AMERICAN JOURNAL OF BIOLOGY AND NATURAL SCIENCES
https://biojournals.us/index.php/AJBNS
ISSN: 2997-7185

Article

Physiological and Histological Characterization of Chemically Induced Nanoplastic Forced Skin Aging in Mice

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Citation: Alshugary A. Physiological and Histological Characterization of Chemically Induced Nanoplastic Forced Skin Aging in Mice. American Journal Of Bioscience And Clinical Integrity 2026, 3(9), 17-27.

Received: 10th Jun 2026
Revised: 11th Jul 2026
Accepted: 20th Aug 2026
Published: 06th Sept 2026

Abstract: Background: NPs and chemical aging, are well documented, but the interactions of these components physiologically on the skin's integrity are not yet well characterized. **Objective:** To elucidate the effects of polystyrene NP exposure and D-galactose mediated accelerated ageing of the mouse skin. **Methodology:** Forty male C57BL/6 mice were divided into four groups: Control, NP exposure, Chemical aging, and Combined exposure. The topical treatments were repeated over 4 weeks. Macroscopic observations, transepidermal water loss (TEWL), elasticity, hydration and molecular analysis were performed. **Results:** Combined exposure showed significant effect on accelerating aging of skin. The combined group had an increase in TEWL values of nearly threefold as compared to the control group, with a value of 15.3±2.1 g/m²/h for the combined group, marking a severe barrier impairment. Skin elasticity dropped to 0.48±0.09 U f and hydration levels to 38.9±7.1. On the molecular level, a significant increase in malondialdehyde (5.1±0.7 mmol/mg) and a dramatic decrease in SOD (55.3±7.5 U/mg) was noted in the combined group. In addition, the pro-inflammatory cytokines, TNF-α and IL-6, were markedly increased to reveal synergic induction of oxidative stress and chronic inflammation by the combination of the two, which was synergistic effects of individual treatments alone. **Conclusions:** Exposure to nanoplastic significantly increases the chemically induced skin aging through disrupted skin barrier, increased oxidative, and inflammatory responses. The results demonstrate the importance of the risk associated with nanoplastics on skin health.

Keywords: D-galactose, nanoplastics, TNF-α, IL-6, Skin Aging

Introduction

The escalating presence of plastic pollution has become a critical environmental and health concern. The breakdown of larger plastic items creates microplastics (MPs) which are plastics smaller than 5 mm and nanoplastics (NPs) which are plastics below 100 nm diameter [1]. Indeed, these widely-distributed particles are found in various ecosystems ranging from aquatic to terrestrial ones, and they are now increasingly found in biological matrices such as human tissues [2]. Their widespread distribution calls into question their long-term effects on human and animal health, especially by primary exposure pathways (ingestion, inhalation and dermal exposure) [3]. Although numerous studies have shown the presence of nanoplastics, their detailed toxicological actions on complex biological systems like skin, are still in development and of critical importance [4]. The skin, the body's largest organ, acts as the primary defensive barrier against environmental risk factors such as pollution, pathogens, radiation among others. It has multi-layered structure (epidermis, dermis, and hypodermis) which acts as a powerful physical and immunological barrier [5]. However, intrinsic and extrinsic

factors, such as chronological ageing, chronic inflammation, or chemical irritants and environmental toxins can affect the integrity of this important barrier [6]. These compromises can facilitate the penetration of exogenous nanoparticles like nanoplastics into deeper deeper skin layers [7]. Nanoplastics can once they pass the barrier of the skin come into interact directly with components of the skin cells and trigger molecular and cellular reactions that lead, including, to tissue damage and an aging phenotype [8].

Irrespective of the experimental model used, exposure to nanoplastics consistently induces oxidative stress [9]. The imbalance between production of Reactive Oxygen Species (ROS) and the antioxidant capacities of the cells results in extensive damage to cellular macromolecules including DNA, proteins and lipids [10]. Of note, this oxidative damage plays a significant role in cellular dysfunction, senescence and rapid biological ageing. Additionally, a clear correlation can be established between nanoplastic exposure to inflammatory responses activation [11]. Nanoplastics are found to induce high production of pro-inflammatory cytokines, which are major contributors in inflammation. A chronic low-grade inflammatory state is a characteristic of ageing (inflammaging) and is of great importance in the pathogenesis of many diseases of ageing such as dermatological diseases [12]. The constant inflammatory response may be caused by direct contact of nanoplastics with immune cells, or through the oxidative stress mediated damage on cells, causing tissue damage and premature ageing of skin. Another important mechanism of action of nanoplastic induced damage and accelerated ageing is cellular senescence, which is characterised by an irreversible cell cycle arrest and a senescence associated secretory phenotype (SASP). Aging causes a buildup of senescent cells that add to dysfunction and inflammation of tissues. Several studies have shown that nanoplastics induce senescence through mitochondrial dysfunction, autophagic flux impairment and activation of DNA damage response [13]. These changes augment the aging phenotype. Nano-sized microplastics induce both inflammation and senescence in vitro using skin cell lines, demonstrated by upregulation of important molecules that produce key markers of aging, including p16 and p21. Molecular mechanisms include mitochondrial oxidative stress, mitochondrial membrane potential depolarization, and Gasdermin D mitochondrial recruitment. This process results in leakage of mitochondrial DNA to the cytoplasm, activation of AIM2 inflammasome and inflammation and ageing. The results indicate a complexity of the molecular mechanisms that nanoplastics can affect in skin pathology and premature aging.

Because of their genetic tractability, short lifespan, and physiological similarities to human skin, rodent models, and particularly mice are essential experimental models to study the effects of environmental contaminants on the physiology and histology of skin ageing [14]. Models of chemically induced forced skin ageing include the application of topical or systemic chemical agents that stimulate ageing; they are designed to be a controlled system to explore ageing phenotypes in a shorter period of time. This manipulation partially represents the chronological or photo-aging, allowing efficient research on possible treatments and/or exacerbating factors such as exposure to nanoplastics [15]. Histological characterization is the examination by light microscopy of stained tissue sections, evaluating structural modifications including epidermal thickness, integrity of dermis collagen and elastic fibers, inflammatory infiltrate and senescent cells. These analyses can yield essential data about the structure and composition of the skin. At the same time, the physiological characterization assesses, for example, transepidermal water loss, skin elasticity and hydration. Together, these assessments offer a holistic view of aging and environmental stressors' impact on skin health. Although the individual toxicological effects of nanoplastics and the usefulness of chemically induced skin ageing models are available, no in vivo studies have investigated their combined impact. In particular, the synergistic changes in the physiological and histological functions of nanoplastic exposure in a chemically accelerated skin aging mouse remain to be characterized. The aim of this study is to physiologically and histologically define chemically-induced nanoplastic-forced skin aging in the mouse. This study aims to characterize the combined effect of nanoplastic exposure and chemical aging on skin's health by examining both macroscopic changes of skin as well as examination of the skin's structure and molecular markers of oxidative stress and inflammation and senescence.

Materials and Methods

Study Design

In this study, an in vivo experimental design was employed to examine the combined effect of plastic nanoparticles and chemically induced skin ageing with the use of a mouse model. For accurate comparison of physiological, histological and molecular changes, mice were assigned randomly into various experimental groups.

Experimental Animals

To fully represent the results, a total of 40 C57BL/6 male mice of (8-10) weeks old were used. Animals were acclimated for one week on ad libitum diet at 12:12 light-dark facility at a temperature of 22 ± 2°C and 55 ± 5% humidity. The mice were divided into four main groups (n = 10 mice, respectively): the Control Group with age-induced by the chemically induced aging agent and nanoplastics placebo; Nanoplastic Exposure Group with the chemically induced aging agent placebo and exposed to nanoplastics; Chemically Induced Skin Aging Group with placebo nanoplastics and age induced by the chemically induced aging agent; and Combined Exposure Group exposed to both the chemically induced aging agent and nanoplastics. Non-invasive measurement devices were used to carry out physiological skin assessments at specific time points – baseline and two weeks after, and at the end of the study. These evaluations involved macroscopic observations to assess apparent changes in skin with a standardized scoring-system, including assessment of skin redness, dryness, wrinkles and skin thickness. To measure skin barrier function, Transepidermal Water Loss (TEWL) was also evaluated with the help of a Tewameter® TM 300 (Courage + Khazaka electronic GmbH, Germany) [16]. Moreover, skin elasticity was tested by Cutometer® (MPA 580, Courage + Khazaka electronic GmbH, Germany) for assessment of mechanical behavior and skin hydration was tested by a Corneometer (CM825, Courage + Khazaka electronic GmbH, Germany) to evaluate the stratum corneum hydration.

Nanoplastics Preparation and Application

The polystyrene nanoparticles used had a diameter of 50 nm and a concentration of 100 μg/mL. A nanoplastic suspension was formulated in physiological saline which contained 0.05% Tween 20 and dispersed for 30 minutes using ultrasonication to achieve well dispersed. A specific skin area (shaved back) was treated with nanoplastic for a 4 week period by applying 50 μL of nanoplastic three times a week [17].

Chemicals Used to Induce Skin Aging

The accelerated aging of skin was caused by chemical induction, in which 100 mg/kg B.W of D-galactose was directly applied onto the designated area of the skin and at a dose of 50 μL daily for 4 weeks [18].

Histological studies of the skin

By the conclusion of the study, mice were deeply anesthetized and sacrificed, and subsequently samples of skin from the treated area were taken. The samples were then fixed in 10% neutral buffered formalin, embedded in paraffin and sectioned at (4-5) μm. Histological," assessment included Hematoxylin and Eosin (H&E) staining for general skin morphology, epidermal thickness and presence of inflammatory cells [19]. With light microscope, sections were analyzed and digital image were captured for quantitative analysis with the use of image J software (nih, USA).

Molecular Indicators Analysis

The rest of the samples of skin were immediately removed and frozen in liquid nitrogen with storage at -80 °C for molecular indicator analysis, the levels of malondialdehyde (MDA) and the activity

of antioxidant enzymes superoxide dismutase (SOD) and glutathione (GSH) were measured using commercial test kits [20]. In addition, various pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) were determined in extracts of skin using enzyme-linked immunosorbent assay (ELISA) [21].

Statistical Analysis

All data were presented as Mean ± SD. One-way analysis of variance (ANOVA) and Tukey's post hoc tests were used for multiple comparisons between groups. A p-value less than 0.05 was considered statistically significant. Data were analyzed by the Graphpad prism software version 9 (GraphPad Software, San Diego, CA, USA).

Results

Physiological Assessments of the Skin

A set of time points was chosen to assess the effects of nanoplastics (NPs) and the aging-inducing chemical (D-galactose) on skin barrier function and mechanical properties by comprehensive physiological assessment of the skin. The results evidenced differences between the experimental groups, indicating that exposure to either one or both had an adverse effect.

1. Macroscopic Observations

At the macroscale, changes in mouse skin were observed among the different groups of animals. The control group had normal skin with no signs of ageing and damage. However, the nanoplastic and chemical aging groups started to demonstrate slight erythema and aridity 2 weeks after exposure started. These changes were far more pronounced in the combined exposure group (nanoplastics + D-galactose) with accentuated erythema, skin dryness, and wrinkling, and an apparent thickening of the skin, suggesting that the combination of both treatments has a strong aging promoting effect.

2. Transepidermal Water Loss (TEWL)

The trans-epidermal water loss (TEWL) is an important skin barrier function parameter. The TEWL of exposed groups was found to be increased progressively as compared to the control group. The most severe impairment was observed in the exposure group of which combined exposure group was the most affected, with a significant increase in TEWL ($p<0.001$) representing severe impairment of the skin barrier function. The TEWL increased in the individual nanoplastic and D-galactose groups but the change was less pronounced, nonetheless the latter did not differ significantly from the control ($p<0.01$). The present research highlights the relevance of nanomaterials derived from plastics in combination with D-galactose in breaking the barrier function of the skin. Mean TEWL values are given in (**Table 1**).

Table 1. The skin elasticity mean values obtained from the experimental groups.

Group	TEWL (g/m²/h) ± SD
Control	5.2 ± 0.8
Nanoplastics	8.5 ± 1.2
Chemical Aging (D-gal)	10.1 ± 1.5
Combined Exposure	15.3 ± 2.1

Note: $p<0.001$ for the combined exposure group vs. control; $p<0.01$ for the nanoplastic and chemical aging groups vs. control

3. Skin Elasticity

A Cutometer® was used to assess skin elasticity and the results indicated that there was a progressive decrease in skin elasticity in exposed groups. The greatest effect was in the combined exposure group with the lowest elasticity values ($p<0.001$) which reflect the highest loss of mechanical properties of the skin. This was followed by the chemical aging group, which in turn was followed by the nanoplastic group with significant decrease with respect to the control group ($p<0.01$). This

indicates that nanoplastics and D-galactose exposure is associated with damage to elastic fibers in the skin which reduces skin elasticity. The mean skin elasticity values are presented in (**Table 2**).

Table 2. Experimental group mean values for skin elasticity

Group	Skin Elasticity (Uf) ± SD
Control	0.85 ± 0.05
Nanoplastics	0.72 ± 0.08
Chemical Aging (D-gal)	0.65 ± 0.07
Combined Exposure	0.48 ± 0.09

Note: $p<0.001$ for the combined exposure group vs. control; $p<0.01$ for the nanoplastic and chemical aging groups vs. control.

4. Skin Hydration

Exposed groups had a significant reduction in stratum corneum hydration compared to controls with the most drastic reductions in the combined exposure group ($p<0.001$), skin hydration measurements were taken using a Corneometer®. There was also a marked reduction in skin hydration in both the nanoplastic and chemical aging group when compared with the control group ($p<0.01$). This loss of hydration is correlated with an impaired barrier function and water binding capacity of the skin, which leads to macroscopically perceptible dry skin. (**Table 3**) shows the mean skin hydration measurements.

Table 3. The mean skin hydration values for the experimental groups are shown

Group	Skin Hydration (Corneometer Units) ± SD
Control	75.2 ± 4.5
Nanoplastics	60.1 ± 5.8
Chemical Aging (D-gal)	55.7 ± 6.2
Combined Exposure	38.9 ± 7.1

Note: $p<0.001$ for the combined exposure group vs. control; $p<0.01$ for the nanoplastic and chemical aging groups vs. control.

Analysis of Molecular Indicators

To determine the possible mechanism of changes observed in the physiological and histological assessment, molecular markers involved in oxidative stress and inflammation were examined in the skin samples.

1. Oxidative Stress Indicators

Malondialdehyde (MDA) levels, one of the markers of lipid peroxidation and oxidative stress, were significantly higher in the exposed groups, leading to the combined exposure group ($p<0.001$). On the other hand, the activity of antioxidant enzymes, including superoxide dismutase (SOD) and glutathione (GSH) reduced in these groups which showed disproportion between the oxidants and antioxidants. These changes were greatest in the combined exposure group ($p<0.001$), and in the chemical aging and nanoplastic groups ($p<0.01$). Overall, these findings indicate that nanoplastics and D-galactose combined together trigger the oxidative stress in skin cells, which can lead to cellular damage and accelerate aging. (**Table 4**) shows the mean values of the oxidative stress indicators.

Table 4. Mean values of oxidative stress indicators in the different experimental groups

Group	MDA (nmol/mg protein) ± SD	SOD (U/mg protein) ± SD	GSH (μmol/mg protein) ± SD
Control	1.2 ± 0.2	125.5 ± 10.3	15.8 ± 1.5
Nanoplastics	2.8 ± 0.4	90.2 ± 8.7	10.1 ± 1.2
Chemical Aging (D-gal)	3.5 ± 0.5	80.1 ± 9.1	9.5 ± 1.1
Combined Exposure	5.1 ± 0.7	55.3 ± 7.5	6.2 ± 0.9

Note: $p<0.001$ for the combined exposure group vs. control; $p<0.01$ for the nanoplastic and chemical aging groups vs. control.

2. Pro-inflammatory Cytokines

Pro-inflammatory cytokines showed that pro-inflammatory levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) were significant in both the nanoplastic group and the D-galactose group, with the nanoplastic + D-galactose group having the highest level ($p<0.001$). Also observed was a dose dependent up-regulation of the pro-inflammatory cytokine, interleukin-1 beta (IL-1β) in all the exposed groups with study levels being most distinct in the combined exposure group. This indicates that there is a strong inflammatory process in the affected skin, playing a large role in the rapid ageing process and skin destruction. (**Table 5**) gives the mean values of the pro-inflammatory cytokines.

Table 5. The mean values of pro-inflammatory cytokines in the experimental groups

Group	TNF-α (pg/ml) ± SD	IL-1β (pg/ml) ± SD	IL-6 (pg/ml) ± SD
Control	15.2 ± 2.1	8.5 ± 1.2	10.1 ± 1.5
Nanoplastics	35.8 ± 4.5	18.2 ± 2.5	25.3 ± 3.1
Chemical Aging (D-gal)	42.1 ± 5.2	22.5 ± 3.0	30.7 ± 3.8
Combined Exposure	68.5 ± 7.8	35.1 ± 4.2	55.9 ± 6.5

Note: $p<0.001$ for the combined exposure group vs. control; $p<0.01$ for the nanoplastic and chemical aging groups vs. control.

Histological Assessments of the Skin

Histological samples of the skin were taken after the end of the study period for detailed skin histological evaluation for microscopic structural changes in sync with the physiological ones. Hematoxylin and Eosin (H&E) for the evaluation of changes in epidermal thickness, collagen fiber density, elastin fiber integrity and inflammatory cell infiltration. Histological pictures were examined in H&E stained sections which showed marked alterations in skin structure (**Fig. 1**). A thin and well-organized epidermis was found in the control group and the cell layers in the epidermis were well-defined and the dermis consisted of longitudinally arranged collagen fibers with low cell density. Chemical aging and combined exposure groups in contrast, had significantly more (hyperkeratosis) epidermal thickening: the skin's response to stress and damage. Infiltrating inflammatory cells were also observed in the dermis of the various groups, and more in the combined exposure group, indicating the strong and persistent inflammatory reaction. There were comparable, though not as great, changes in the nanoplastic group, with significant changes still present when compared to the control group.

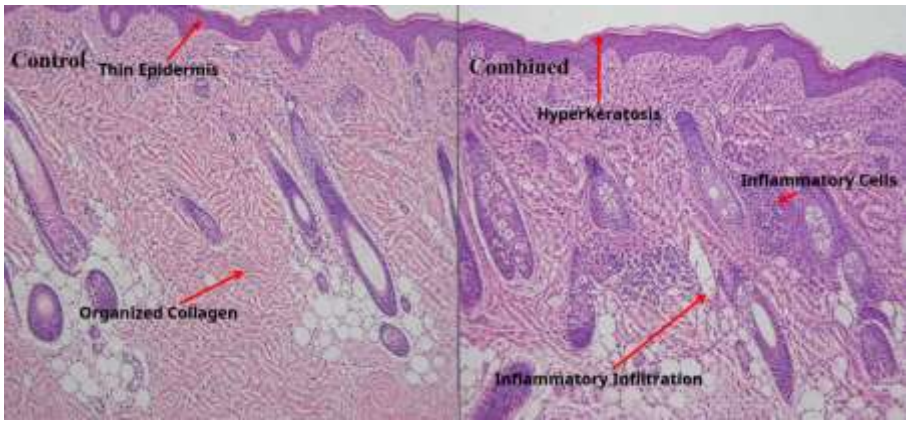

Figure 1. Histological sections of hematoxylin and eosin (H&E) stained mouse skin from the control and combined exposure group

Discussion

In this study, the physiological and histological effects of aging due to nanoplastics (NPs) exposure and chemical aging using D-galactose in mice were thoroughly analyzed. The results clearly revealed that both exposure to NP and D-galactose were able to accelerate skin aging and when combined their effects are significantly augmented, which is in agreement with the increasing understanding of the effect of environmental pollutant exposure on skin health [22]. Nanoplastics are becoming more problematic in the environment because they are the products of degradation of larger plastic debris that creates concerns concerning potential biological impacts especially on sensitive organs, such as the skin. D-galactose is a proven aging inducer and is useful as a model for aging accelerated processes to gain a better understanding of the aging mechanism when used together with aging stressful factors. This study highlights the importance of studying the interactions between anthropogenic pollution and endogenous ageing mechanisms.

Macroscopically, exposed groups showed evident signs of premature aging, including skin redness, dryness, wrinkles, and an increase in thickness, which were more pronounced in the co-exposure group than in the other groups. These modifications are related to the overall decrease of the mechanical properties and skin barrier. Erythema or pink/redness is a typical sign of how the skin responds to inflammation and is regularly seen due to chronic exposure to irritants and aging itself. Dryness (xerosis) indicates a damaged stratum corneum and loss of the capacity of water retention as a characteristic of aging skin. Wrinkle formation is a direct result of degradation of the extracellular matrix, especially the collagen and elastin fibers, which results in a loss of integrity and resiliency. Chronic inflammation/irritation may lead to increased skin thickness (acanthosis) which is a compensation response to the chronic inflammation process and is a change in the keratinocytes' proliferation process. A skin barrier loss, manifested by an important TEWL (Transepidermal Water Loss), is one of the main signs of a lack of protection against external factors [23]. A high TEWL indicates that the stratum corneum is broken down and this enables more harmful substances to penetrate and also contributes to greater dehydration. The ability of nanoplastics to pass through the skin barrier to trigger functional abnormalities has been suggested in previous studies and could be due to regulation of the tight junctions or lipid bilayers that may allow other pro-aging compounds to enter [24]. It is worth noting that the skin elasticity decreased in both exposure groups, particularly the co-exposure group, caused by that elastic fibre and collagen degraded [25]. Both collagen (tensile strength) and elastin (elasticity) degrade and cause sagging and diminished recoil when degraded by matrix metalloproteinases (MMPs), which are often increased during oxidative stress and inflammation. This is a well-recognized sign of skin ageing, which is exacerbated by external factors [26]. Furthermore, there was a substantial reduction in the level of skin hydration in all exposed groups, corroborating an impaired capacity of the skin to hold water and therefore a skin appearance of dryness [27]. This loss of hydration can be explained by the loss of natural moisturizing factors (NMFs), hyaluronic acid, and by damage to the lipid barrier, all influenced negatively by oxidative stress and inflammation.

The study provided critical insights at the molecular level for understanding the mechanisms that underlie these changes. The results indicated that the level of lipid peroxidation products namely malondialdehyde (MDA) was significantly raised and the activities of antioxidant enzymes like superoxide dismutase (SOD) and glutathione (GSH) have significantly decreased in the exposed groups [28]. This imbalance shows that the presence of nanoplastics and D-galactose is making the skin cells succumb to oxidative stress with the result that they suffer damage and age more quickly [29]. Excessive reactive oxygen species (ROS) in the body and an inadequate ability to eliminate them is a phenomenon known as oxidative stress. ROS is capable of damaging various cellular components, such as lipids, proteins and DNA, which results in cellular dysfunction and senescence. One of the intermediates of the lipid peroxidation process that takes place as a consequence of ROS generation is MDA, and this level is directly related to oxidative damage of cell membranes. SOD catalyzes the dismutation of superoxide radicals to oxygen and hydrogen peroxide and GSH is one of the most important antioxidants that will reduce multiple ROS and allows cells to maintain their redox balance. Overall, the decrease in SOD and GSH activity indicated a loss of this intrinsic antioxidant defense mechanism of the skin, leading to increased susceptibility of skin cells to oxidative attack. Nanoplastics are also able to produce ROS, which can damage cells possibly due to the small size, and the high surface area meaning they could interact with cellular membranes, organelles and cause mitochondrial dysfunction [30]. D-galactose also increases oxidative stress, however, through some other mechanisms to induce aging [31]. D-galactose-induced accumulation of advanced glycation end products (AGEs) promotes ROS production and thus increases oxidative damage.

Moreover, levels of pro-inflammatory cytokines were also taken and the exposed populations showed a statistically significant increase in the level of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) which reflects high inflammatory response values [32]. Sustained chronic low-grade inflammation (inflammaging) is playing a major role on various age-related diseases, skin diseases being one of them [33]. Among the key players of inflammation, TNF-α and IL-6 are probably the most important mediators of inflammation that regulate the extent of recruitment of immune cells and the subsequent activation of downstream pathways that can contribute to a reduction in tissue function and the promotion of senescence. Chronic increases in the expression of these cytokines leads to a pro-inflammatory micro-environment, causing disruption of the normal tissue homeostasis and consequently degradation of the extra-cellular matrix. Nanoplastics also have the potential of inducing inflammatory response as they are perceived by immune cells as foreign and can activate immune cells to produce pro-inflammatory mediators through, but not limited to, the inflammatory some pathway [34]. The synergistic effect of co-exposure to nanoplastics with D-galactose has been found indicating the ability of environmental factors to act in synergy to generate additive harmful impact on skin, thereby exacerbating the skin ageing process [35]. The synergy is especially notable because it indicates that the effect of the combination is more severe than the sum of the individual effects, which might be due to common or overlapping mechanism(s) of oxidative stress and inflammatory response. For example, it is possible that the AGEs generated by D-galactose may make cells more susceptible to the action of the ROS generated by NP, and that NP may increase the susceptibility to the action of AGEs generated by D-galactose, resulting in a vicious cycle of damage. The complex interaction between environmental pollutants and chemical factors is emphasized here in regards to skin aging. The findings offer compelling evidence of the potential of nanoplastics, particularly in conjunction with other aging factors, to disrupt the integrity and function of the skin. This indicates that detailed molecular mechanisms of these interactions and preventive measures to reduce the detrimental effects induced by exposure of nanoparticles and nanoplastics on the skin require further investigation [36]. Future research is needed to establish specific cells targets and the mechanism of action that underpins this synergistic toxicity and to determine possible options to intervene with antioxidant or anti-inflammatory compounds or agents in order to reverse these negative effects. The knowledge about these complex interactions would be important for making public health strategies effective to combat environmental aging accelerators.

Conclusion

This study has explored in detail how exposure to nanoplastics (NPs) and aging induced by D-galactose negatively influences skin health in mice. Physiologically, the observed rise of redness, dryness, wrinkles, and skin thickness, with the impairment of its barrier function and the loss of its elasticity, demonstrate the impact that these stresses have on the skin. On the molecular level, the study revealed key mechanisms, such as the increased oxidative stress (measured as MDA) and reduced antioxidant enzyme activity, as well as a strong pro-inflammatory reaction (measured as increased levels of pro-inflammatory cytokines (TNF-α, IL-6). All of these molecular defects contribute to cell damage and an early aging of the skin cells. Future studies should aim to unravel the complex interaction at molecular level between these stress factors and determine specific cell targets, allowing the development of specific interventions, which could be used to mitigate the effects of these stressors on skin integrity and protect the skin from environmental and metabolic skin aging, enabling new preventative and therapeutic approaches.

Ethical approval

The study was conducted after obtaining ethical approval from the Scientific Research Ethics Committee at Al-Furat Al-Awsat University, Al-Musayyib Technical Institute.

Conflict of interest

No conflict of interest.

Funding

Self-funded.

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