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REVIEW

Targeting microRNA for improved skin health

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Abstract

Background: In human skin, miRNAs have important regulatory roles and are involved in the development, morphogenesis, and maintenance by influencing cell proliferation, differentiation, immune regulation, and wound healing. MiRNAs have been investigated for many years in various skin disorders such as atopic dermatitis, psoriasis, as well as malignant tumors. Only during recent times, cosmeceutical use of molecules/natural active ingredients to regulate miRNA expression for significant advances in skin health/care product development was recognized.

Aim: To review miRNAs with the potential to maintain and boost skin health and avoid premature aging by improving barrier function, preventing photoaging, hyperpigmentation, and chronological aging/senescence.

Methods: Most of the cited articles were found through literature search on PubMed. The main search criteria was a keyword "skin" in combination with the following words: miRNA, photoaging, UV, barrier, aging, exposome, acne, wound healing, pigmentation, pollution, and senescence. Most of the articles reviewed for relevancy were published during the past 10 years.

Results: All results are summarized in Figure 1, and they are based on cited references.

Conclusions: Thus, regulating miRNAs expression is a promising approach for novel therapy not only for targeting skin diseases but also for cosmeceutical interventions aiming to boost skin health.

KEYWORDS
cosmetics, microRNA, Skin health

1 | INTRODUCTION

MicroRNAs (miRNAs, miRs) are a group of short (~22 nucleotides) single-stranded RNAs, which are highly conserved gene regulators.[1] Although not coding for any protein by themselves, miRNAs can regulate the expression of other protein-coding gene at post-transcriptional level. To this end, miRNAs guide the RNA-induced silencing complex (RISC) to bind to the 3′ untranslated region (3′UTR) of the target messenger RNAs (mRNAs) in a sequence-specific manner, which leads to translation inhibition, and/or degradation of their target mRNAs.[1-3] It has been shown that miRNAs play an important role in almost all the biological and physiological processes, whereas abnormal miRNAs expression and function have been discovered in many diseases. Nowadays, modulation of the disease-related miRNAs

has been shown to be beneficial in several clinical trials, thus making miRNAs a promising candidate for novel therapy.[4]

In human skin, miRNAs are involved in the development, morphogenesis, and maintenance by influencing cell proliferation, differentiation,[5,6] immune regulation,[7] and wound healing.[8,9] The roles of miRNAs have been investigated for more than a decade in various skin disorders such as atopic dermatitis, psoriasis, as well as tumors.[10-15] Unlike the traditional ways of turning on or shut off specific targets, miRNAs exert their biological functions by fine-tuning protein-coding genes as mild regulators.[3] Thus, miRNAs may be ideal candidates in targeting to improve skin health and prevent premature aging.

1.1 | MiRNAs in skin barrier functions

The skin, especially the epidermal epithelium, is a mechanical, chemical, biological, and immunological barrier protecting the body from the external environment and dehydration.[16] Cornified envelope, tight junctions (TJ), lipids, and microbiome are essential components of the barrier. Ghatak et al demonstrated that miRNAs are fundamental for skin barrier function by using Dicer-ablated mice. Dicer, an enzyme that cleaves double-stranded RNA (dsRNA) and pre-microRNA (pre-miRNA) into small interfering RNA and microRNA, plays a vital role in re-establishing the barrier function of the skin post-wounding via a miRNA-dependent mechanism.[17]

In atopic dermatitis (AD), miR-143 has been shown to target IL-13Rα1, thus blocking the IL-13-induced dysregulation of filaggrin, loricrin, and involucrin, which are important proteins for the epidermal barrier.[18] Inhibition or overexpression of miR-155-5p alters the expression of protein kinase inhibitor α (PKIα) TJ proteins such as occludin and claudins, thymic stromal lymphopoietin TSLP and consequently regulates allergic inflammation.[19] Moreover, overexpression of miR-214 resulted in decreased epidermal thickness due to reduced keratinocyte proliferation and accelerated terminal differentiation in the epidermis by targeting β-catenin. In chronic wounds, Roy et al characterized biofilm-induced miR-146a and miR-106b.[20,21] These miRs silenced Zonula occludens-1 (ZO-1) and Zonula occludens-2 (ZO-2) and compromised tight junction function, resulting in leaky skin as measured by TEWL (trans-epidermal water loss). Intervention strategies aimed at inhibiting biofilm inducible miRNAs may be effective in restoring the barrier function of host skin.[21]

Numerous miRNAs are associated with keratinocyte differentiation by extracellular calcium levels.[22] Among them, epidermally expressed MiR-203 regulates calcium-induced keratinocyte differentiation by activation of the protein kinase C (PKC) and activator protein 1 (AP-1) pathway.[23] Interestingly, oleic acid, a naturally occurring fatty acid, also a constituent of sebum, has been shown to upregulate miR-203 expression to induce keratinocyte differentiation along with involucrin expression by targeting p63.[24] More relevant studies are still needed to map the relationship between regulatory/structural components of epidermal barrier and miRNAs, in order to better understand the cosmeceutical potential of miRNA targeted technologies.

1.2 | MiRNAs in photoaging

Ultraviolet radiations like UVA and UVB are the primary cause for human skin aging. Srivastava et al revealed many changes in miRNA expression in the skin exposed to UV.[25] Among them, miR-34a, miR145, and miR-383 were the common ones regulated by both chronological aging and photoaging, implying their crucial role in the skin aging processes.

Syed et al[26] showed that miRNA expression was altered by UVB in both keratinocyte and fibroblasts, which could be categorized as a short-term or a long-lasting regulation after UV exposure. Comparing the samples from young and elderly human facial skin,[27] miR-124 was identified as the most upregulated miRNA in the senescent skin. In cultured human keratinocytes, miR-124 expression was increased by UVB irradiation in a dose-dependent manner, and overexpression of miR-124 enhanced the number of SA-β-gal positive keratinocytes, revealing a link from UVB to miR-124 and senescence.[27]

Using human primary keratinocytes, Kraemer et al revealed the different changes in miRNA expression by either UVA or UVB irradiation.[28] Among them, miR-23a was remarkably upregulated by UVA treatment, and RRAS2 (related RAS viral oncogene homolog 2) was identified as its direct target. Also, in the human keratinocyte cell line (HaCaT), miR-23a was shown to be upregulated by UVB irradiation. MiR-23b regulated DNA damage repair and apoptosis and protected HaCaT cells from UVB damage via regulation of topoisomerase-1 \caspase7\STK4.[29]

Degueurce et al[30] identified miR-21-3p as a UV- and PPARβ/δ-activated pro-inflammatory miRNA in keratinocytes, and in human ex vivo skin, inhibition of miR-21-3p reduced UV-induced inflammation. In human diploid fibroblasts, a genome-wide screening for UVB-regulated microRNAs was performed to identify miRNA-mRNA interaction network mediating UVB-induced senescence, where a parallel activation of the p53/p21(WAF1) and p16(INK4a)/pRb pathways was observed.[31] Interestingly, among these miRNAs, miR-101 was further studied, and Ezh2 was identified as its target to modulate UVB-induced senescence. Using UVA-irradiated human dermal fibroblasts, miR-155 was found to directly control c-Jun expression at the post-transcriptional level and might function as a protective miRNA in human dermal fibroblasts (HDFs) with a potential for the treatment of photoaging.[32] In another study, UVA-induced photoaging in fibroblasts resulted in specific patterns of miRNA response, and miR-146a was able to antagonize UVA-induced photoaging partially through targeting Smad4.[33] Using miRNA microarrays, it was determined that *Entella asiatica* (a culinary vegetable and medicinal herb) and troxerutin (a natural flavonoid rutin mainly found in extracts of *Sophora japonica*) exerted protective effects against UVB-induced damage by regulating the expression profile of variable miRNAs.[34]

Thus, targeting above discussed/referred miRNAs could be an attractive approach to "master regulate" UV-induced aging processes in the skin.

1.3 | MiRNAs in skin pigmentation

Localized melanin/age spots/hyperpigmentation is a critical aging sign in Chinese women.[35] Skin pigmentation is a vital process of defense against UV light that involves highly interactive cellular players: melanocytes, keratinocytes, and fibroblasts.[36,37] The cause of hyperpigmentation is the excessive accumulation of melanin pigments in the epidermal basal layer.[38] Melanin pigments are synthesized in the melanosomes, which are specific organelles produced by melanocytes residing at the basal layer of the epidermis, and melanosomes containing melanin pigments are transported to the neighboring keratinocytes.[38]

An interesting study documented that exosomes secreted by keratinocytes from donors with different phototypes could control melanocyte pigmentation, which was modulated by UVB.[39] More than 30 miRNAs were reported to be differentially expressed between exosomes from Caucasian and dark skin keratinocytes, including miR-200a, miR-132, and miR-203. Furthermore, miR-3196 was the only one miRNA upregulated by UVB irradiation in Caucasian keratinocyte exosomes. However, exosomes from UVB-irradiated Caucasian keratinocytes with miR-3196 inhibition lost the ability to upregulate melanin production in melanocytes.[39] Later research also suggested that keratinocyte secreted exosomes containing miR-330-5p inhibited expression of tyrosinase (TYR), an enzyme controlling melanin production, in melanocytes.[40]

Both UV and airborne pollutants are known to induce oxidative stress on the skin.[41] Shi et al verified that oxidative stress could enhance miR-25 expression in both melanocytes and keratinocytes.[42] By targeting MITF (microphthalmia-associated transcription factor, a master regulator of melanocyte development, survival, and function), miR-25 contributed to melanocyte dysfunction, inhibited TYR activity, and decreased melanin content.[36] Besides, miR-25 inhibited the production and secretion of SCF (stem cell factor) and bFGF (basic fibroblast growth factor) from keratinocytes, thus impairing their paracrine protective effect on the survival of melanocytes under oxidative stress conditions.[36] In addition, multiple microRNAs have been reported to directly target MITF mRNA, such as miR-137,[43] miR-218,[44] and miR-508.[45]

MiRNAs also regulate skin pigmentation through other mechanisms. MiR-21a-5p positively regulated melanogenesis by targeting SOX5, a potential transcriptional inhibitor of MITF.[46] On the contrary, miR-27-3p[47] inhibited melanogenesis by targeting Wnt3a, while miR-125b reduced melanin content by inhibiting the expression of pigmentation-related genes such as TYR, TYRP1, DCT, and SH3BP4.[48] Overexpression of miR-145 resulted in hypopigmentation, as this miRNA targeted the genes implicated in the first step of melanogenesis (SOX9, MITF, TYR, and TYRP1), as well as the genes involved in melanosome transport (MYO5A and RAB27A).[49] Moreover, miR-203 could reduce melanosome transport and promote melanogenesis by targeting KIF5B and also negatively regulating the CREB1/MITF/Rab27a pathway.[50] Interestingly, miR-211 regulated melanocyte stem cell maintenance and pigmentation by targeting TGF-β receptor 2,[51] while the overexpression of miR-340 led to an increased dendrite formation and melanosome transport. Interestingly, downregulation of miR-340 inhibited these processes.[52]

A good example for epigenetic regulation to hyperpigmentation is achieved by giving an active ingredient of *Lansium Domesticum* leaf extract, which has 100% natural component, acting on miR-490-3p, resulting in lighten pigmented spots on the skin by reducing tyrosinase and melanin levels.[53] These studies reveal an important role of miRNAs in regulating pigmentation processes in the skin and appear as potential targets to prevent undesired hyperpigmentation of aging skin in certain ethnicities.

1.4 | MiRNAs in chronological skin aging and senescence

The characteristics of intrinsic or chronological aging include visible signs such as thin and dry skin, fine wrinkles, decreased elasticity, aberrant pigmentation, epidermal and dermal thinning.[54-57] Besides, the number of senescent cells increases during chronological aging of human skin.[58-62] Many miRNAs have been identified as critical regulators in chronological aging in various animal models and cell types.[63] Röck et al[64] have profiled miRNA expression in fibroblasts isolated from young and old human donors and identified miR-23a-3p as a miRNA that was highly expressed in both aged and senescent fibroblasts. Furthermore, in the skin of old mice, miR-23a was found to be increased, which led to down-regulation of hyaluronic acid by directly targeting hyaluronan synthase 2 (HAS2). One interesting study in HDFs demonstrated that inhibition of miR-23a stimulated autophagy and rescued UV-induced premature senescence in fibroblasts.[65] In another study,[66] the miRNA expression between the young and elderly human dermis was compared, where miR-34 and miR-29 families were found to be highly expressed in the aged than the young dermis. A computationally constructed miRNA-target gene network revealed that miR-34 family, miR-29 family, and miR-424 may play a dominant role in the regulatory network involving cell adhesion, collagen synthesis, focal adhesion, insulin, and ErbB signaling pathway. Similarly, altered levels of miR-34 in aged human dermis have correlated with the phenotype of senescent HDFs in vitro, with reduced expression of COL1A1 and elastin, but with an induced MMP-1 expression, which might be regulated through interaction with p16.[66] Recently, Srivastava et al performed a microarray analysis of the skin from three age groups of individuals—18-25 years, 40-50 years, and over 70 years—and reported that miR-34a was increased with age.[25]

To explore epidermal aging, Muther et al performed miRNA expression profiling in human keratinocytes from young and elderly subjects, and both strands of miR-30a were found to be overexpressed in aged keratinocytes, human epidermis, and reconstructed skin model mimicking chronological aging.[67] Overexpression of miR-30a impaired epidermal differentiation and induced apoptosis in keratinocytes, by targeting several key regulators of skin homeostasis, such as LOX (lysyl oxidase), IDH1 (isocitrate dehydrogenase), and AVEN (apoptosis and caspase activation inhibitor). Tinaburri et al discovered a higher level of miR-200a in elderly human keratinocytes

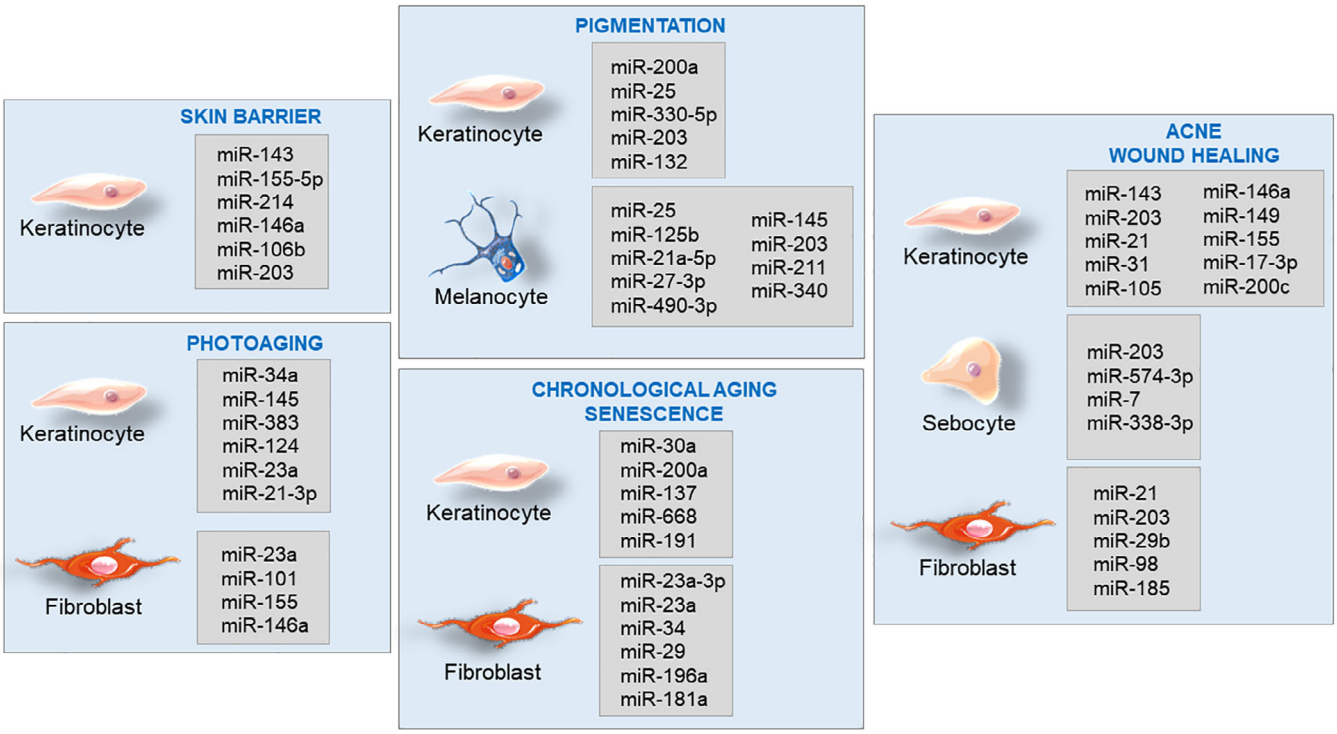

FIGURE 1 Collection of skin miRs, expressed in different cell types, associated with skin barrier, photoaging, pigmentation, chronological aging, senescence, acne, and wound healing

and its role in keratinocyte aging: miR-200a reduced oxidative DNA repair activity, while inducing several senescence features through upregulation of p16 and IL-1β.[68] Shin et al identified senescence-inducing miRNA profile in normal human keratinocytes. Overexpression of miR-137 or miR-668 induced senescence in proliferating human keratinocytes with a notable increase in senescence-associated β-galactosidase activity, p16INK4A, and p53.[69] Another study reported that miR-191 triggered keratinocyte senescence by targeting SATB1 and CDK6.[70] One example for modulation in the miRNA expression for cosmetic purpose was demonstrated using *Plantago lanceolata* extract, which reduced the levels of miR-29 and miR-196a, known for exerting negative control on the synthesis of collagens and elastin. Moreover, by decreasing the expression of miR-30e and miR-181a, *P lanceolata* extract helped prolong cell survival and reduced the appearance of senescent phenotypes in fibroblasts.[71]

Thus, miRNAs are important regulators of some key processes in the skin during chronological aging/senescence and, therefore, could be considered as a target tool to prevent or delay premature skin aging.

1.5 | MiRNAs in acne and acne wound healing

Acne is a chronic inflammatory disease of the pilosebaceous unit. Although the mechanisms of acne vulgaris development are complicated, some key features have been well characterized, including hyperseborrhea (increased sebum production), altered sebum fatty acid composition, follicular hyperkeratinization, epithelial hyperproliferation, systemic and local hormonal imbalance, inflammation, and bacterial colonization by *Cutibacterium acnes*. Other triggers of acne can be UV radiation, airborne pollution, smoking, dietary factors, and stress.[72] Interestingly, Xia et al showed that *Staphylococcus epidermidis* inhibited *C. acnes*-induced inflammation in the skin via the induction of miR-143 in both human keratinocytes and a mouse model, and miR-143 in turn directly targeted TLR2 to inhibit *C. acnes*-induced pro-inflammatory cytokines.[73] Another pathway to target TLR-2 is via miR-105. This approach has already been proposed in cosmetogenomics. Briefly, *Syringa vulgaris* (Lilac) extract had the potential to reduce the expression of TLR2 via miR-105 upregulation. Reduced number of bacterial binding sites resulted in the induction of less pro-inflammatory cascade.[74]

When acne breaks out, the wound healing process initiates to recover the skin integrity, which includes inflammatory response, cell proliferation, and migration, and also extracellular matrix (ECM) remodeling. MiR-203, a skin-specific miRNA, promotes keratinocyte differentiation but restricts cell proliferation and migration.[23,75,76] On the other hand, miR-21 has both anti-inflammatory and pro-migratory roles in keratinocytes via regulating PTEN and also in fibroblasts, as reviewed below.[77-79] MiR-31 is one of the major miRNAs promoting re-epithelialization, as it can enhance keratinocyte proliferation, migration,[80,81] and differentiation,[82] by regulating epithelial membrane protein 1 (EMP-1), hypoxia-inducible factor 1 (FIH-1), Notch signaling, and Ras/MAPK pathway. Schneider et al detected reduced sebaceous lipogenesis in DICER-impaired human SZ95 sebocyte, implying global miRNA activity is essential for lipid synthesis. The

expression of several miRNAs was found to be altered during sebaceous lipogenesis, including upregulation of miR-203, miR-574-3p, and downregulation of miR-7. Functionally, overexpression of miR-574-3p led to a significant increase in lipid synthesis.[83] Interestingly, Liu et al found that miR-338-3p has inhibited TNF-α-induced lipogenesis in human sebocytes by targeting PREX2a to suppress PI3K/AKT signaling events.[84] Modulation of several miRNAs, such as miR-146a overexpression,[85-88] miR-149 overexpression,[89] and miR-155 inhibition,[90,91] was able to restrict the inflammatory response of keratinocytes and improve wound healing. MiR-17-3p promotes keratinocyte proliferation and migration.[92] On the contrary, miR-200c inhibits keratinocyte migration and delays re-epithelialization of human ex vivo wounds.[93]

Acne scars can be divided into three main types: atrophic, hypertrophic, or keloidal (based on a net loss or gain in collagen), where atrophic acne scars are the most common type.[94] The multi-player miR-21 also functions in fibroblasts to promote cell proliferation, migration, and fibrogenesis from normal skin or hypertrophic scars.[95-98] Interestingly, both downregulation[78,99] and upregulation[100] of miR-21 impair wound healing in vivo by impairing re-epithelialization and granulation of tissue formation. MiR-203 is also a multi-player by decreasing cell proliferation, invasion, and ECM production of keloid fibroblasts by repressing EGR1 and FGF2.[101] Local inhibition of miR-203 accelerated wound closure and reduced scar formation in vivo associated with an increased re-epithelialization, skin attachment regeneration, and collagen reassignment.[102]

Local delivery of miR-29b in vivo has improved wound remodeling with reduced contraction, increased collagen III/I ratios, and thus reducing excessive scar formation via suppression of TGF-β1-Smad-CTGF signaling.[103,104] MiR-98 could directly target the COL1A1 gene, reduce viability, and increase apoptosis of fibroblasts.[105] In hypertrophic scar fibroblasts, miR-185 suppressed cell growth and directly targeted TGF-β1 and Col-1 genes.[106] Thus, miRNA-based potential approaches in anti-acne and acne scar skin care are an attractive idea and require more research to identify the best miRNA candidates or miRNA targets for therapy.

2 | CONCLUSION

Here we summarized miRNAs (Figure 1) that could be useful for combating premature skin aging with a focus on improving skin barrier function, preventing photoaging, hyperpigmentation, and chronological aging/senescence. Thus, miRNAs are promising targets in cosmeceutical research for exclusive skincare product development aiming to improve skin health.

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CONFLICT OF INTEREST

All authors have read and approved the final version of the manuscript. The authors report no conflicts of interest in this work. The only data associated with this article are presented in Figure 1. No additional data are associated with this article.

AUTHOR CONTRIBUTIONS

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TRANSPARENCY STATEMENT

The corresponding author confirms that the manuscript is an honest, accurate, and transparent account of the study being reported.

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