotic proteins, including the upregulation of pro-apoptotic proteins such as Bax and caspase 9, along with the

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downregulation of the anti-apoptotic protein Bcl-2 (*Zhu et al. 2022*) and caspase 3 (*Shan et al. 2022*).

Given the skin toxicity and heightened inflammatory response induced by PM2.5, ongoing therapeutic interventions and scientific research are focused on mitigating these adverse effects. Natural substances, which are one of the alternative therapies, exhibit anti-inflammatory properties and promote the inhibition of excessive ROS formation (*Bae et al. 2021; Liao et al. 2020b*). These protective effects possibly be achieved through the application of phenolic compounds, flavonoid compounds, non-flavonoid phenolic compounds and phytosterols via the ROS/MAPK, COX2/PGE2 pathways (*Diao et al. 2021; Greenhough et al. 2009; Son et al. 2011*).

Methodology

Search strategy

In this study, we aim to understand the reviewed publications from the top list of academic search engines in the field of medicine, namely Google Scholar and PubMed. These search engines were searched for articles published between 1999 and 2024. The following search terms were used in the search along with the relevant Medical Subject Headings (MeSH) terms identified for each database: ((("particulate matter"[MeSH Terms] OR ("particulate"[All Fields] AND "matter"[All Fields]) OR "particulate matter"[All Fields]) AND ("biological products"[MeSH Terms] OR ("biological"[All Fields] AND "products"[All Fields]) OR "biological products"[All Fields] OR ("natural"[All Fields] AND "products"[All Fields]) OR "natural products"[All Fields]) AND ("skin"[MeSH Terms] OR "skin"[All Fields]) NOT ("clinical trial"[Publication type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All fields])) AND (1999:2024[pdat]). The publications were selected according to the inclusion and exclusion criteria of the most suitable manuscripts from the databases mentioned.

Eligibility criteria

The research question was created and developed according to the PICOS framework (population, intervention, comparison, outcome and study design). To be eligible for inclusion in this study, the research had to meet the following inclusion and exclusion criteria: the study

design focused on skin cell lines exposed to particulate matter 2.5, which is the same for other pollutants, e.g. Particulate matter 10 um (PM10) or ambient air or air pollutants or dust particles; the studies focused on the treatments with natural products that are not chemical products; preclinical experimental studies, including in vitro and in vivo studies; the work was published in English and as a complete original paper. We excluded narrative reviews, expert opinions and papers published in other languages.

A total of 78 articles were selected and identified with corresponding title manuscripts that contributed to the cell analysis. The screening phase was then based on the content of the abstract and keywords such as “natural products”, “active ingredients”, “phytochemicals”, “antioxidants”, “skin”, “keratinocytes”, “fibroblasts" and “particulate matter below 2.5 or PM2.5”. Approximately 37 of 78 articles were excluded based on the inclusion and exclusion criteria established for this review. A total of 41 articles were extracted as references in this review study.

The importance of natural products to protect against PM2.5-induced skin damage

Many recent studies have reported the use of natural products to protect the skin from particulate matter. Natural products and their structural counterparts have traditionally made a significant contribution to pharmacotherapy and have played a crucial role in drug development. For example, a medicinal plant widely used in Southeast Asia, *Centella asiatica*, served as an alternative medicine for atopic dermatitis, a skin condition characterized by an abnormal immune response triggered by environmental factors such as air pollution (*Lee et al. 2020*). Phenolic compounds (PCs) are naturally occurring antioxidants found in secondary plant metabolites. Due to their structure, which contains hydroxyl groups, PCs may have the ability to scavenge free radicals such as reactive oxygen species *(Platzer et al. 2022*). Flavonoid compounds can exert protective properties such as antioxidant, anti-inflammatory and anti-aging effects on the skin (*Diao et al. 2021*). Their hydroxyl groups are responsible for neutralizing free radicals through their scavenging activity (*Panche et al. 2016*). Phytosterols (PS) are isolated from plant species and have anti-inflammatory, antioxidant, antidiabetic and chemopreventive effects (*Salehi et al. 2021*). Through the NF-κB and MAPK signaling pathways, PS can suppress the expression of COX-2, PGE2, and pro-inflammatory cytokines, thereby reducing the levels of inflammatory mediators (*Diao et al. 2021*).

Results

The protective effect of natural products based on the classification of phytochemical structures

Phenolic compounds, presented in a variety of foods including fruits, vegetables and beverages, which can exhibit antioxidant, anti-inflammatory, anti-allergic and anti-cancer properties as well as cardioprotective and other health-promoting functions, making them widely utilized in functional foods (*Alara et al. 2021*). Polyphenols are a class of chemical molecules that contain multiple hydroxyl structural units on aromatic rings, which supports their strong antioxidant properties. Based on the differences in the molecular backbone structure of polyphenols, the compounds are generally categorized into phenolic acids, flavonoids, stilbenes and lignans. Flavonoids, the largest group of polyphenols, are divided into seven subgroups according to their chemical and biological properties: Flavanols (yellow), flavanones (purple), flavones (light blue), flavonols (red), isoflavones (dark blue), anthocyanins (green) and others (orange) (*Wang et al. 2022a; Zhang et al. 2022*). These colors are used to visually distinguish the different flavonoid subgroups based on their structural characteristics. Aponins are a type of triterpene glycosides that taste bitter. Structurally, saponins are glycosides, i.e. sugars bound to one or more organic molecules. In this review, the effects of bioactive compounds extracted from natural products were presented based on plant organic chemicals (Fig. 1) and the mentioned compounds for protection against particulate matter-induced skin damage were summarized in Table 1.

Grammar issues, suggested revisions e.g. Phenolic compounds, which are present in a variety of foods including fruits, vegetables, and beverages, exhibit antioxidant, anti-inflammatory, anti-allergic……. support

Phenolic compounds— sulforaphane from broccoli and sprouts

Sulforaphane, a polyphenolic compound found in cruciferous vegetables such as broccoli, is produced through the conversion of glucoraphanin by myrosinase, an enzyme present in plants. Once ingested, it is metabolized via the mercapturic acid pathway, where it conjugates with glutathione and undergoes biotransformation, leading to the formation of active metabolites (*Kensler et al. 2013; Vanduchova et al. 2018*). Sulforaphane, containing an isothiocyanate group, plays a critical role in protecting against electrophilic toxicities by inducing phase II enzymes, which function as an indirect antioxidant defense system (*Fahey & Talalay 1999*). This property makes sulforaphane highly versatile and effective in safeguarding cells from various oxidative stresses and reactive oxygen species (ROS). Growing evidence demonstrates that the

administration of sulforaphane enhances the antioxidant capacity of animal cells, improving their ability to withstand oxidative stress (*Barton & Ollis 1979*). Dermatological study reveals that sulforaphane supports collagen homeostasis while suppressing melanogenesis, potentially mitigating premature aging effects induced by PM2.5 exposure (*Andres et al. 2018*). Additionally, it disrupts melanogenic paracrine mediators, inhibiting the production of melanogenic proteins and melanin in melanocytes (*Jung et al. 2013*). In keratinocytes, sulfonamide reduces the expression of NF-κB-mediated cytokines such as tumor necrosis factor α, interleukin-1β, interleukin-6 and cyclooxygenase-2 (*Fernando et al. 2019*). Sulforaphane has been reported to decrease the expression of matrix metalloproteinase-1, phospho-NF-κB and cysteine-rich protein, while significantly increasing the production of procollagen type I, indicating the anti-inflammatory effect and remodeling of the damaged tissue (*Quan et al. 2012*).

Phenolic compounds— rosmarinic acid from rosemary, sage and peppermint

Rosmarinic acid (RA), a phenolic compound present in herbs such as rosemary, sage, and peppermint, exhibits protective effects against PM2.5-induced skin damage, primarily attributed to its antioxidant, anti-inflammatory, and anti-apoptotic properties (*Zhou et al. 2022*). RA protects skin keratinocytes by reducing oxidative stress markers including lipid peroxidation, protein carbonylation and DNA damage, which are critical for maintaining cellular integrity under environmental stress conditions. In addition, RA stabilizes intracellular calcium levels and mitochondrial membrane potential, preventing mitochondrial dysfunction and apoptosis, primarily by downregulating pro-apoptotic proteins such as Bax and caspases, while upregulating anti-apoptotic proteins such as Bcl-2 (*Herath et al. 2024*). RA also exerts anti-inflammatory effects by modulating the NF-κB signaling pathway, which plays an important role in inflammation and immune responses. In models of allergic rhinitis exposed to PM2.5, RA reduced inflammation by decreasing pro-inflammatory cytokines such as IL-4 and IL-13 and increasing IFN-γ, thereby balancing the Th1/Th2 response (*Zhou et al. 2022*). This suggests that the protective role of RA against PM2.5-induced damage extends beyond antioxidant activity to include modulation of inflammatory pathways (*Zhou et al. 2022*). Overall, RA provides a multi-layered protective mechanism against PM2.5-induced skin damage, highlighting its potential as a therapeutic agent to alleviate skin problems caused by environmental pollutants

Protective effects of the flavonoid family

Flavonone—Hesperidin from citrus fruit extracts

Hesperidin (3,5,7-trihydroxyflavanone 7-rhamnoglucoside, hesperetin-7-rutinoside) is a flavonoid compound which extracted from many citrus fruits (*Pyrzynska 2022*). Hesperidin has also been investigated for its protective effects against PM 2.5 damage in human HaCaT keratinocytes (*Herath et al. 2022*). Treating the cells with hesperidin before exposing the cells to PM 2.5 increased the viability of the treated cells compared to the cells not pre-treated with hesperidin (*Fernando et al. 2022b*). Treatment of hesperidin has been proposed as a potential drug because it has similar effects compared to N-acetylcysteine (NAC; a known antioxidant) by inhibiting intracellular ROS formation, cellular oxidative stress damage, mitochondrial dysfunction, autophagy and cellular apoptosis in cells induced by PM 2.5 (*Fernando et al. 2022b; Herath et al. 2022*). Hesperidin increased cell survival from 68% (without pretreatment with hesperidin) to 82% (with pretreatment with hesperidin) after exposure to PM 2.5 (*Fernando et al. 2022b*). Previous studies have shown that the target of hesperidin is an antioxidant defense system via the Keap1-Nrf2 (Kelch-like ECH-Associating protein 1 nuclear factor erythroid 2 related factor 2) pathway, which is one of the defense mechanisms against oxidative and electrophilic stress (*Aggarwal et al. 2020; Lu et al. 2016*). PM2.5 leads to mitochondrial damage by altering mitochondrial morphology and alters mitochondrial respiratory chain function, resulting in mitochondrial dysfunction (*Guo et al. 2017*). Mitochondrial injury causes mitochondrial membrane permeability transition (MMPT), resulting in mitochondrial membrane depolarization and impaired ATP production, which in turn leads to cellular apoptosis, autophagy and damaged mitochondria (*Fernando et al. 2022b*). Hesperidin has been found to have cytoprotective effects on HaCaT keratinocytes, reducing mitochondrial ROS formation induced by PM 2.5 and preventing mitochondrial depolarization (*Fernando et al. 2022b; Herath et al. 2022*). In terms of mechanism, hesperidin is able to inhibit the opening of the MMPT pore, thereby reducing Ca2+ accumulation and preventing activation of the intrinsic pathway of apoptosis (*Falode et al. 2022*).

Together with the in vitro skin damage study, hesperidin can penetrate the skin barrier to reach the dermis layer and protect the extracellular matrix from oxidative stress (*Addor 2017*). Hesperidin shows the ability to neutralize free radicals and indirectly increase the activity of antioxidant enzymes such as superoxide dismutase and catalase (*Estruel-Amades et al. 2019*). In

addition, hesperidin as a dietary supplement and pharmaceutical agent has been reported to prevent the biosynthesis of melanin and decrease the activity of tyrosinase in both normal human melanocytes and B16F10 cells (*Katiyar et al. 2014*).

Flavonols—Quercetin from berry fruit extracts

The extract from the leaves of *Thunbergia laurifolia* (STLE) is a natural antioxidant consisting of caffeic acid, rosmarinic acid, quercetin, isoquercetin, catechin and apigenin. The study of STLE suggests that STLE effectively inhibits PM2.5-induced oxidative stress in keratinocytes by causing upregulation of Nrf2, enhanced nuclear translocation and upregulation of p62 (*Jirabanjerdsiri et al. 2022*). Quercetin is a flavonoid compound in fruits and vegetables that has potential health-promoting effects, such as anti-inflammation, antioxidants and alleviation of allergy symptoms. Rutin, one type of flavonoid containing a glycoside of quercetin, found in plants such as citrus fruits, mulberries, cranberries, etc. These flavonoid compounds thus have common health benefits such as antioxidant properties, reduction of oxidative stress and anti-inflammation (*Muvhulawa et al. 2022*). In dermatology, quercetin has benefits for the skin by protecting against skin-damaging factors such as UV radiation, histamine and toxic chemical compounds and has anti-allergic properties by reducing irritation and itching caused by the release of histamine (*Qi et al. 2022*).

Flavanols—Catechins from green tea extracts

Catechins, a group of flavonoids found in green tea, are considered a potential treatment for skin diseases due to their antioxidant and anti-aging effects (*Aljuffali et al. 2022*). Catechins, the bioactive components found in green tea, consist of chemical structures including epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG) (*Cardoso et al. 2020; Tian et al. 2021*). Their chemical properties enable them to scavenge reactive oxygen species (ROS), which contribute to the antioxidant, anti-inflammatory, and anti-carcinogenic effects. (*Wang et al. 2022b*). EGCG has the greatest anti-inflammatory potential due to the scavenging capabilities of its hydroxyl groups (*Cardoso et al. 2020*). Catechins possess the ability to chelate metal ions, further enhancing their antioxidant activity. EGCG inhibited TPA-induced DNA binding of NF-kappaB and cAMP response element binding protein (CREB) by blocking p38 MAPK activation, causing an inactivation of the signaling

pathway. This result explains how EGCG inhibits COX-2 in the skin in the model (*Kundu & Surh 2007*). Some studies have found that green toe extract (GTE) mitigates the damage caused by PM2.5 exposure through anti-inflammatory and antioxidant mechanisms. In addition, the restoration of impaired epidermal lipid homeostasis also plays an important role in reducing the damage, suggesting the effect of GTE on PM2.5-altered gene expression in keratinocytes. Regarding the dosage used, a study by Zhengzheng Liao (2020) investigated the effect concentration of green tea extract (GTE) in keratinocytes using the MTT assay and a morphological study, using a three-dimensional epidermal tissue model (3D-ETM) and mass spectrometry. The polyphenol content of the GTE sample was 750 μg/ml (*Liao et al. 2020a*). Furthermore, the results show that GTE works primarily by reducing the effects of PM2.5 on keratinocytes. After treatment with GTE, there was a downregulation of cytokine signaling in the immune system and wound healing, including HMGCS1 and LDLR genes, which are strongly associated with the inflammatory response (*Liao et al. 2020a*).

Flavanols— Fisetin from various fruits and vegetables

Fisetin, a bioactive flavonoid found in various fruits and vegetables such as strawberries, apples persimmons, onions, cucumbers and grapes, is known for its potent antioxidant, anti-inflammatory and anti-apoptotic properties. It has been demonstrated to protect skin keratinocytes by inhibiting PM2.5-induced oxidative stress and apoptosis primarily through the suppression of ER stress responses (*Molagoda et al. 2021*). It effectively downregulates ER stress markers such as GRP78, phosphorylated eIF2α, ATF4 and CHOP, thereby reducing ER stress-induced apoptosis. In addition, fisetin reduces the production of ROS, lowers cytosolic calcium levels and prevents mitochondrial dysfunction, which is critical for attenuating cell damage caused by PM2.5 exposure. By modulating the expression of pro-apoptotic proteins such as Bax and caspases while upregulating anti-apoptotic proteins such as Bcl-2, fisetin provides comprehensive protection against PM2.5-induced keratinocyte apoptosis (*Molagoda et al. 2021*).

Tanin—Diphlorethohydroxycarmalol (DPHC), a phlorotannin, from algae extracts

Diphloroethohydroxycarmalol (DPHC) is a bioactive compound classified as an algal polyphenol, derived from *Ishige okamurae*, a type of brown algae (*Bak et al. 2023; Diao et al. 2021*). DPHC has been previously reported to provide health benefits, including antioxidant and

radioprotective effects (*Ahn et al. 2011*). Due to its health benefits and antioxidant effects, dermatological studies have been published in which DPHC was found to be able to reduce PM 2.5-induced skin dysfunction, oxidative stress, autophagy, endoplasmic reticulum (ER) stress and mitochondrial damage, and apoptosis (*Zhen et al. 2019*). DPHC enhances cell viability by preventing oxidative stress-induced DNA damage, consequently resulted in the inhibition of matrix metalloproteinase-1 (MMP-1), also known as collagenase enzyme, and activation of the nucleotide excision repair (NER) system (*Zhen et al. 2019*). Additionally, previous findings support the protective effect of DPHC by inhibiting lipid peroxidation and cell damage (*Zhang et al. 2021*). Treatment of DPHC can reduce the production of CCAAT-enhancer-binding protein (CHOP), glucose-regulated protein 78 (GRP78) and inositol-requiring enzyme 1 (IRE1)-α, the three of these proteins are involved in cell apoptosis via the activating transcription factor 6 (ATF6) signaling pathway (*Zhang et al. 2021*). Notably, DPHC demonstrates effects similar to hesperidin in mitigating PM2.5-induced mitochondrial damage, which results from increased mitochondrial ROS and disruptions in membrane permeability balance. DPHC plays a role in decreasing Bcl-associated X protein (Bax) and increasing anti-apoptotic Bcl-2 proteins, thereby suppressing PM 2.5-induced mitochondrial damage (*Zhang et al. 2021*).

Stilbenes—Resveratrol from grape extracts

Resveratrol (3,5,4′-trihydroxy-trans-stilbene), a natural polyphenol that can be found and extracted from grape skins and seeds (*Salehi et al. 2018*), has many health benefits, most notably antioxidant, anti-inflammatory, protective effects against cardiovascular disease and cancer (*Meng et al. 2020*). Resveratrol also shows effects that can inhibit PM 2.5-induced inflammation on the skin (*Shin et al. 2020a*). In a previous study, resveratrol was reported to be safe in skin cells, including human keratinocytes, at a concentration of 1μM or less (*Shin et al. 2020a*). Regarding the pharmacokinetics of resveratrol, 70% of resveratrol is absorbed via the gastrointestinal tract but later metabolized, resulting in extremely low bioavailability (*Shaito et al. 2020*). A reduction in intracellular ROS was observed in cells pre-treated with resveratrol, as resveratrol can inhibit AhR activation by PM and thus inhibit the AhR pathway. In addition, resveratrol can also suppress the JNK/MAPK signaling pathway, which regulates COX2/PGE2 and inflammatory cytokines induced by PM (*Shin et al. 2020a*). Resveratrol can also reduce the expression of proinflammatory cytokines and IL-8, which contribute to skin inflammation and

photoaging. Additionally, it lowers the levels of MMP-1 and MMP-9, enzymes responsible for degrading the skin's extracellular matrix (*Michalak-Stoma et al. 2021; Shin et al. 2020a*). As far as the dosage of resveratrol is concerned, the dosage of 0.1-1μM shows the most beneficial effects depending on the dose (*Shin et al. 2020a*).

Saponin—Ginsenoside from ginseng extracts

Ginsenosides, a class of saponins found in ginseng, are characterized by hydroxyl groups attached to a steroid-like backbone with sugars and a distinctive four-ring structure *(Khan et al. 2015*). Ginsenoside Rb1 has shown a protective effect against PM2.5-induced ROS production. Pretreatment with ginsenoside Rb1 shows an increase in cell viability from about 70% (without pretreatment) to 90% (with pretreatment). In terms of its scavenging capacity, the superoxide anion signal is reduced from 2241 to 2024 and the hydroxyl radical generated by the Fenton reaction is reduced from 2844 to 2065 as measured by the xanthine oxidase system. Ginsenoside Rb1 showed protection against PM2.5-induced DNA degradation and apoptosis in HaCaT keratinocytes and normal human dermal fibroblasts (NHDF) through the pro-apoptotic protein Bax and the anti-apoptotic proteins Bcl-2 and Mcl-1. Ginsenoside Rb1 has a protective effect against PM2.5-induced mitochondrial damage by decreasing ROS production and reducing Ca2+ overload. This is evidenced by measuring ATP levels in HaCaT and NHDF cells, where cells exposed to PM2.5 alone had ATP levels of 0.795 and 0.233, respectively, while pretreatment with ginsenoside Rb1 increased ATP levels to 0.94 and 0.283, respectively (*Wee et al. 2011*). In terms of dosage, ginsenoside Rb1 at a dosage of 40μM has been shown to be effective in protecting cells through multiple mechanisms leading to a reduction in ROS, oxidative stress, apoptosis and mitochondria (*Wee et al. 2011*). In addition, ginseng has a wide range of health benefits, such as boosting the immune system, improving central nervous system (CNS) function, alleviating stress and scavenging free radicals (*2024; Wee et al. 2011*) (*Leung & Wong 2010*).

Flavonoids—from *Cornus officinalis* extract

Cornus officinalis extract, particularly its ethanol extract (EECF), has shown significant protective effects against PM2.5-induced skin damage by attenuating oxidative stress, mitochondrial dysfunction and apoptosis in skin cells. EECF exerts its protective effect by scavenging ROS and reducing oxidative damage. Studies show that EECF attenuates lipid

peroxidation, protein oxidation and DNA damage in PM2.5-exposed keratinocytes *(Fernando et al. 2020)*. In addition, EECF reduced intracellular and mitochondrial Ca2+ levels, protecting cells from mitochondrial depolarization, a key event leading to cell apoptosis. In addition, EECF inhibited the upregulation of pro-apoptotic proteins such as Bax and cleaved caspase-3, while enhancing the expression of anti-apoptotic proteins such as Bcl-2, further preventing PM2.5-induced apoptosis. These results suggested that *Cornus officinalis* extract serves as an effective ingredient in skin care products designed to protect the skin from environmental pollutants such as PM2.5 *(Fernando et al. 2020)*.

Flavonoids— Isovitexin, an isomer of vitexin from bamboo leaves, mung beans and fenugreek seeds

Isovitexin, an isomer of vitexin, is a naturally occurring flavonoid with significant antioxidant and protective properties against PM2.5-induced skin damage. Isovitexin has been shown to reduce PM2.5-induced ROS in human keratinocytes, thereby mitigating oxidative stress and preventing cell damage. Isovitexin protects skin cells by inhibiting ROS production, as demonstrated in studies where pretreatment with isovitexin significantly reduced intracellular ROS levels in keratinocytes exposed to PM2.5. The compound exhibits potent free radical scavenging activity against DPPH, ABTS and superoxide anion radicals, indicating a strong antioxidant capacity. In addition, isovitexin enhances stem cell properties in keratinocytes by upregulating the expression of stem cell markers such as CD133 and β-catenin, which play a role in skin regeneration and repair(*Chowjarean et al. 2019*). These results suggested that isovitexin not only protects the skin from the damaging effects of PM2.5, but also promotes skin health by enhancing the regenerative capacity of keratinocytes.

***Lycium barbarum polysaccharide (LBP)*—from Lycium barbarum (goji berry)**

Lycium barbarum polysaccharide, extracted from the fruit of *Lycium barbarum*, has demonstrated protective effects against PM2.5-induced skin damage through its antioxidant, anti-inflammatory and anti-apoptotic properties. LBP protects skin cells, especially HaCaT keratinocytes, by inhibiting oxidative stress markers, reducing reactive oxygen species (ROS) levels and restoring antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). In addition, LBP alleviates ER stress by downregulating stress-related

proteins such as GRP78 and CHOP, which are involved in apoptotic pathways. By mitigating these stress responses, LBP reduces apoptosis, demonstrating its ability to maintain skin cell viability under PM2.5 exposure. Furthermore, LBP modulates autophagy, a process that is often dysregulated in response to PM2.5, by affecting the expression of autophagy-related proteins such as LC3-II and p62. This regulation helps maintain cellular homeostasis and prevents excessive autophagy that could otherwise lead to cell death. The combined antioxidant, anti-apoptotic, and autophagy-regulating properties of LBP render it a promising therapeutic agent against PM2.5-induced skin damage (*Zhu et al. 2022*).

Farnesol--a natural benzylsemiterpene

Farnesol, a component of essential oil from various plants such as citronella, lemongrass, tuberose, cyclamen, rose, neroli, balsam and musk with anti-inflammatory and antioxidant properties, provides a significant protective effect against PM2.5-induced skin damage due to its anti-inflammatory, antioxidant and tissue-reparative properties. Farnesol exerts its protective effect by reducing the production of pro-inflammatory cytokines such as IL-6 and TNF-α, which are elevated in response to PM2.5 exposure. In addition, liposomes loaded with farnesol (lipo-fern) enhance its therapeutic efficacy by improving skin penetration and reducing cytotoxicity. Studies have shown that Lipo Fern can effectively alleviate acute and chronic inflammation, restore damaged epidermis and dermis and promote hair follicle regeneration. This underlines its potential as a therapeutic agent against PM2.5-induced skin damage (*Wu et al. 2021*).

4-O-Feruloylquinic acid (FQA)—from *Phellodendron amurense*

Phellodendron amurense (PAE), also known as Amur cork tree, has shown significant protective effects against PM2.5-induced skin damage through its anti-inflammatory and antioxidant properties. PAE has been demonstrated to mitigate these effects by inhibiting calcium influx and regulating signaling via proteinase-activated receptor-2 (PAR-2), which plays a key role in inflammatory responses. Studies have shown that PM2.5 induces an intracellular calcium influx (Ca2+) that triggers inflammatory pathways in keratinocytes. PAE significantly reduces this Ca2+ influx and thus attenuates the inflammation caused by PM2.5. In addition, PAE downregulates pro-inflammatory cytokines such as IL-6, IL-8 and TNF-α, which are

upregulated by PM2.5 exposure. In addition to its anti-inflammatory effects, PAE also helps maintain the integrity of the skin barrier by preventing the downregulation of proteins such as zonula occludens-1 (ZO-1) and occludin, both of which are crucial for tight junctions in skin cells. In addition, *Phellodendron amurense* contains 4-O-feruloylquinic acid (FQA), a compound responsible for its protective effect. FQA replicates the protective effect of PAE by inhibiting Ca2+ influx and reducing the expression of PAR-2. This suggests that *Phellodendron amurense* extract, particularly FQA, provides significant protection against PM2.5-induced skin damage by modulating inflammatory pathways and maintaining the skin's barrier function (*Choi et al. 2020*).

Drug resistance may not be the most significant issue when it comes to using natural products as alternatives to chemical drugs for treating skin diseases

Discussion

Given the potential for drug resistance associated with medicine treatments, alternative therapies derived from natural products have emerged as a viable option by reducing drug interactions and drug resistance, and mitigating adverse effects associated with the drug metabolisms. Although, a notable drawback is that the chemical composition and antioxidant properties of the plant material are highly variable, as they depend on environmental conditions, harvest timing, transportation and storage conditions (*Hering et al. 2021*). Therefore, methodological improvements must focus on optimizing the extraction process while considering external factors such as temperature, light, and air to ensure consistency in the quality and efficacy of plant materials (*Pyrzynska 2022*) (*Biesaga 2011*). Some studies suggest that the source of extraction and the food matrix can significantly influence the bioactive compounds and their antioxidant properties (*Cobb 2014*). Different parts of the fruit exhibit varying levels of bioactive compounds. For instance, the peel of citrus fruits contains higher levels of antioxidants compared to the pulp, primarily due to its greater concentration of flavonoids, vitamin C, and carotenoids (*Hu et al. 2018*). Hesperidin extracted from orange peels showed moderate antioxidant activity against DPPH free radicals at 36%, while vitamin C showed a higher ability (100%) under the same conditions (*Al-Ashaal & El-Sheltawy 2011)*. Apart from skin damage, several types of vitamins showed protective effects of biological agents in a variety of organ systems, for example, vitamin D protects respiratory epithelial cells (*Chatsirisupachai et al. 2024*). Previous studies have shown that quercetin has low solubility and poor bioavailability,

which limits its potential to be synthesized into a highly effective drug (*Alizadeh & Ebrahimzadeh 2022*). Therefore, further research is needed to investigate the long-term effects at higher doses, as the potential risks of high doses of quercetin have increased renal toxicity and estrogen-dependent cancer in some studies (*Andres et al. 2018*). Apart from *in vitro* studies, research in the field of application is essential as there is insufficient work on the therapeutic dosage and side effects of natural products in human skin. Since natural products have the potential to be alternative therapeutic substances, further research and development of natural extraction procedures are required to minimize the restricted stability and bioavailability of natural compounds.

Conclusion and future prospectives

Several natural substances possess distinct advantages in shielding skin cells, particularly keratinocytes, from PM2.5-induced damage because PM2.5 damages keratinocytes by inducing the production of ROS, oxidative stress, and inflammation. Based on their chemical structure with phenolic compounds: Sulforaphane, hesperidin, quercetin, catechin, diphloroethohydroxycarmalol, resveratrol and ginsenoside show their potential properties in antioxidation and anti-inflammation. These bioactive compounds in the natural products are believed to reduce ROS production, prevent mitochondrial dysfunction and inhibit cellular apoptosis. Therefore, natural compounds hold great promise as therapeutic agents for preventing PM2.5-induced skin damage and promoting healthy skin regeneration. Their incorporation into health management strategies presents significant potential for the development of highly effective health products and treatments. However, further research is essential to elucidate their mechanisms of action, interactions, optimal therapeutic doses, toxic thresholds, and potential side effects.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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801 ## Figure and Table legend
802
803 **Figure 1: Graphical abstract represents the mechanistic findings on the protective effects of**
804 **herbal chemicals against fine particulate matter-induced skin damage obtained from in**
805 **vitro studies**
806 Figure was drawn in part using images from Servier Medical Art. Servier Medical Art by Servier
807 is licensed under a Creative Commons Attribution 4.0 Unported License
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809

810 **Table 1.** Summary table of natural products to protect against PM2.5-induced skin cell damage