**Review Article**

**Role Of Micro RNAs in Skin Aging and its Potential Therapeutic Interventions**

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**Abstract**

The skin is the largest and most important organ of the body. Skin aging has profound effects on the quality of life of an individual mostly associated with the morphological and anatomical changes which include wrinkle formation and sagging. Age associated changes in the skin are caused by many extrinsic and intrinsic factors. Intrinsic aging is driven by biological and genetic factors, while extrinsic aging is influenced by environmental factors. Recent findings show the contribution of (microRNAs) miRNAs in skin aging, particularly replicative senescence. MicroRNAs post-transcriptionally regulate the expression of genes that control a variety of functions like collagen modulation, elastin synthesis, and others. This review explores the role of miRNAs in skin aging and details their specific role in pathways such as collagen synthesis. This paper also describes the types and characteristics of skin aging, structural alteration in different layers of skin. Moreover, the intricate relationship between environment and genetic factors that causes skin aging, emphasizing the role that miRNAs play in this complex process are emphasized. In addition, potential therapeutic interventions of miRNA in skin aging and anti-aging and skin care technology.

**Keywords**

Skin aging, miRNA, collagen, cellular senescence, therapeutic interventions, skin structure.

**Abbreviations**

miRNA- Micro RNA

ROS- Reactive oxygen species

MMP -Matrix metalloproteinases

PTPs or RPTP - Protein tyrosine phosphatases

MAPK- Mitogen-activated protein kinases

 ERK - Extracellular signal-regulated kinases

RTK - Receptor tyrosine kinases

AKT- Protein kinase B

TGF-β- Tumor growth factor beta

**Introduction**

Being the largest and most diverse organ in the body, the skin serves a variety of functions, such as regulating body temperature, shielding the body from external agents and infections, and resisting moisture. The entire skin layer serves as a barrier to shield the body from the elements [1]. It consists of 3 different layers: the hypodermis, dermis, and epidermis. Primarily, the epidermis is composed of keratinocytes. Furthermore, it is composed of melanocytes and Merkel cells. The second layer, the dermis, helps with blood and nutrient circulation. It is composed of blood vessels, connective tissues, nerves, etc. The hypodermis, the bottom layer of skin, stores energy and connects the skin to bones and muscles. It is made up of connective tissues and adipose tissues [1,2] . Aging is an inevitable phenomenon that leads to a gradual loss of tissue integrity. **Figure 1** depicts the structure of normal and aged skin.

 

**FIGURE 1** shows the structure of aged skin in comparison to normal young skin. A) Normal skin contains elastin, collagen, fibroblast, and fat cells in different layers of skin in connected manner. B) Aged skin with destructed elastin, collagen, fibroblast, and fat cells in skin layers. During aging synthesis of collagen and elastin decreases and their network will break that leads to the wrinkling and sagging of skin.

The most apparent manifestation of this skin aging, marked by various changes, including the development of wrinkles, sagging, and pigmented spots [3] . Similar to other organs, a steady loss of functionality and regenerative capacity is a hallmark of skin aging. The skin is the most noticeable organ in the body, and all alterations, including aging, can be easily observed. Aging is a broader concept encompassing overall alterations in the appearance of skin and dermal tissues, along with their functions.

 It is interesting to note that cellular senescence is a concept that describes the condition in which individual cells experience permanent growth arrest. Hayflick and Moorhead were the first to define aging on a cellular level by demonstrating the limited dividing capacity of human primary fibroblasts. The replication process causes telomeres to become unable to retain their length, which results in what is called the Hayflick limit. As a result, cells lose their capacity to multiply and go into an irreversible cell cycle arrest, which is known as cellular senescence [2,4] . Cellular senescence is one of the several factors that results in skin aging.

 Skin aging is a more complex phenomenon that includes both morphological and functional changes in the skin over time. Moreover, the aging phenomenon affects the skin in various ways, including thinning of the epidermis and a remarkable decrease in turnover rate. The integrity of the skin and its physiological features are also affected. Although men and women age differently, their appearance also varies in terms of skin, but internal and external factors are the same [5,6]. This natural progression involves an intricate interaction among intrinsic or extrinsic factors, based on which it is classified into intrinsic aging and extrinsic aging [4,6]. Genetic and biological components are considered intrinsic or internal variables, whereas environmental exposure and lifestyle choices are extrinsic or external factors. The effects of intrinsic aging on the skin are like those on other internal organs. It’s also known as chronological aging because time is another factor causing it. In addition, the two main signs of natural aging are the flattening of cells in the epidermal-dermal junction and the thinning of the dermis, which is a layer of skin. Moreover, elastin and collagen in the skin break down over time, reducing the integrity and stability of the skin[7]. In contrast, extrinsic aging, also known as photoaging, is induced by sun exposure and manifests itself in exposed parts of the skin, such as back of the arms and the face [8]. It is marked by visible signs such as dark spots, wrinkles, and a rough, leathery skin texture. Additionally, reduced elasticity, abnormal coloring, graying hair, and hair loss are other results of photoaging [9].

Though skin aging is a normal aspect of life, the outward indicators of aging can have a big impact on how someone feels about themselves. Therefore, it is essential to know the cosmetic elements. Skin aging has functional consequences in addition to these cosmetic ones. With age, the change in skin structure may compromise its protective functions. To detect abnormal growth and maintain homeostasis, the skin depends on molecular signals owing to its diverse functions and cell types [10]. These pathways contribute to morphological and functional changes in the skin. However, a common hallmark of aging is the up and downregulation of protein expression associated with the electron transport chain. While this is a cause, or a consequence of the aging is still a matter of debate [11]. To comprehend the genetic aspects of aging, several studies have been conducted on the protein and gene expression of diverse aging model systems. An emerging focus in these investigations is on small non-coding RNAs, especially microRNAs, which act as potent post-transcriptional regulators [12]. Over the last decade, research on miRNAs has revealed their role in all cellular processes. These small regulatory molecules play integral roles in fundamental cellular activities like cell proliferation, differentiation, aging, etc. [13]. It also plays a crucial role as biomarkers in different diseases.

MicroRNAs(miRNAs) are non-coding RNA that are found in all organisms and plants. It contains approximately 25 nucleotides in length. These molecules are involved in post-transcriptional regulation of expression of genes by binding to their target [14]. Recently, it has been discovered that miRNAs are significant regulators of aging and senescence. These short RNAs play an important role in modulating the expression of mRNA targets, leading to translational repression or degradation of mRNA. Thereby promoting the degradation of proteins or preventing translation [7]. There are several miRNAs that are generally involved in many skin activities including collagen modulation, differentiation of keratinocytes etc. However, they are essential in the aging of the skin because they alter the expression of genes related to cellular functions and the synthesis of collagen. Altered expression of miRNAs prevents proliferation of cells, affects elastin production, imbalance the skin cell turnover, increased oxidative stress etc. [2,10]. Moreover, miRNAs have become common regulators for a range of skin disorders and can function as new biomarkers or therapeutic targets for etiology or treatment. In short, miRNAs have a variety of functions in skin biology and their intricate role make them more potential candidates for further studies and research in the field of dermatology and skin therapy [2]. In this present review, our objective is to focus on the contribution of miRNAs in skin aging. The primary objective of this review is to deliver extensive knowledge in the field of skin aging and the role of miRNAs in the aging process. These understandings of miRNA involvement in aging provides basics for developing innovative therapies and pioneering new era in anti-aging interventions and skin care technology.

**Skin Aging- types and characteristics**

Aging of the skin, also known as cutaneous aging, is a complex and natural process. The appearance and functionality of skin will gradually change because of numerous biological and physiological processes leading to aging [15]. Skin wrinkling, dry skin, skin thinning, and sagging are the primary characteristics [3]. In addition, it causes age spots, hyperpigmentation, decreased elasticity, and other issues. The skin that serves as the body's barrier is constantly exposed to a variety of external and internal stimuli, which causes a progressive loss of regeneration potential [4]. Along with structural and functional alterations in extracellular matrix components like collagen, elastin, and others, aging processes also bring about phenotypic changes in cutaneous cells [16]. Skin aging occurs in two forms: intrinsic and extrinsic. Natural aging, another term of intrinsic aging, is mainly caused by genetic factors while extrinsic aging is influenced by environmental factors such as sunlight [6,9,13]. Apart from that, apoptosis, DNA damage, and telomere shortening are some of the aspects that cause skin aging.

 Intrinsic aging, or natural aging, is the term for a natural physiological process that causes wrinkles on dry skin [9,17]. Histologically, a flat epidermal-dermal interface and the absence of dermal papillae are characteristics of skin that is intrinsically aged. Normal epidermal differentiation and cellular polarity, however, seem to be preserved [13,18]. Collagen synthesis declined along with the decreased ability of wound healing. Moreover, atrophy of the dermis may arise due to reduced repair capability, which will not be able to restore collagen fibers degraded by this process [8]. The number of blood vessels also decreased which causes a decreased blood supply to the cells. Apart from genetic factors, other elements that drive intrinsic aging are hormones and time [19]. It’s an interesting fact that the telomere, the terminal region of the eukaryotic chromosome, significantly influences intrinsic aging. Telomeres contain a short sequence of nucleotides, TTAGGG. Repeated cycles of replication ultimately lead to the loss of protection at the end of the chromosome (particularly that sequence), making it susceptible to end-to-end fusions. This condition is incompatible with regular cell functioning. Most cells can divide up to 60 or 70 times over their lifetimes before entering senescence, which is a state in which they are still viable but unable to divide [8,19]. Oxidative stress also contributes to skin aging, eventually causing the accumulation of oxidative damage to proteins, lipids, and other constituents of cells. It’s connected to a gradual reduction in antioxidant capability and an increase in the formation of reactive oxygen species (ROS). Inflammation, which causes ROS production as well as activation of pro-inflammatory cytokines [8,20]. Another element contributing to skin aging over time is a modification in the levels of growth factors and apoptosis. Moreover, hormones like melatonin have been observed to decrease as well. At the same time, signaling molecules also play a vital role in aging. Particularly, certain signaling molecules became more abundant with age, whereas others, such as chemokines, declined and caused the destruction of various skin functions [21]. Histological alteration observed in the skin includes changed stratum corneum permeability, decreased water loss that is attributed to a hardened and thickened stratum corneum, and changed lipid composition causes greater cellular cohesiveness. In addition, the number of fibroblasts and mast cells in the dermis also decreased [22].

Extrinsic aging is mainly affected by skin exposure to environmental factors such as sunlight and pollution. Lifestyle also contributes to photoaging. These substances will degrade the collagen and elastin fibers of the skin [16]. Paul Gerson Unna observed in their study that there was a transformation in the skin of sailors, particularly in regions that were exposed to the sun, leading to premature aging. Studies noted that UV radiation is the key element in extensive aging, by which 80% of facial aging occurs [23]. The process of UV-induced skin aging is complex and can be initiated by multiple signaling pathways, such as DNA destruction by telomere, protein oxidation, mitochondrial damage, and other signaling initiated by receptors [24]. In addition, during the late 19th century, Harry Daniell found that smokers appear older than non-smokers. So, alcohol and smoke also contribute to extrinsic aging [25,26]. The histological signature of photoaging is characterized by dermal elastosis, marked by the presence of thickened, intertwined, and finally granular elastic structures [18]. In contrast to intrinsic aging, photo-aged skin forms thick layers with irregular pigmentation, large wrinkles, and elastosis [27,28]. Compared to chronologically aged skin, photoaged skin has a thicker epidermal layer. Furthermore, UV exposure can increase keratinocytes and melanocytes [22,29]. The prevalence of pathologically altered elastic fibers, sometimes known as "solar elastosis," is the most prominent histological characteristic of photoaging. The activation of matrix metalloproteinases (MMPs) is the main cause of the destruction of elastin and collagen structures. Furthermore, lymphocytes, mast cells, eosinophils, and other inflammatory cells are elevated in extrinsic aging [22]. However, all skin layers will be affected by aging and show changes in terms of their roles and morphology [30].

 **Skin Structure**

Skin is the largest part of the body that gives protection from outside environments. It covers around 8% of the human body and occupies 1.8 m2 of surface area [11,31]. Moreover, it’s a complex and dynamic organ with various functions. In addition, skin maintains the homeostasis of the body by preventing the loss of electrolytes, proteins, and fluids, along with temperature regulation [1,32] The epidermis, dermis, and hypodermis are three distinct layers that make up the skin and are functionally connected layers [33] . The structure of the skin is illustrated in **Figure 2**.



**FIGURE 2** illustrates the structure of skin. A- EPIDERMIS is the outer layer of akin that comprises Stratum corneum, Stratum lucidum, Stratum granulosum, Stratum spinosum, Stratum basale. B- DERMIS is the second layer beneath the epidermis. It consists of Papillary dermis and Reticular dermis. This layer is characterized by hair follicles, sweat glands, and sebaceous glands. C-HYPODERMIS, which is the deepest layer comprises nerve and fat cells.

The ectoderm-derived outermost layer of the skin is termed the epidermis. It protects the body from the outside environment and includes UV protection, thermoregulation, and immunoprotection. Keratinocytes, melanocytes, inflammatory cells, Langerhans cells and neuroendocrine cells are major types of cells in the epidermis. Among these, keratinocytes cover a major portion of the epidermis, and they're interlinked by tight junctions [11].
They generate keratin, contributing water-resistant qualities to the skin. Melanocytes synthesis the melanin pigment that gives color along with UV protection [33,34]. This epidermis is arranged in several layers, including the stratum spinosum, stratum basalis, stratum granulosum, and stratum corneum (figure 2A). The outer layer of the epidermis is referred to as the stratum corneum, which is made up of flattened keratinocytes that provide protection from external factors. The stratum basalis is the innermost layer of the epidermis, where new cells are formed. As they move towards the surface, the cells become flattened eventually [4]. In a recent study, keratin fibers got stiffened in naturally aged skin, and water movement also decreased in the stratum corneum [22,35]. The number of melanocytes and Langerhans cells decreased which will lead to thinning of the epidermis [22].

Under the epidermis lies the dermis. The dermal layer is mainly involved in nutrient supply to the cells of the skin. It’s a connective tissue layer composed of collagen fibers and elastin fibers, which are interconnected. This layer is abundant with lymph, nerves, hair follicles, and sweat glands [2,11]. In addition, it’s also populated with lymphocytes, macrophages, dendritic cells, etc. Apart from nutrient supply, it also provides oxygen and detects touch and pain [1]. Dermis cells are mostly presented by fibroblasts and are predominantly involved in extracellular matrix (ECM) components. The ECM is composed of collagen and glycosaminoglycan that are embedded with mast cells, neural cells, and endothelial cells [36]. Dermis are classified into two layers: the reticular and papillary dermis (figure 2B), which work together to perform all functions. The papillary dermis connects the epidermis and blood vessels, while the reticular dermis provides strength to the skin [37]. The density and thickness of dermal collagen decreases in chronologically aged skin. Although photoaging leads to a decrease in the number, size of blood vessels, and can induce angiogenesis [22,38].

The hypodermis, termed as subcutaneous layer, is situated just below the dermis and is consist of loose-areolar connective tissues with abundant adipose tissue and less collagen content. It’s the deepest layer of skin (figure 2C). This layer enables cutaneous mobility. Metabolic energy is stored in the adipose tissues of the hypodermis, and it also provides thermal insulation [39]. This layer contributes to body insulation and offers a protective cushion for internal organs. In addition, vitamin D is also produced in this layer [1]. The hypodermis of aged skin exhibits reduced capability in both maintaining protective barriers and recovering from damage [4,40]. Aging also leads to decreased cell proliferation in the basal layer, causing the hypodermis to thin and reducing the contact between the dermis and the epidermis. Consequently, this reduces nutrient supply to the epidermis and weakens the renewal capacity of cells [4].

Approximately 30,000 dermal cells perish every minute, emphasizing the continual renewal processes inherent in the skin. Successful skin development and regular physiological functions hinge on the coordinated interplay of genetic networks and regulatory factors [41]. The skin maintains a constant self-regeneration mechanism to replenish injured or old cells in spite of constant exposure to environmental pollutions and facilitate tissue repair. However, if its regenerative ability decreases with age, it can trigger cellular senescence, paving the way for the onset of various dermatological conditions [42].

**Pathways involved in aging.**

Aging consists of several interconnected processes that are driven by genetic programming, continuous external inputs, and internal metabolic reactions. All organs and systems are impacted by aging, though at varying rates [11,43]. As aging causes the morphological and physiological functions of the skin to deteriorate gradually, like all other organs. As a result of the progressive diminishing of the cellular constituents, mechanical protection is weakened. Thereby, the immune response is slowed, which will lead to an imbalance in thermoregulation [44]. The elevated level of MMPs and matrix-degrading enzymes, which are primarily released by epidermal keratinocytes and dermal fibroblasts, causes a decrease in extracellular matrix (ECM) formation in the dermis, which results in the morphological manifestation [45]. These MMPs are implicated in the degradation of collagen fibers, which is a characteristic feature of intrinsic aging, and the partial degradation of elastin fibers, a process associated with extrinsic aging. Imbalances in oxidative stress and inflammatory processes further intensify the activity of MMPs, which will also contribute to skin aging [30].

Even though both types of aging differ, it appears that identical molecular pathways underlie both forms of skin aging. In fact, the breakdown of the extracellular matrix by upregulated MMPs and the production of ROS are shared characteristics of skin aging in both types. The term ROS is used for free oxygen radicals and other oxygen-derived molecules that are highly reactive. As aging occurs, ROS accumulates, which leads to the of protein tyrosine phosphatases (PTPs or RPTP) inactivation and thereby activates receptor tyrosine kinases (RTKs). Activated RTKs undergo phosphorylation, triggering downstream signaling pathways. This phosphorylation cascade activates three families of mitogen-activated protein kinases (MAPK), such as extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK), and p38MAPK. Subsequently, the transcription factor AP-1 (activator protein-1) gets activated downstream of these MAPK pathways. This activation leads to the expression of various matrix metalloproteinases (MMP), including MMP-1, MMP-3, and MMP-9, while simultaneously inhibiting the expression of procollagen-1. Basically, ROS-induced signaling prompts a cascade of molecular reactions that activate pathways involved in the breakdown of the ECM and inhibit procollagen-1 expression. Inhibition of procollagen-1 expression disrupts the regular synthesis of collagen, which causes the loss of structural and functional integrity of dermal tissues. Ultimately, it causes problems related to elasticity and thereby aging [22,46,47]. Molecular mechanisms of ROS involved in skin aging comparing to normal mechanism are illustrated in **Figure 3A and Figure 3B**. The function and morphology of the skin were also declined by senescent cell accumulation. Even though the basic mechanisms are still being worked out, there is mounting evidence supporting the existence of disease-causing pathways that lead to cutaneous aging. Extrinsic and intrinsic aging can occur simultaneously or concurrently. While genetic and epigenetic mechanisms control all these processes. Regulation of non-coding RNAs like miRNA, long ncRNA, etc., modification of histones, and methylation of DNA are some of the mechanisms involved [11]. Meanwhile, miRNAs continue to be one of the most mysterious aspects of the study of aging biology, despite all the available data. The expression of certain miRNAs can function as a biological indicator for aging, including photoaging and natural aging as well as age-related disorders [3,31]

**A**



**FIGURE 3A** depicts formation of collagen and elastin in normal skin. 1)Under normal conditions when the ligands are absent, Receptor protein tyrosine phosphatase (RPTP) is activated. 2) it will inhibit the receptor tyrosine kinase (RTK) activity on cell membrane by binding to it. 3) This dephosphorylated RTK will lower the signalling pathway 4) it leads to the transcription and 5) production of collagen and elastin.

 **B**

 

**FIGURE 3B depicts the pathway under the influence of intrinsic and extrinsic factors.**

1-Intrinsic and extrinsic factors result in the production of reactive oxygen species (ROS), which will accumulate in the cell. 2- ROS inhibits RPTP by binding to the catalytic site. 3- RTK is phosphorylated and activated. 4- Activation of mitogen-activated protein kinases (MAPK) triggers other downstream signaling pathways, including extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK), protein kinase B (AKT), and p38. 5- Nuclear factor κB and transcription factor activator protein-1 (AP-1) are subsequently activated. 6- This will regulate gene expression. Altered gene expression inhibits collagen synthesis in two ways. 7a- Increase the expression of MMPs (MMP-1, 3, 9). Collagen production decreased. 7b- Inhibit the TGF-β and SMAD signaling pathways. Decrease the synthesis of procollagen 1 which will reduce collagen and elastin.

**Role of microRNAs in skin aging and Therapeutic interventions.**

Short, single-stranded, non-coding RNAs are called microRNAs. It contains about 25 nucleotides in length. These miRNAs will regulate the gene expression [14]. Several miRNAs have been found in both plants and mammals. It was discovered first in Caenorhabditis elegans, which is found in most of the eukaryotes, including humans. It’s interesting to note that most studies show that many protein-coding genes are regulated by these miRNAs at a translational and transcriptional level. MiRNA is estimated to be about 1–5% of the human genome and to control at least 30% of genes that code for proteins [48–52]. However, the finding by Boehm and Slack reveals the role of miRNAs that regulate the age of C. elegans and establishes the significance of miRNA in the skin aging process [53]. Furthermore, most of the miRNAs are synthesized from DNA sequences to become primary miRNAs, or pri-miRNAs, which are then processed to become precursor miRNAs, or pre-miRNAs, and ultimately mature miRNAs. MiRNAs often decrease expression by interacting with the 3′ UTR of target mRNAs [38]. However, there have also been reports of miRNA interaction with other parts, including the 5′ UTR, gene promoters, and UTR at 5’ region. Meanwhile, research has shown that miRNAs regulate the rate of translation and transcription by shuttling between various cellular compartments [54,55]. Many biological processes rely on these regulators. Moreover, it is necessary for the normal growth of animals. Recent findings also revealed that miRNAs play a key role in regulating cutaneous aging and senescence. Many of the miRNAs have been up- or down-regulated with aging at the tissue or organism level [11,56]. In the context of the aging pathway that was outlined before, miRNA has the capacity to regulate various molecules. It provides additional control over the signaling cascade linked with ROS-induced aging. It’s an interesting fact that the first investigation done on miRNAs associated with aging in human epidermal keratinocytes revealed a set of regulated miRNAs [11].

MiRNAs have the ability to regulate the levels of ROS either directly or indirectly. Moreover, it can regulate RPTPs, TGF-β and other proteins associated with redox homeostasis, as well as proteins like RTKs, AKT, MAPKs, etc., thereby regulating the downstream signaling cascade. Redox homeostasis refers to the balance between the production and elimination of ROS inside the cell. By targeting the mRNAs of these constituents, they can regulate ERK, JNK, etc. If miRNAs downregulate the expression of PTPs and other proteins, it will result in the accumulation of ROS, which leads to the breakdown of the ECM and the inhibition of procollagen 1. This will ultimately lead to the reduced production of collagen and the loss of structural and functional integrity of dermal tissues, which is a hallmark of aging [57]. **Figure 4** depicts the involvement of miRNAs in the regulation of gene expression in skin biology at the post-transcriptional level (in various pathways).



Figure 4 illustrates the role of different miRNAs in various signaling pathways that lead to downregulation of collagen synthesis. In figure, PI3K, AKT, PTEN, and TGF-β is inhibited by different miRNAs as shown, that in turn inhibit the collagen synthesis.

It’s an interesting fact that miR-668 and miR-137 were upregulated during organismal aging, which can also promote the aging of keratinocytes in humans [31,58]. The study conducted by Rivetti et al. finds that the upregulated miR-181 expression, miR-130, and miR-138 target sirtuin 1 (Sirt 1) and p63 mRNAs [59]. It’s suggested that sirt1 activity is important for the replicative senescence of keratinocytes. On the other hand, p63 is actively involved in aging [60,61]. Additionally, miR-191 inhibits the G1-S phase transition, which results in cell cycle arrest. This quiescent stage contributes to the aging process. MiR-152 can drastically reduce dermal fibroblast adhesion by suppressing integrin alpha 5, a signaling protein involved in cell-surface-mediated processes [13,31]. Moreover, activation of p53, MAPK, and several other pathways is caused by decreased levels of miR-106 and miR-17 in aged dermal fibroblasts [62]. Putting it all together, specific miRNAs have the ability to hinder the normal aging of cells by promoting cell proliferation. The expression of miRNA is modified when skin comes into contact with UV light for prolonged time, the levels of miR-27a, miR-145, miR-383, and miR-1246 are elevated, while those of miR-155, miR-663b, miR-3648, and miR-6879 are reduced [63]. Meanwhile, UVA radiation downregulates miR-155, which causes c-Jun to be upregulated. This influences the activity of the collagen gene in human fibroblasts [64]. Premature aging is the main result of photoaging. Human dermal fibroblasts are more sensitive to solar radiation than epidermal keratinocytes. Some miRNAs and their role in dermal aging are depicted in **Table 1**. Meanwhile, the therapeutic potential of miRNAs in skin aging is an evolving and active research area nowadays.

|  |  |  |  |
| --- | --- | --- | --- |
| **miRNA** | **Cell type affected** | **Upregulated/Down regulated** | **Reference** |
| miR-124 | UV radiation induces this in keratinocytes.  | Upregulated | [65] |
| miR-23 a | Keratinocytes and fibroblasts | Upregulated | [66] |
| miR-779 | Langerhans cells | Upregulated | [11] |
| miR-365 | fibroblasts | Upregulated | [11] |
| miR-124 | keratinocytes | Upregulated | [66] |
| miR-142 | melanocytes | Altered | [66] |
| miR-9 | Langerhans | Upregulated | [11] |
| miR-25 | Melanocytes | Upregulated | [11] |
| miR-151a-5p | Langerhans cells | Up regulated  | [67] |
| miR-20a | Langerhans cells | Upregulated | [11] |
| miR-106a | Fibroblast | Down regulated | [11,68] |
| miR-148a | Primary human fibroblast | Up regulated | [68,69] |
| miR-574-3p | Senescent fibroblast | Upregulated | [11] |
| miR-93 | Epidermis | Upregulated | [11] |
| miR-146a | Fibroblast | Down regulated | [13,68] |
| miR-191 | keratinocytes | Upregulated | [13,70] |
| miR-29a | fibroblasts | Upregulated | [13,71] |
| miR-181a | Keratinocytes/fibroblasts | Upregulated | [64] |
| miR-155 | fibroblast | Downregulated | [59,72] |

**TABLE 1** represents mi-RNAs that affect different skin cells which leads to skin aging. The table also says whether the expression level is up/down regulated in each cell.

Therapeutic interventions in anti-aging target preventing or slowing down aging or effects related to aging. Beyond aesthetic concerns, skin aging is linked to several factors of physical health and overall quality of life. Therefore, anti-aging therapy is essential and contributes to a high quality of life. Many miRNAs have become universal regulators for a range of skin conditions and can function as potential therapeutic targets and new biomarkers for the etiology and pathogenesis of disease [2]. MiR-29, miR-124, and miR-152 are involved in the generation and regulation of collagen synthesis. Numerous studies have shown that increased levels of miR-29 inhibitors raise the amounts of elastin mRNA and protein in vitro or in vivo. Several studies have shown that miR-29 will increase the concentration of MMPs and thereby decrease collagen synthesis. Hence, increasing the expression of collagen, fibrillin, and elastin in skin fibroblasts results from suppressing miR-29 with a miR-29 antagonist. Such research may lead to the development of very potent cosmetic treatments to stop the aging process of the skin [73,74]. Hence, modulating their function could influence the ability of the skin to maintain its integrity and strength. So, these can be considered novel biomarkers and therapeutic targets. miRNAs have greater significance in anti-aging mechanisms since they are essential for the molecular regulation of several aging-related processes [75,76]. A study by Wing-fu Lai et al. describes the evidence of age-associated changes in miRNA expression, which highlights the potential of miRNA as a target and a tool for antiaging therapy [77]. Further research on miRNA finds miR-101 helps to modulate senescence induced by UV-B radiation and another research shows miR-146a inhibits the UV induced aging by targeting smad-4 [66]. Antiaging treatment is an ongoing research area and miRNA has great relevance in it. Silencing gene expression by using miRNAs is one method for reducing the aging of skin. **Figure 5** depicts miRNA-based method for skin aging therapy [77]. The modification of miRNA expression emerges as a valuable focus in the cosmetic area, offering potential for the development of skincare products [66]. Current research is shedding light on the molecular mechanisms behind several aspects of aging, including the connection between some aging processes and individual gene activity. Thus, by inhibiting those undesirable gene activities, miRNAs may be utilized to create new cosmetic designs and products, especially for skin care purposes like anti-aging. The expression of tyrosinase, an enzyme essential for melanin synthesis, can be reduced using miRNAs. This technique is a new and practical method for skin whitening [73,78]. Research on miRNA and anti-aging is still in progress, and in order to create focused and efficient therapies, deeper knowledge about the regulatory network is necessary.

 

FIGURE 5 shows miRNA-based therapy. Identified the miRNAs that altered the expression level leading to aging. Suitable therapeutic miRNA is also selected. Then by using proper delivery set up, miRNA transferred to the aged cell by targeting the mRNA.

**Conclusion**

Skin aging is a complicated, integral phenomenon. It comprises 2 types: natural and photoaging (extrinsic). Intrinsic aging is primarily caused by genetic factors, while extrinsic aging is caused by environmental factors. Intrinsically aged skin shows smooth, thin, saggy, pale morphology, while extrinsic aging mainly affects exposed areas, such as the neck, face, etc. Deep wrinkling, changes in pigmentation, roughness, etc. are the main features of photoaging. The commonly known skin-aging mechanism is the degradation of collagen by MMPs due to the accumulation of ROS. Dermal aging is characterized by interconnected processes at the cellular, molecular, and organ levels. Despite ongoing research, the identification of distinctive biomarkers for aging remains a topic of exploration. In this paper, we concentrate on the role of miRNA in skin aging. We have explained the current knowledge on miRNA’s roles in molecular pathways and an insight into the therapeutic functions also. MiRNAs play an important role in cellular and molecular functions of the skin because of their ability to control expression of genes after transcription. Their complex regulatory roles that play in skin aging and dermatology make them attractive biomolecules for further study and potential therapeutic interventions. But nowadays, the main problem or challenge in this therapeutic intervention is in knowing the molecular mechanisms of aging. Further research on the miRNAs linked to skin aging includes detection of new targets and their roles. Moreover, this will provide information regarding regulation of aging mechanisms at cellular and molecular levels. Investigating miRNAs as biomarkers for dermal aging and exploring their role in diagnosis and prognosis are the main future scope of this study. By focusing on these perspectives for future research, researchers can expand their knowledge in this area. This, in turn, can open pathways for effective therapeutic interventions for maintaining skin health and reducing impacts of aging.

**DECLARATIONS**

**Authors contributions**

Ashikha Shirin Usman PP collected articles and wrote manuscripts. Durairaj Sekar initiated the study, revised, and finalized the manuscript.

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**REFERENCES**

[1] S. Horsburgh, N. Fullard, M. Roger, A. Degnan, S. Todryk, S. Przyborski et al., MicroRNAs in the skin: role in development, homoeostasis and regeneration, Clin Sci 131 (2017), pp. 1923–1940.

[2] G. Singhvi, P. Manchanda, V. Krishna Rapalli, S. Kumar Dubey, G. Gupta and K. Dua, MicroRNAs as biological regulators in skin disorders, Biomedicine & Pharmacotherapy 108 (2018), pp. 996–1004.

[3] M. Rahmouni, V. Laville, J.-L. Spadoni, R. Jdid, L. Eckhart, F. Gruber et al., Identification of New Biological Pathways Involved in Skin Aging From the Analysis of French Women Genome-Wide Data, Front Genet 13 (2022), .

[4] E. Csekes and L. Račková, Skin Aging, Cellular Senescence and Natural Polyphenols, Int J Mol Sci 22 (2021), pp. 12641.

[5] M.A. Farage, K.W. Miller, P. Elsner and H.I. Maibach, Characteristics of the Aging Skin., Adv Wound Care (New Rochelle) 2 (2013), pp. 5–10.

[6] N. Puizina-Ivić, Skin aging., Acta Dermatovenerol Alp Pannonica Adriat 17 (2008), pp. 47–54.

[7] T. Smith-Vikos and F.J. Slack, MicroRNAs and their roles in aging, J Cell Sci 125 (2012), pp. 7–17.

[8] J. Uitto and E.F. Bernstein, Molecular mechanisms of cutaneous aging: connective tissue alterations in the dermis., J Investig Dermatol Symp Proc 3 (1998), pp. 41–4.

[9] A.S. Wang and O. Dreesen, Biomarkers of Cellular Senescence and Skin Aging, Front Genet 9 (2018), .

[10] P.A. Sotiropoulou and C. Blanpain, Development and Homeostasis of the Skin Epidermis, Cold Spring Harb Perspect Biol 4 (2012), pp. a008383–a008383.

[11] M. Gerasymchuk, V. Cherkasova, O. Kovalchuk and I. Kovalchuk, The Role of microRNAs in Organismal and Skin Aging, Int J Mol Sci 21 (2020), pp. 5281.

[12] M. Hackl, S. Brunner, K. Fortschegger, C. Schreiner, L. Micutkova, C. Mück et al., miR‐17, miR‐19b, miR‐20a, and miR‐106a are down‐regulated in human aging, Aging Cell 9 (2010), pp. 291–296.

[13] M. Mancini, A.M. Lena, G. Saintigny, C. Mahé, N. Di Daniele, G. Melino et al., MicroRNAs in human skin ageing, Ageing Res Rev 17 (2014), pp. 9–15.

[14] C.S. Shreya Reddy, A.S. Usman P.P, D.M. Ganapathy, A. K.P. and D. Sekar, MicroRNA-21 as a biomarker in terminal stage oral squamous cell carcinoma (OSCC) in the South Indian population, Oral Oncology Reports 9 (2024), pp. 100139.

[15] F. Boismal, K. Serror, G. Dobos, E. Zuelgaray, A. Bensussan and L. Michel, Vieillissement cutané, médecine/sciences 36 (2020), pp. 1163–1172.

[16] S. Zhang and E. Duan, Fighting against Skin Aging, Cell Transplant 27 (2018), pp. 729–738.

[17] Y. Pathak, The Skin Aging Process and Anti-Aging Strategies, Biomed J Sci Tech Res 42 (2022), .

[18] M. El‐Domyati, S. Attia, F. Saleh, D. Brown, D.E. Birk, F. Gasparro et al., Intrinsic aging vs. photoaging: a comparative histopathological, immunohistochemical, and ultrastructural study of skin, Exp Dermatol 11 (2002), pp. 398–405.

[19] K. Hensley and R.A. Floyd, Reactive oxygen species and protein oxidation in aging: a look back, a look ahead., Arch Biochem Biophys 397 (2002), pp. 377–83.

[20] G.R. Guimarães, P.P. Almeida, L. de Oliveira Santos, L.P. Rodrigues, J.L. de Carvalho and M. Boroni, Hallmarks of Aging in Macrophages: Consequences to Skin Inflammaging, Cells 10 (2021), pp. 1323.

[21] M.E. Swift, A.L. Burns, K.L. Gray and L.A. DiPietro, Age-Related Alterations in the Inflammatory Response to Dermal Injury, Journal of Investigative Dermatology 117 (2001), pp. 1027–1035.

[22] H. Lee, Y. Hong and M. Kim, Structural and Functional Changes and Possible Molecular Mechanisms in Aged Skin, Int J Mol Sci 22 (2021), pp. 12489.

[23] A. Vierkötter and J. Krutmann, Environmental influences on skin aging and ethnic-specific manifestations, Dermatoendocrinol 4 (2012), pp. 227–231.

[24] M. Yaar and B.A. Gilchrest, Photoageing: mechanism, prevention and therapy, British Journal of Dermatology 157 (2007), pp. 874–887.

[25] V.G. Clatici, D. Racoceanu, C. Dalle, C. Voicu, L. Tomas-Aragones, S.E. Marron et al., Perceived Age and Life Style. The Specific Contributions of Seven Factors Involved in Health and Beauty., Maedica (Bucur) 12 (2017), pp. 191–201.

[26] Smooth Tobacco and Wrinkled Skin, New England Journal of Medicine 280 (1969), pp. 53–53.

[27] M. Berneburg, H. Plettenberg, K. Medve-König, A. Pfahlberg, H. Gers-Barlag, O. Gefeller et al., Induction of the Photoaging-Associated Mitochondrial Common Deletion In Vivo in Normal Human Skin, Journal of Investigative Dermatology 122 (2004), pp. 1277–1283.

[28] M. Toutfaire, E. Bauwens and F. Debacq-Chainiaux, The impact of cellular senescence in skin ageing: A notion of mosaic and therapeutic strategies., Biochem Pharmacol 142 (2017), pp. 1–12.

[29] A. Han, A.L. Chien and S. Kang, Photoaging, Dermatol Clin 32 (2014), pp. 291–299.

[30] U. Blume-Peytavi, J. Kottner, W. Sterry, M.W. Hodin, T.W. Griffiths, R.E.B. Watson et al., Age-Associated Skin Conditions and Diseases: Current Perspectives and Future Options, Gerontologist 56 (2016), pp. S230–S242.

[31] R. Krishnan, R. Rajeswari, J. Venugopal, S. Sundarrajan, R. Sridhar, M. Shayanti et al., Polysaccharide nanofibrous scaffolds as a model for in vitro skin tissue regeneration, J Mater Sci Mater Med 23 (2012), pp. 1511–1519.

[32] A. V. Nguyen and A.M. Soulika, The Dynamics of the Skin’s Immune System, Int J Mol Sci 20 (2019), pp. 1811.

[33] J.M. Abdo, N.A. Sopko and S.M. Milner, The applied anatomy of human skin: A model for regeneration, Wound Medicine 28 (2020), pp. 100179.

[34] James WD, Elston D and Berger T, Andrew’s diseases of the skin E-book, clinical dermatology (2011), .

[35] K. Biniek, J. Kaczvinsky, P. Matts and R.H. Dauskardt, Understanding age-induced alterations to the biomechanical barrier function of human stratum corneum, J Dermatol Sci 80 (2015), pp. 94–101.

[36] K. Pfisterer, L.E. Shaw, D. Symmank and W. Weninger, The Extracellular Matrix in Skin Inflammation and Infection., Front Cell Dev Biol 9 (2021), pp. 682414.

[37] Thomas M. Brown; and Karthik Krishnamurthy., Histology,Dermis, StatPearls Publishing, 2022.

[38] J.H. Chung and H.C. Eun, Angiogenesis in skin aging and photoaging., J Dermatol 34 (2007), pp. 593–600.

[39] Abraham L Kierszenbaum and Laura Tres, Histology and Cell Biology: An Introduction to Pathology, 5th ed.elsevier, 2019.

[40] E.-H. Choi, M.-Q. Man, P. Xu, S. Xin, Z. Liu, D.A. Crumrine et al., Stratum Corneum Acidification Is Impaired in Moderately Aged Human and Murine Skin, Journal of Investigative Dermatology 127 (2007), pp. 2847–2856.

[41] J. Fore, A review of skin and the effects of aging on skin structure and function., Ostomy Wound Manage 52 (2006), pp. 24–35; quiz 36–7.

[42] H.-C. Huang, T.-M. Chang, Y.-J. Chang and H.-Y. Wen, UVB irradiation regulates ERK1/2- and p53-dependent thrombomodulin expression in human keratinocytes., PLoS One 8 (2013), pp. e67632.

[43] A.E. Berman, O. V Leontieva, V. Natarajan, J.A. McCubrey, Z.N. Demidenko and M.A. Nikiforov, Recent progress in genetics of aging, senescence and longevity: focusing on cancer-related genes., Oncotarget 3 (2012), pp. 1522–32.

[44] E. Makrantonaki and C.C. Zouboulis, William J. Cunliffe Scientific Awards. Characteristics and pathomechanisms of endogenously aged skin., Dermatology 214 (2007), pp. 352–60.

[45] S.M. Kang, S. Han, J.-H. Oh, Y.M. Lee, C.-H. Park, C.-Y. Shin et al., A synthetic peptide blocking TRPV1 activation inhibits UV-induced skin responses., J Dermatol Sci 88 (2017), pp. 126–133.

[46] L. Rittié and G.J. Fisher, Natural and sun-induced aging of human skin., Cold Spring Harb Perspect Med 5 (2015), pp. a015370.

[47] L.F.Z. Batista, B. Kaina, R. Meneghini and C.F.M. Menck, How DNA lesions are turned into powerful killing structures: insights from UV-induced apoptosis., Mutat Res 681 (2009), pp. 197–208.

[48] H.E. Kinser and Z. Pincus, MicroRNAs as modulators of longevity and the aging process, Hum Genet 139 (2020), pp. 291–308.

[49] M.P. Perron, Protein interactions and complexes in human microRNA biogenesis and function, Frontiers in Bioscience 13 (2008), pp. 2537.

[50] N. Rajewsky, microRNA target predictions in animals., Nat Genet 38 Suppl (2006), pp. S8-13.

[51] W. Liu, S.-Y. Mao and W.-Y. Zhu, Impact of tiny miRNAs on cancers., World J Gastroenterol 13 (2007), pp. 497–502.

[52] L.-A. Macfarlane and P.R. Murphy, MicroRNA: Biogenesis, Function and Role in Cancer., Curr Genomics 11 (2010), pp. 537–61.

[53] M. Boehm and F. Slack, A developmental timing microRNA and its target regulate life span in C. elegans., Science 310 (2005), pp. 1954–7.

[54] M. Ha and V.N. Kim, Regulation of microRNA biogenesis, Nat Rev Mol Cell Biol 15 (2014), pp. 509–524.

[55] J. O’Brien, H. Hayder, Y. Zayed and C. Peng, Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation., Front Endocrinol (Lausanne) 9 (2018), pp. 402.

[56] A. de Lencastre, Z. Pincus, K. Zhou, M. Kato, S.S. Lee and F.J. Slack, MicroRNAs both promote and antagonize longevity in C. elegans., Curr Biol 20 (2010), pp. 2159–68.

[57] J. He and B.-H. Jiang, Interplay between Reactive oxygen Species and MicroRNAs in Cancer., Curr Pharmacol Rep 2 (2016), pp. 82–90.

[58] K.-H. Shin, A. Pucar, R.H. Kim, S.D. Bae, W. Chen, M.K. Kang et al., Identification of senescence-inducing microRNAs in normal human keratinocytes., Int J Oncol 39 (2011), pp. 1205–11.

[59] P. Rivetti di Val Cervo, A.M. Lena, M. Nicoloso, S. Rossi, M. Mancini, H. Zhou et al., p63–microRNA feedback in keratinocyte senescence, Proceedings of the National Academy of Sciences 109 (2012), pp. 1133–1138.

[60] M. Wlaschek, I. Tantcheva-Poór, L. Naderi, W. Ma, L.A. Schneider, Z. Razi-Wolf et al., Solar UV irradiation and dermal photoaging., J Photochem Photobiol B 63 (2001), pp. 41–51.

[61] Z. Chen, T.-P. Shentu, L. Wen, D.A. Johnson and J.Y.-J. Shyy, Regulation of SIRT1 by oxidative stress-responsive miRNAs and a systematic approach to identify its role in the endothelium., Antioxid Redox Signal 19 (2013), pp. 1522–38.

[62] Y. Dong, H. Chen, J. Gao, Y. Liu, J. Li and J. Wang, Bioactive Ingredients in Chinese Herbal Medicines That Target Non-coding RNAs: Promising New Choices for Disease Treatment., Front Pharmacol 10 (2019), pp. 515.

[63] Y. Zhang, C. Yang, S. Yang and Z. Guo, MiRNA-27a decreases ultraviolet B irradiation-induced cell damage., J Cell Biochem 121 (2020), pp. 1032–1038.

[64] J. Song, P. Liu, Z. Yang, L. Li, H. Su, N. Lu et al., MiR-155 Negatively Regulates c-Jun Expression at the Post-transcriptional Level in Human Dermal Fibroblasts in vitro : Implications in UVA Irradiation-induced Photoaging, Cellular Physiology and Biochemistry 29 (2012), pp. 331–340.

[65] M. Harada, M. Jinnin, Z. Wang, A. Hirano, Y. Tomizawa, T. Kira et al., The expression of miR-124 increases in aged skin to cause cell senescence and it decreases in squamous cell carcinoma, Biosci Trends 10 (2016), pp. 454–459.

[66] X. Li, S. Ponandai-Srinivasan, K.S. Nandakumar, S. Fabre, N. Xu Landén, A. Mavon et al., Targeting microRNA for improved skin health., Health Sci Rep 4 (2021), pp. e374.

[67] N.N. Hooten, M. Fitzpatrick, W.H. Wood, S. De, N. Ejiogu, Y. Zhang et al., Age-related changes in microRNA levels in serum, Aging 5 (2013), pp. 725–740.

[68] C. Stratz, T.G. Nührenberg, H. Binder, C.M. Valina, D. Trenk, W. Hochholzer et al., Micro-array profiling exhibits remarkable intra-individual stability of human platelet micro-RNA., Thromb Haemost 107 (2012), pp. 634–41.

[69] A. ElSharawy, A. Keller, F. Flachsbart, A. Wendschlag, G. Jacobs, N. Kefer et al., Genome-wide miRNA signatures of human longevity., Aging Cell 11 (2012), pp. 607–16.

[70] A.M. Lena, M. Mancini, P. Rivetti di Val Cervo, G. Saintigny, C. Mahé, G. Melino et al., MicroRNA-191 triggers keratinocytes senescence by SATB1 and CDK6 downregulation., Biochem Biophys Res Commun 423 (2012), pp. 509–14.

[71] I. Martinez, D. Cazalla, L.L. Almstead, J.A. Steitz and D. DiMaio, miR-29 and miR-30 regulate B-Myb expression during cellular senescence., Proc Natl Acad Sci U S A 108 (2011), pp. 522–7.

[72] M. Mancini, A.M. Lena, G. Saintigny, C. Mahé, N. Di Daniele, G. Melino et al., MicroRNAs in human skin ageing, Ageing Res Rev 17 (2014), pp. 9–15.

[73] P. Zhang, J. Chen, T. Li and Y.Y. Zhu, Use of small RNA as antiaging cosmeceuticals., J Cosmet Sci 64 (2013), pp. 455–68.

[74] P. Zhang, A. Huang, J. Ferruzzi, R.P. Mecham, B.C. Starcher, G. Tellides et al., Inhibition of microRNA-29 enhances elastin levels in cells haploinsufficient for elastin and in bioengineered vessels--brief report., Arterioscler Thromb Vasc Biol 32 (2012), pp. 756–9.

[75] T.P. Lehmann, U. Guderska, K. Kałek, M. Marzec, A. Urbanek, A. Czernikiewicz et al., The Regulation of Collagen Processing by miRNAs in Disease and Possible Implications for Bone Turnover, Int J Mol Sci 23 (2021), pp. 91.

[76] C.E. Condrat, D.C. Thompson, M.G. Barbu, O.L. Bugnar, A. Boboc, D. Cretoiu et al., miRNAs as Biomarkers in Disease: Latest Findings Regarding Their Role in Diagnosis and Prognosis., Cells 9 (2020), .

[77] W.-F. Lai, M. Lin and W.-T. Wong, Tackling Aging by Using miRNA as a Target and a Tool, Trends Mol Med 25 (2019), pp. 673–684.

[78] J.S.K. Chen and D.T.S. Wu, Application of intronic microRNA agents in cosmetics., Methods Mol Biol 936 (2013), pp. 325–41.