Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/45/20240584

Potential applications of nanomaterials to treat skin photoaging

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Abstract. Skin photoaging is a pathological condition induced by ultraviolet radiation. Among the three types of Ultraviolet radiation, UVA and UVB are the two that can penetrate the epidermis and induce various symptoms of skin photoaging. Symptoms include wrinkles, reduced skin thickness, inflammation, and skin cancers in the worst situations. Skin photoaging is multifactorial. Excessive reactive oxygen species (ROS) and dermal extracellular matrix (ECM) degradation are the two significant features of skin photoaging. Ultraviolet radiation also induces cellular senescence and apoptosis of several skin cells like keratinocytes, dermal fibroblasts, and immunosuppression. Topical administration of natural-derived and synthetic products and laser resurfacing therapies are currently used to treat skin photoaging. However, topical delivery of drugs has difficulty penetrating the epidermis, whereas laser treatments have relatively severe side effects. Nanomaterials, including nanoparticles and nanofibers, can encapsulate drugs to achieve a controlled topical drug release system with higher permeability and efficacy. Nanomaterials are biodegradable, non-toxic, and have high biocompatibility, making them potentially less invasive and having good side effect profiles when used in therapies. Thus, nanomaterials have the potential to be applied in treating skin photoaging, but the optimal doses, efficacy, and safety profiles require to be reconfirmed and improved in future studies.

Keywords: Skin photoaging, Nanomaterials, Reactive oxygen species, Ultraviolet radiation, Laser resurfacing

1. Introduction

Skin and mucosa of various body canals comprise a vital defensive barrier of human bodies towards the outer environment. In addition, the skin regulates body temperature and prevents dehydration. Thus, maintaining the typical properties and functioning of the skin is sufficiently necessary. Many products from both cosmetical and clinical fields, including drugs, creams, and injections, support skin

DOI: 10.54254/2753-8818/45/20240584

homeostasis. On the contrary, skin ageing is harmful to its homeostatic state. Ageing of the skin can be categorised into two types, which are intrinsic and extrinsic ageing. Intrinsic ageing corresponds to inevitable natural skin ageing. In contrast, the primary cause of extrinsic skin ageing is Ultraviolet radiation (UVR). UVR-induced skin ageing, also called skin photoaging, results from overexposure to sunlight [1]. Skin photoaging causes wrinkle formation, thinning of the skin thickness, long-lasting skin inflammation, DNA damage of various skin cells, and even carcinogenesis [2].

The pathogenesis of skin photoaging is complex. The primary culprits involve inflammation, ROS generation, ECM degradation, immunosuppression, apoptosis, and cellular senescence. Current treatments mainly target the above hallmarks of skin photoaging, ranging from topical administrations of natural-derived to synthetic products. For instance, ascorbic acid exerts anti-inflammatory effects by decreasing the ROS-induced overexpression of pro-inflammatory cytokines such as TNF-α and IL-1β. Skin rejuvenation is also promoted by ascorbic acid via upregulation of TGF-β and VEGF expressions, two tissue healing mediators [3]. Moreover, ablative and non-ablative lasers treat skin photoaging by stimulating collagen synthesis in the dermis [4,5]. However, the effects of the current treatments are relatively transient and show short-lived outcomes. Therefore, improving the efficacy of the current therapies can be one potential therapeutic direction.

Nanomaterials like nanoparticles and nanofibers pave the way for the above direction. Topical treatments cannot reach the innermost layer of the skin, while laser treatments have adverse events like scars, infections, and hyperpigmentation [1]. Nanomaterials, with their advantages of ready accessibility into cells and less severe side effects profiles, can serve as drug platforms or further scavengers of photodamage to skin cells. This review will describe in detail the mechanisms and the current treatments of skin photoaging and the potential applications of nanomaterials to treat skin photoaging.

2. Mechanisms of skin photoaging

2.1. Effects of UVR on skin photoaging

Skin photoaging refers to the pathological skin conditions on morphological, histological, biochemical, and molecular changes when the skin is overexposed to ultraviolet (UV) radiation. Wrinkles, increased fragility, and skin laxity are the three significant symptoms of skin photoaging. At the cellular level, photoaging changes the formation of the cutin cell morphology, leading to its irregular shape and loss of polarity. The extent of photoaging may vary by skin type, ethnicity, and geographic location. UVR is mainly divided into three components: ultraviolet A (UVA) radiation, ultraviolet B (UVB) radiation, and ultraviolet C (UVC) radiation [6]. Among them, the ozone layer only absorbs UVC radiation, so UVA and UVB radiation can reach human skin. UVR can be absorbed by skin pigments, triggering photochemical reactions and clinical symptoms such as skin ageing and photocarcinogenesis.

2.2. Molecular basis of skin photoaging

2.2.1. Contributions of UVR to skin photoaging

The primary skin damage caused by photoaging can be attributed to UVR. Among the UVRs, UVA radiation penetrates the epidermis and dermis, while UVB radiation only penetrates the epidermis. The main damaged skin layers are the epidermis and dermis. Cellular senescence and severe degradation affect two significant dermis components, dermal fibroblasts, and dermal ECM, respectively. Excessive UVR also damage keratinocytes in the epidermis. UVR-induced skin photoaging is categorised into UVR-induced direct and indirect skin damage.

2.2.2. UVR-induced direct skin damage

The direct skin damage caused by UVR is mainly associated with alterations of nucleic acids and protein structures and their functions. UVB radiations are the culprits of this process. In terms of DNA alterations, it leads to three pre-mutagenic lesions formation, which are Dewar valence isomers, cyclobutene-pyrimidine dimers (CPDs), and 6–4 pyrimidine–pyrimidinone ((6-4)-PP). Dewar valence

DOI: 10.54254/2753-8818/45/20240584

isomers are a more unstable form of (6-4)-PP, caused by irradiation of (6-4)-PP with about 320 nm UV radiations—all three lead to keratinocyte apoptosis by arresting cell replication at the stage of transcription. For RNA alterations, various types of RNA, like mRNA, absorb UVB radiations at transcription and translation for transient periods. Thus, dysfunctional proteins are synthesised. UVB radiations are predominantly absorbed by epidermal proteins enriched with aromatic amino acids like disulfide-bonded cysteine (Cys), Cys, tyrosine (Tyr), and tryptophan (Trp). These proteins generate free radicals like disulfide radical anions (RSSR-) and superoxide anions (O_2^-) via photoionisation or structural modification. Free radicals or ROS activate various downstream signalling pathways to cause skin damage [7]. Structure-modified proteins form aggregates that disrupt skin homeostasis and are involved in the pathogenesis of diseases like skin ageing [8].

2.2.3. UVR-induced indirect skin damage

Unlike those direct ones, UVR-induced indirect skin damage confers most of the impairment on the skin—for instance, persistent inflammation via various pathways like MAPK, NF-κB, and ECM degradation. The culprit behind UVR-induced indirect skin damage is ROS. The body has a self-defensive system against ROS-induced photoaging called the antioxidant system. However, when the ROS concentration increased dramatically and saturated the body's antioxidant system's capacity, a consequent pathological condition termed oxidative stress occurs. ROS equilibrium and homeostasis within the skin cells are broken during oxidative stress. ROS is mainly produced by numerous endogenous photosensitisers within the epidermis, including DNA, NADPH, urocanic acid, melanin, and aromatic amino acids. These photosensitisers predominantly absorb UVB radiations in order to achieve skin protection from UVR-induced impairments. Besides the production mentioned above of ROS by photoionisation of Trp, Tyr, and Cys within irradiated proteins in the epidermis keratinocytes, NADPH in those keratinocytes catalyses molecular oxygen conversion to O_2^-. On the other hand, melanin and urocanic acid act as protective methods for the skin, for they absorb the most portions of UVB radiations. However, the protections are accompanied by harm. The isomerisation of trans-urocanic acid into cis-urocanic acid and enhanced melanin synthesis is triggered by excessive UVB absorption, followed by ROS generation [2].

2.2.3.1. UVB-induced inflammation

ROS generated from UVB radiations accounts for one of the features of skin photoaging: persistent inflammation via activating various signalling pathways. The primary target of ROS is the mitochondrial-activated protein kinase (MAPK) pathway. ROS triggers the phosphorylation of the signalling proteins of the MAPK pathway, following different cascades and leading to MAPK activation. Activator protein 1 (AP-1), nuclear factor kappa B (NF-κB), and cyclooxygenase 2 (COX-2) are among the various transcription factors (TFs) that are activated after the activated MAPK enters the nucleus. Extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK (p38 kinase) are three main sub-pathways involved in MAPK activation. The phosphorylation of ERK, p38 kinase, and JNK requires the phosphorylation of corresponding upstream proteins, which are MEK1 and MEK2, MEK3 and MEK6, and MEK4 and MEK7, respectively. Pro-inflammatory cytokines like IL-1, TNF-α, and IL-6 are secreted by UVB-irradiated keratinocytes, activating the p38/JNK pathway. In addition, UVB-irradiated epidermal cells upregulate the expression of COX-2 via the same pathway, producing pro-inflammatory mediators like prostaglandin 2 (PGE_2). Besides COX-2, NF-κB is highly involved in the UVB-induced inflammation. ROS generated from UVB radiations activates the phosphorylation of IκB kinase (IKK). Consequently, the inhibitor of NF-κB (IκB) is degraded by proteasomal degradation and ubiquitination. IκB confers inhibitory effects on proteins in the NF-κB family, making them inactive via binding to IκB. is highly associated with inflammation. The expression of several pro-inflammatory cytokines, including IL-1α, IL-1β, IL-6, IL-8, and TNF-α, is induced by the NF-κB activation [9,10].

2.2.3.2. UVB & UVA-induced ECM degradation

DOI: 10.54254/2753-8818/45/20240584

Skin dermal ECM is mainly comprised of collagen, elastin, and fibrillin. Collagen synthesis is altered by UVB radiations, and the amount of these ECM components is consequently reduced. Thus, dermal ECM degradation occurs. Transforming growth factor-beta (TGF-β) gene activation induces dermal collagen synthesis. TGF-β binds to TGF-β receptor II (TβR II) to activate TβR I kinase. Two TFs, Smad2 and Smad3, are subsequently phosphorylated and activated. Smad4 is then combined with them to form a complex. The complex binds to and activates the TGF-β gene at its promoter region to induce collagen synthesis after entering the nucleus. However, Smad7 inhibits the above signalling pathway to inhibit collagen synthesis after being activated by UVB radiation. Excessive ROS activate the MAPK pathway to upregulate the expressions of various kinds of metalloproteinases (MMPs) like collagenase (e.g. MMP1), gelatinase (e.g. MMP9), and stromelysins. C-Jun and c-fos, two downstream TFs of the MAPK pathway, form the AP-1 complex. AP-1 upregulates various MMPs via binding to its response element. Besides, stimulation of dermal fibroblasts increases the production of IL-6, which upregulates the expression of MMP1 and MMP9. MMPs target and degrade extensive contents of dermal ECM. Furthermore, UVA radiation possesses higher penetration properties, reaching deep into the dermis. Thus, although UVA radiation causes fewer effects on the skin than UVB radiation, the direct cellular and molecular alterations to all cutaneous layers lead to inflammation, apoptosis, dermis remodelling, and mutations. Furthermore, dermal fibroblasts are highly sensitive to UVA radiations. Therefore, synergistic enhancement of ROS generation by UVA and UVB radiation significantly impairs the integrity of skin ECM [2].

2.2.3.3. UVB-induced apoptosis and cellular senescence

ROS generated from UVB induces the apoptosis of various skin cells, including keratinocytes and dermal fibroblasts. Upon UVB radiation, mitochondrial DNA mutations accumulate and disrupt electron transfer of the mitochondrial electron transport chain, leading to declined ATP production. The reduced energy production results in the release of cytochrome C (cyt C) into the cytosol. Subsequent binding of Cyt C to the apoptotic protease activating factor-1 (apdf-1) forms the apoptosome complex. Recruiting of Caspase 9 is followed and, in turn, activates Caspase 3. Caspase 3 cleavages various cellular components like DNA, causing DNA fragmentation, chromatin condensation, and eventually apoptosis. Peroxidase, thioredoxin reductase, glutathione–S-transferases, and glucose-6-phosphate dehydrogenase comprise the antioxidant system within the mitochondria. Nuclear factor erythroid 2-related factor 2 (Nrf2) is the primary regulator of this system, and UVR targets Nrf2 to impair the mitochondrial antioxidant system [11].

On the other hand, the senescence of keratinocytes, dermal fibroblasts, and other skin cells is regulated by the p53/p21 pathway. UVB-induced DNA damage causes upregulation of the p53 gene and further activation of the p21 gene. Increased p21 proteins lead to the upregulation of the p16 gene and cause the cell cycle arrest for DNA repair to occur. Upon UVR, the state of the cells enters stable cell cycle arrest, which is called cellular senescence. If the repair fails, the p53 gene triggers cell apoptosis. Besides activating the p21 gene, increased p53 proteins activate B-cell lymphoma 2 (Bcl-2) family. The proapoptotic proteins of this family induce the mitochondria to release cyt C into the cytosol [12].

2.2.4. UVR-induced immunosuppression

Immunosuppression makes an individual more susceptible to photocarcinogenesis. UVR induce immunosuppression in skin cells by reducing epidermal Langerhans cells (LCs). UVR-induced isomerisation of trans- to cis-urocanic acid and loss of co-stimulatory molecule probably accounts for the damaged abilities of LCs to migrate and present antigens. Regulatory T cells are activated due to the deduced number and activity of LCs and pro-inflammatory cytokines. They result in T helper 2 (Th2) cell polarisation, increasing the number of Th2 cells. Consequently, epidermal LCs release IL-12, an immunosuppressive cytokine. In addition, cis-urocanic acid triggers keratinocytes to release another immunosuppressive cytokine called IL-10 [2].

DOI: 10.54254/2753-8818/45/20240584

3. Current treatment against uvr-induced skin photoaging

3.1. Mechanisms of current treatment against UVR-induced skin photoaging

Therapeutic approaches to treat skin photoaging mainly target scavenging excessive ROS and promoting collagen synthesis in the dermis. Thus, topical creams containing various natural or synthetic drugs and laser treatments are commonly used due to their accessibility to the damaged skin areas.

The first-line therapy is topical retinoids. Retinoids like tretinoin bind to the retinoic acid receptor (RAR) and activate the RAR pathway, suppressing AP-1 expression and subsequent MMP production. Therefore, type I and III collagen synthesis are promoted indirectly [1]. Other candidates from natural-derived products for topical administrations can be categorised into polyphenols and polysaccharides.

Most polyphenols are metabolites of plants. They possess anti-inflammatory, antioxidant, and immunomodulatory properties. Polyphenols can be classified into flavonoids and nonflavonoids based on differences in chemical structures. In general, polyphenols exert their anti-inflammatory and antioxidant effects by attenuating the NF-κB pathway, increasing Nrf2 activity, and inhibiting ROS production. Proanthocyanidins and β-carotene are both flavonoids. NF-κB and MAPK pathways are inhibited by proanthocyanidins to inhibit ROS generation. β-carotene can prevent singlet molecular oxygen production and subsequent O_2^- -formation. Besides these functions, polyphenols can modulate the release of pro-inflammatory cytokines. For instance, chafuroside B, a flavonoid, suppresses TNF-α, IL-10, and PGE_2 production to counteract UVB-induced immunosuppression. In addition, topical administration of green tea extract declines the expression of the p53 gene. Thus, cellular senescence and apoptosis of keratinocytes can be alleviated.

Polysaccharides, unlike polyphenols, exist in plants, animals, and bacteria. They also hold antioxidant, antitumor, and immunomodulatory properties. Among various polysaccharides, β-glucans show significant advantages in treating skin photoaging for their ROS scavenging ability and their promotion of skin rejuvenation. For instance, β-glucans isolated from barley can scavenge hydroxyl radicals across various molecular sizes. The scavenging activity is further enhanced as β-glucans can promote the synthesis of superoxide dismutase and catalase. These two enzymes are involved in antioxidant systems to scavenge ROS like O_2^-, hydroxyl, peroxide, and peroxynitrite. For skin rejuvenation, β-glucans can induce re-epithelialisation via binding to dectin-1 or β-glucan receptors expressed on skin keratinocytes. The binding triggers the keratinocyte proliferation and migration. ECM deposition, fibroblast maturation, and angiogenesis are also induced by β-glucans to counteract skin ECM degradation and promote skin ECM regeneration. Another polysaccharide, hyaluronic acid (HA), is widely used in treating skin photoaging. High molecular weight hyaluronic acid (HMWHA) can bind to membrane receptors CD44 expressed on cells. After binding, HMWHA activates the RhoA-like Rho GTPase signalling pathway after binding, promoting cell migration and proliferation. Besides the CD44 receptors, Intercellular Adhesion Molecule 1 (ICAM-1) and Receptors for HA-mediated mobility (RHAMM) expressed on cells are targets for HA to bind. HA is also a carrier for delivering antioxidants and growth factors locally to induce tissue regeneration [3].

Ablative and non-ablative lasers are the primary laser treatments against UVR-induced skin photoaging. Ablative laser resurfacing uses tiny light beams with uniform diameters to vaporise water and coagulate the epidermis and superficial dermis. The heat from water vaporisation and tissue coagulation exerts thermal energy on the skin. The thermal energy stimulates the proliferation and division of fibroblasts to induce collagen stimulation in the dermis. This thermal energy also attracts mesenchymal and pericapillary cells to promote re-epithelialisation in the epidermis. Together, ablative laser resurfacing triggers and enhances skin rejuvenation [13].

Non-ablative laser resurfacing shows similar mechanisms and efficacy. The two procedures differ because non-ablative lasers coagulate the dermis, whereas cooling systems protect the epidermis. The collagen fibres in the dermis are coagulated and stimulated to contract and rearrange by the thermal energy to trigger ECM and dermal collagen synthesis. Thus, skin rejuvenation is promoted [4].

DOI: 10.54254/2753-8818/45/20240584

3.2. Improvements and limitations of current treatment against UVR-induced skin photoaging

Topical administrations of natural-derived products show good biocompatibility, biodegradability, and low toxicity. However, they require an extended time to reach or cannot reach the dermis.

The original ablative laser resurfacing for laser treatments is a field CO_2 laser. It is a gas laser which emits light beams. It has a high efficacy in promoting skin rejuvenation, but it requires significant downtime and increases the risk of developing hyperpigmentation and scarring after postoperative inflammation. Another ablative laser is Erbium yttrium aluminium garnet (2940nm Er: YAG), and it has a similar efficacy to a full-field CO_2 laser. Moreover, Er:YAG has higher water absorption than full-field CO_2 laser. It means less tissue in the dermis is coagulated during ablation and damaged by excessive thermal energy so that Er:YAG has less downtime and the skin can rejuvenate faster after the operations. A newer version of ablative laser is a 2910nm erbium:glass fibre (Er:glass) fibre laser (UltraClear; Acclaro Medical). The 2910nm Er:glass laser possesses versatility in treating patients based on individual severity, location of photoaged skin, and skin types. The energy emitted at the 2910nm wavelength is at peak absorption by water and minimal absorption by melanin and haemoglobin. In this way, the 2910nm Er:glass laser enables maximal tissue ablation and minimal damage caused by excessive thermal energy. Thus, downtime and the risk of post-inflammatory hyperpigmentation are reduced. In addition, the 2910nm Er:glass laser can be used on all skin types by adjusting the depth of laser penetration into the skin accordingly. The 2910nm Er: glass laser also has superficial and deeper modes for mild to moderate and severe photoaging. The laser delivery is fractionated. This type of delivery advantages in potentially having no requirement for anaesthesia for the superficial mode and shows less severe adverse events for the deeper mode, only topical numbing [5].

Compared to ablative laser, non-ablative laser resurfacing is less effective and requires a series of treatment sessions. It also shows fewer side effects than ablative lasers because the wavelength causes less skin destruction. Side effects include scars and infections. Unlike ablative laser resurfacing, non-ablative lasers have a cooling system that contacts the skin and shields the epidermis from excessive thermal energy. The 675nm (RedTouch laser from Deka M.E.L.A, Calenzano, Italy) has been developed to produce higher efficacy and better side effects profiles—the 675nm wavelength targets directly for either type I or III collagen. Minimal binding to haemoglobin and high binding affinity for collagen fibres and melanin are shown for the 675nm wavelength. Therefore, thermal energy generated from collagen absorption of light energy transfers directly and preferentially to collagen fibres rather than other chromophores. Thus, less thermal damage is caused in surrounding areas, and new collagen is synthesised faster. Furthermore, the 675nm laser can treat hyperpigmentation as it also shows a high binding affinity for melanin. Regarding efficacy and safety, the 675nm laser therapy requires no anaesthesia, is side effect-free, has less downtime, and has faster patient recovery time with short sessions [4].

4. Potential application of nanomaterials to treat skin photoaging

4.1. Nanoparticles/nanofibers in treating skin photoaging

Nanomaterials have the potential to treat skin photoaging. Compared to topical administration of drugs, nanomaterials can be used to improve the topical delivery of various drugs due to their advantages in the controlled release of drugs, increased permeability, and reduced partitioning. Compared to laser treatment, nanomaterials have merits for their nontoxic, biodegradable, and highly biocompatible properties, as well as being less invasive and destructive.

Nanomaterials generally exert therapeutical effects against skin photoaging by scavenging ROS, inhibiting cell cycle arrest, and inhibiting ECM degradation. When UVR irradiates skin cells, the p53/p21 pathway is activated, followed by upregulation of the p16 gene to lead the cells to enter cellular senescence. During cellular senescence, the cell division arrests at the G1/S phase. In the meantime, persistent DNA damage induced by UVR causes the cell to undergo stable cell cycle arrest. Increased senescence-associated β-galactosidase (SA-β-gal) activity represents increased senescent cells. Increased DNA damage response protein (γH2AX) expression is detected when persistent DNA damage

DOI: 10.54254/2753-8818/45/20240584

occurs [14]. In addition, cellular senescence can be indicated by increased p16 gene expression. The choice of the p16 gene expression level as a biomarker for cellular senescence is due to the p53 and p21 gene expression levels changing transiently and may decrease over time [15].

Several nanomaterials have been developed and can potentially treat skin photoaging. For instance, Ultrasmall Prussian blue nanoparticles (USPNMPs) are nanozymes that confer photoaging resisting activity against UVA-induced skin photoaging. In contrast to endogenous enzymes, enzymes composed of nanomaterials have lower costs for manufacturing and possess increased catalytic stability. Prussian blue is an iron-based metal-organic framework that can be used as a coordination polymer. Constructed Prussian blue nanoparticles (PBNPs) mimic various endogenous enzymes to scavenge excessive ROS. However, PBNPs show low permeability and weak catalytic activity. Thus, USPNMPs are developed with a 3.4nm size to achieve increased permeability and higher efficacy in scavenging ROS. Human dermal fibroblasts pre-treated with USPNMPs reverse the increased SA-β-gal activity induced by UVA radiations and significantly decrease the γH2AX expression in UVA-irradiated human dermal fibroblasts. The p16, p21 and p53 protein levels are diminished after pre-treatment of UVA-irradiated human dermal fibroblasts with USPNMPs. The above data shows that cellular senescence in UVA-irradiated human dermal fibroblasts can be alleviated by USPNMPs. Besides resisting senescence, the ERK/AP-1 pathway is also inhibited by USPNMPs to prevent the synthesis of MMPs. Moreover, USPNMPs can inhibit the secretion of senescence-associated secretory phenotypes (SASPs) like TNF-α and MMPs by senescent cells. Thus, USPNMPs present anti-inflammatory and ROS scavenging, inhibiting ECM degradation [14].

4.2. Nanoparticles/nanofibers used in drug delivery systems

Nanomaterials are also widely applied in controlled drug release systems. Liposomes, nanoemulsions, and solid lipid nanoparticles (SLNs) are used for skin application [14]. The advantages of using nanomaterials to construct drug delivery systems include increased permeability through the epidermis and accessibility into the dermis, declined drug partitioning within tissues, controlled and constant topical release of delivered drugs, nontoxicity, high biodegradability and biocompatibility.

Nanofibers are novel nanomaterials with properties such as high surface area, strength rate, and low basis weight. Poly ε-caprolactone (PCL) can construct nanofibers that can be used for drug delivery systems. Encapsulated myrtle extract within PCL has been demonstrated to possess high efficacy in promoting the proliferation of fibroblasts with a controlled topical release of myrtle. Myrtle extract is rich in flavonoids and can upregulate heat shock protein 90kDa beta family (Hsp90b) gene expression via sirtuin 1 (SIRT1). Flavonoids are anti-inflammatory and antioxidant. Inhibition of heat shock proteins alters the equilibrium of hydrogen peroxide to cause oxidative stress. Thus, myrtle extracts exert ROS scavenging activity [16]. The whole nanodevice that achieved controlled topical delivery of myrtle release is NanoPCL-M. NanoPCL-M also shows the ability to counteract cellular senescence. NanoPCL-M upregulates the Hyaluronan Synthase 2 (HAS2) gene. The HAS2 gene encodes the enzymes highly involved in HA production, and the expression of the HAS2 gene is vital for cell cycle progression. HA promotes cell migration and proliferation. Taken together, NanoPCL-M resists cellular senescence and induces fibroblast migration and proliferation. Regarding inhibition of ECM degradation and further cellular senescence resistance, NanoPCL-M increases SIRT1 and SIRT2 gene expressions. SIRT1 inhibits the synthesis of MMPs, and proper cell proliferation and cell cycle progression are highly associated with SIRT2 [17].

Another drug delivery system uses modified SLNs to encapsulate metformin. Metformin shows attenuation of cellular senescence of human dermal fibroblasts. However, due to different doses and administration periods, the anti-senescence effect must be reconfirmed in separate experiments. Metformin is a hydrophilic drug. Thus, it is not easy to penetrate the epidermis. Therefore, metformin needs to possess higher permeability. SLNs are selected to be the carriers of metformin due to its solid nature and lipophilicity. In addition, SLNs are nontoxic and biodegradable. The solid nature made SLNs possess substantially low drug mobility so that partitioning of metformin in tissues is reduced, and controlled topical release of metformin is achieved. Approximately 80 percent of metformin is

DOI: 10.54254/2753-8818/45/20240584

constantly released for 18 days. The property of SLNs being lipophilic increases the permeation of metformin across the epidermis. It is clear to infer that loading hydrophilic drugs into lipophilic carriers leads to low entrapment efficiency (EE). Thus, modified SLNs delivering metformin comprise cholesterol-lysine conjugate (Chol-Lys), for the more amphiphilic products are formed when conjugating lipids with different compounds. The structure of cholesterol is more hydrophilic, and its hydrogen bonding capacity increases after binding to lysine. In this way, modified SLNs can encapsulate a sufficient amount of metformin and increase EE up to 60% compared to below 50% EE for non-modified SLNs. Metformin-loaded Chol-Lys nanoparticles or metformin-loaded SLNs show reduced p16 gene expression than metformin in its aqueous form. Thus, Metformin-loaded SLNs can resist cellular senescence, and drug-free SLNs can be used to deliver other hydrophilic drugs to achieve enhanced permeation into the epidermis and better efficacy [14].

5. Conclusion

This article summarises the molecular basis of skin photoaging. Among the UVRs, UVA and UVB radiations can impair the skin. They damage the skin via DNA alterations, ROS generation, cellular senescence and apoptosis, persistent inflammation, and dermal ECM degradation. DNA damage within dermal fibroblasts and keratinocytes activates the p53/p21 pathway and subsequent upregulation of p16 gene expression, causing cell cycle arrest. DNA repair is insufficient when UVR induce persistent DNA damage. Thus, cells enter cellular senescence and eventually undergo apoptosis. Senescent cells also secrete SASPs, including TNF-α and MMPs. MMPs can degrade dermal ECM. UVB radiations induce ROS synthesis by impairing endogenous antioxidant systems to break ROS equilibrium and cause oxidative stress. Excessive ROS activate signalling pathways like MAPK and NF-κB to cause persistent inflammation. ROS also activate MMPs to degrade dermal ECM and reduce the number of LCs to induce immunosuppression. The mechanisms, improvements, and limitations of current treatment against UVR-induced skin photoaging are also discussed. Topical administration of natural-derived and synthetic products shows high efficacy in scavenging ROS, anti-inflammation, and promoting collagen synthesis to induce skin rejuvenation. However, the drugs require substantial time to penetrate the skin and exert their effects. Improvements in ablative or non-ablative laser resurfacing significantly improve their side effects profiles, with only topical numbing for deeper mode of fractionated ablative lasers and side-effect free for non-ablative lasers. Laser treatments have higher efficacy in treating skin photoaging by promoting skin rejuvenation via stimulating dermal fibroblasts to synthesise type I and III collagen. In addition, less downtime and faster patient recovery time are achieved. To address the obstacles encountered in topical drug therapies and laser treatments, nanomaterials possessing the properties of nontoxicity, high biodegradability, and biocompatibility, controlled topical drug release, and less invasion and destruction to the skin have the potential to be applied in treating UVR-induced skin photoaging. Nanomaterials with certain modifications can also load drugs with difficulty penetrating the skin to construct controlled drug release systems. However, the optimal doses, efficacies, and safety profiles of these nanomaterials loaded with drugs require reconfirmation and improvements to be carried out in future studies.

References

[1] Hani R, Khayat L, Rahman AA, Alaaeddine N. Effect of stem cell secretome in skin rejuvenation: a narrative review. Mol Biol Rep. 2023 Sep;50(9):7745–58.

[2] Tanveer MA, Rashid H, Tasduq SA. Molecular basis of skin photoaging and therapeutic interventions by plant-derived natural product ingredients: A comprehensive review. Heliyon. 2023 Mar;9(3):e13580.

[3] Fernandes A, Rodrigues PM, Pintado M, Tavaria FK. A systematic review of natural products for skin applications: Targeting inflammation, wound healing, and photo-aging. Phytomedicine. 2023 Jul;115:154824.

DOI: 10.54254/2753-8818/45/20240584

[4] Piccolo D, Crisman G, Dianzani C, Zalaudek I, Fusco I, Conforti C. New 675 nm Laser Device: The Innovative and Effective Non-Ablative Resurfacing Technique. Medicina (Mex). 2023 Jul 4;59(7):1245.
[5] Selim MM, Lowery JA, Maredia HS, Zelickson BD. Clinical evaluation of a new fractional ablative 2910 nm erbium laser on photodamaged skin: A pilot study. Lasers Surg Med. 2023 Oct;55(8):715–23.
[6] Sklar LR, Almutawa F, Lim HW, Hamzavi I. Effects of ultraviolet radiation, visible light, and infrared radiation on erythema and pigmentation: a review. Photochem Photobiol Sci Off J Eur Photochem Assoc Eur Soc Photobiol. 2013 Jan;12(1):54–64.
[7] Svobodova A, Walterova D, Vostalova J. Ultraviolet light induced alteration to the skin. Biomed Pap Med Fac Univ Palacky Olomouc Czechoslov. 2006 Jul;150(1):25–38.
[8] Kriegenburg F, Poulsen EG, Koch A, Krüger E, Hartmann-Petersen R. Redox control of the ubiquitin-proteasome system: from molecular mechanisms to functional significance. Antioxid Redox Signal. 2011 Oct 15;15(8):2265–99.
[9] Bode AM, Dong Z. Mitogen-activated protein kinase activation in UV-induced signal transduction. Sci STKE Signal Transduct Knowl Environ. 2003 Jan 28;2003(167):RE2.
[10] thusamy V, Piva TJ. The UV response of the skin: a review of the MAPK, NFkappaB and TNFalpha signal transduction pathways. Arch Dermatol Res. 2010 Jan;302(1):5–17.
[11] ch-Machin MA, Bowman A. Oxidative stress and ageing. Br J Dermatol. 2016 Oct;175 Suppl 2:26–9.
[12] Ritter J. Rang & Dale's Pharmacology [Internet]. 10th ed. Oxford (GB): Elsevier Health Sciences Division; 2023. Chapter 6, Cell proliferation, apoptosis, repair and regeneration. [cited 2023 Sep 15]. Available from: https://clinicalkeymeded.elsevier.com/reader/books/9780323873987/epubcfi/6/46[%3Bvnd.vst.idref%3DCH0006_87-97_B9780323873956000068]!/4
[13] Du Y, Zeng J, Li M, Wang Y, Wu Y, Qi R, et al. Efficacy and safety of Resveratrol combined with Ablative Fractional CO_2 laser system in the treatment of skin photoaging. J Cosmet Dermatol. 2021 Dec;20(12):3880–8.
[14] Li Y, Zeng N, Qin Z, Chen Y, Lu Q, Cheng Y, et al. Ultrasmall Prussian blue nanoparticles attenuate UVA-induced cellular senescence in human dermal fibroblasts *via* inhibiting the ERK/AP-1 pathway. Nanoscale. 2021;13(38):16104–12.
[15] Nayeri Rad A, Shams G, Safdarian M, Khorsandi L, Grillari J, Sharif Makhmalzadeh B. Metformin loaded cholesterol-lysine conjugate nanoparticles: A novel approach for protecting HDFs against UVB-induced senescence. Int J Pharm. 2020 Aug;586:119603.
[16] Cruciani S, Santaniello S, Fadda A, Sale L, Sarais G, Sanna D, et al. Extracts from Myrtle Liqueur Processing Waste Modulate Stem Cells Pluripotency under Stressing Conditions. BioMed Res Int. 2019 Jun 11;2019:1–12.
[17] Bellu E, Cruciani S, Garroni G, Balzano F, Satta R, Montesu MA, et al. Natural Compounds and PCL Nanofibers: A Novel Tool to Counteract Stem Cell Senescence. Cells. 2021 Jun 7;10(6):1415.