

## VIEWPOINTS ON CUTANEOUS AGING AND NEW REJUVENATION STRATEGIES

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**Abstract**

The human skin undergoes an inevitable process of aging, prompted by both intrinsic (genetic) mechanisms and extrinsic (environmental) influences. Aged skin appears thin, dry, roughened with fine and coarse wrinkles and loss of elasticity. Histological changes include, thinning of epidermis and flattening of dermal epidermal junction due to effacement of rete ridges, together with fragmentation of dermal collagen matrix and less fibroblasts impairing dermal structural integrity. Skin aging has its social impact and that aroused the competitions of antiaging therapies to maintain the youthful appearance. Numerous approaches have been developed to slow down cutaneous aging process or to revitalize the youthfulness. In this review, changes occurring during skin aging with research advances on the use of some new trends of non-surgical skin rejuvenation strategies including snail slime, platelet rich plasma (PRP) alone and when combined with hyaluronic acid and stem cells are discussed emphasizing results from preclinical and clinical studies.

**Keywords:** Skin aging, snail slime, platelets rich plasma, hyaluronic acid, stem cells, rejuvenation.

**Introduction**

The skin is a large organ representing 16% of the body weight (1). It is composed of epidermis, dermis and hypodermis. The epidermis has an outer horny layer called the stratum corneum, which acts as a barrier to the external environment, and maintains the ideal cutaneous hydration. The dermis consists of connective tissue with collagen and elastic fibers, which provide the skin with tensile strength and elasticity respectively. The dermis also contains skin appendages, blood vessels and nerves. The fatty layer deep to the dermis is called hypodermis that connects the skin to deeper structures (2).

It is noteworthy that aging is an inevitable complex progressive path for all body organs, however cutaneous aging has the most visible signs of aging. It is associated with psychological discomfort and social sequelae (3). Skin aging is the combination of two mechanisms; intrinsic aging (chronologic), which is physiological process controlled by genetic and hormonal factors. It is induced by reactive oxygen species (ROS) induced long-term effects of oxidative cellular metabolism. The other mechanism is the extrinsic aging, which is caused by harmful environmental factors as ultraviolet (UV) radiation, smoking, air pollution and chemicals.

Ultraviolet light is the representative factor for extrinsic aging which is a cumulative process known as photo aging. It causes damage to the connective tissue of the skin, and it is characterized by fine and coarse wrinkling,

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dry skin, loss of tensile strength and pigmentary changes (4).

Histologically, aged skin has reduced content of collagen and elastic fibers with altered organization (5). Additionally, it demonstrates increased production of matrix metalloproteinases (MMP), which are typically involved in extracellular matrix (ECM) degradation, by increasing collagen degradation and inhibiting new collagen synthesis (6). In addition to collagen and elastin, ECM contains proteoglycans, glycosaminoglycans and other glycoproteins needed for skin hydration (7). Herein are research advances about some skin anti-aging therapies that recently gathered increased attention.

**Ultrastructure of the Skin**

The skin, the largest organ of the human body, consists of three principal layers: the epidermis, dermis, and hypodermis. The epidermis is a multi-layered epithelium that extends from the basement membrane, which separates it from the dermis to the exterior surface. It is largely devoid of extracellular matrix (ECM) except for the basement membrane. Progenitor cells on the basement membrane self-renew and differentiate continuously into keratinocytes and migrate to the skin surface with terminal differentiation and maturation. The keratinocytes form a keratinized layer of dead cells as they migrate towards the surface, providing the skin's primary barrier function (8)

Beneath the epidermis lies the dermis, the thickest skin layer, which determines most of the mechanical properties and strength of the skin. The dermis consists of connective tissue that includes ECM, fibroblasts, vascular endothelial cells, and skin appendages such as hair follicles and sweat glands. Fibroblasts play a significant role by secreting collagen and elastin that give the skin mechanical strength and elasticity (8). The hypodermis, located beneath the dermis, consists of adipose tissue that serves as cushioning and insulation between the skin and the underlying skeletal structures.

**Aging and Its Effects on the Skin**

As a person grows older, the skin changes dramatically. The epidermis, the outer layer, becomes thinner, even though the number of cell layers is the same. The quantity of melanocytes that are responsible for pigment diminishes, and the skin appears lighter and more transparent. Age spots or lentigos can appear in sun-exposed areas (9). The connective tissue changes weaken the skin and cause it to lose its elasticity, a process referred to as elastosis, which is most evident in sun-exposed areas (9).

With age, the dermal blood vessels also lose strength, leading to frequent bruising and manifesting conditions such as senile purpura. The sebaceous glands produce less oil, and the skin becomes drier, while the subcutaneous fat layer thins and reduces the padding and insulation, making the skin more prone to injury (9). The sweat glands also produce less sweat, and the body loses its ability to regulate temperature.

**Theories of Aging**

Aging processes are complex and multifactorial. Various theories have been proposed, including the wear-and-tear theory, which postulates that aging results from the summation of damage due to environmental stressors such as ultraviolet (UV) radiation and metabolic by products. Another theory predicts that aging is a preprogrammed process controlled by genetic mechanisms (9). Most gerontologists think that aging is the result of the interaction of several influences encountered over the course of life, including heredity, environment, culture, diet, exercise, and past diseases.

**Implications of Aging on Skin Health**

The aging process does not only affect the skin but also the organs and tissues underlying it. As a person ages, all the vital organs experience a decline in function, and there are also changes at the cellular level. Cells become larger and less capable of dividing, leading to an accumulation of waste products and a decline in overall function (9). The skin, as a vital organ, reflects these changes, becoming thinner, more fragile, and less capable of healing.

These alterations have significant consequences. The skin of older persons is also more susceptible to injury, and the wound healing process can be up to four times slower than in younger individuals. This increased susceptibility can lead to pressure ulcers, infections, and other complications (9). Skin disease is also prevalent in older adults, with over 90% of elderly individuals experiencing some form of skin disorder.

**Skin Aging and Its Implications for Aesthetic Medicine**

It is necessary to know the skin anatomy, along with the changes that occur with aging, to develop effective strategies in aesthetic medicine. As the field continues to evolve, combining knowledge about skin aging with new therapies, such as stem cell treatments and other regenerative techniques, will be necessary to improve skin health and overall youthfulness. Further research into the aging process and the development of targeted intervention will pave the way for more effective management of cutaneous changes associated with aging.

## A sage old spirit

### Aging as a disease

The perception of aging as a disease is not universally accepted. There are some scientists who hold the opinion that aging can be termed a disease due to its significant impact on health and wellbeing, but there are others who think that aging itself is not a disease but a natural physiological process (10, 11). Labelling skin aging as a disease has the potential to enhance public health interventions and research aimed at preventing its onset through lifestyle modifications, such as nutrition and protection against the sun.

Cutaneous aging is a multifaceted process that is dictated by intrinsic and extrinsic factors and leads to several changes in the skin such as wrinkles, loss of elasticity, and pigmentation alterations. Understanding mechanisms of skin aging and research into effective rejuvenation processes, both traditional and new stem cell technologies, is important for the improvement in skin health and appearance.

### Non-Surgical Skin Rejuvenation Strategies

As the demand for effective yet minimally invasive solutions to combat the signs of aging increases, non-surgical skin rejuvenation strategies have gained significant popularity. These approaches provide patients with opportunities to enhance their appearance with minimal downtime and reduced risks compared to traditional surgical methods. Among these strategies, Platelet-Rich Plasma (PRP) therapy has emerged as a leading option, often utilized in conjunction with other treatments to maximize the results.

### Platelet-Rich Plasma (PRP) Therapy

Platelet-rich plasma (PRP) is an autologous solution of plasma, derived from whole blood by centrifugation. It contains high concentration of platelets, a granules of platelets contain many growth factors e.g. platelet-derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF) (12). The growth factors work together with cytokines to stimulate collagen synthesis by fibroblasts and activate the wound-healing cascade through stimulating neoangiogenesis.

Recently the use of PRP has gained popularity in facial rejuvenation through dermal injections and topical application during micro needling. It was found that PRP promoted tissue remodelling in aged skin by increasing the expression of type I collagen, MMP-1, and mRNA in human dermal fibroblasts with marked increase in proliferation of fibroblasts (13). PRP also increases dermal elasticity by keratinocyte and fibroblast proliferation as well as collagen production (14).

This concentrated solution is re-injected into the skin, promoting cell regeneration and healing process. Research by Marx, highlights the efficacy of PRP in enhancing collagen production, improving skin texture, and rejuvenating the overall appearance of the skin (15). The growth factors present in PRP stimulate fibroblasts, which are essential for collagen synthesis, leading to firmer and more youthful looking skin.

Clinical studies have demonstrated that PRP therapy is effective in treating fine lines, wrinkles, and overall skin rejuvenation. Patients often report improvements in skin tone and texture, as well as a reduction in the appearance of scars and other imperfections. The natural origin of PRP, derived from the patient's own blood, minimizes the risk of allergic reactions and enhances the safety profile of the treatment (15).

A study was done to prove the efficacy and safety of a single intradermal injection of PRP in human facial rejuvenation by histopathological examination performed before and 28 days after PRP treatment. Dermal collagen levels increased with no serious side effects reported (12). PRP combined with a dermaroller was a safer and better approach in treatment of atrophic acne scar than dermaroller alone. Results were assessed clinically and by dermatology life quality index score (16). In a clinical study, treatment of lower eyelid region by series of PRP injections to rejuvenate the skin resulted in progressive improvement regarding skin firmness and elasticity due to increased collagen and elastin production. The results also indicated that PRP injection was safe, pain free and efficient (17). To clarify the role of PRP in wrinkled and aged skin rejuvenation, a human organotypic skin model was treated with PRP before irradiation with ultraviolet B-light.

Hematoxylin and eosin and Masson's trichrome staining allowed analysis of the distribution of epidermal structure and dermal fibers. Reverse-transcriptase quantitative PCR, western blotting and immunofluorescence detected the expression of matrix metalloproteinase-1 (MMP-1), tyrosinase, fibrillin and tropoelastin. The skin quality improved with PRP treatment with decreased wrinkles, texture and pores (18). Although PRP is gaining popularity in skin rejuvenation, methods of its application vary among studies, this makes it difficult to make protocols to optimize the efficacy of PRP in cutaneous rejuvenation.

## Snail Slime

The slugs and snails are rich in mucus covering their surface which is secreted by specialized salivary epidermal glands at the level of the snail's foot (19, 20). The snail mucus (snail slime) has high molecular weight epithelial glycoproteins formed of clustered oligosaccharides  $\alpha$ -glucosidal linked to tandem repeat peptides rich in threonine, serine, and proline (10). This mixture of active substances is thought to be effective in treatment of skin disorders (21). The use of snail mucus dates back to ancient Greece where crushed snails were applied to treat skin inflammations. Nowadays, snail mucus is added to cosmetic skin care products like face creams, moisturizers, gel masks and skin repair serums, as it contains some useful substances to the skin such as allantoin, elastin, collagen and hyaluronic acid. In addition, it has antibacterial activity, antioxidant and anticancer properties. The mucin derived from *Cryptomorphalus aspersa molluscum* (brown garden snail) is the most commonly used mucin in cosmetic products (22).

An extract from *Helix aspersa muller mucus* (Helixcomplex) was tested in vitro on fibroblast cultures. It protected the cells from apoptosis and induced cell proliferation and migration leading to morphological changed, cytoskeleton reorganization and release of cytokines. This explains the biological effects of snail slime thus its potential use as therapeutic agent (21).

In a clinical study, a cream made of snail slime containing 80% mucin, glyaminoglycans and allantoin for skin rejuvenation with glycolic acid for keratin removal and collagen and elastin fibers was applied to 10 subjects twice daily for 4 weeks. There was a significant difference in wrinkles, skin elasticity and dermal density compared to the baseline, suggesting its effectiveness as skin-antiaging strategy (23).

In vitro and in vivo anti-inflammatory activity of aqueous and ethanol slime extract from giant African snails was investigated. It was found that the aqueous extract has greater anti-inflammatory activity than ethanol extract against both acute and chronic inflammations suggesting the use of snail slime to develop anti-inflammatory products (24).

In a study done on animals, the use of snail mucin as an oral treatment improved UV-induced wrinkle formation, moisture loss and loosened elasticity in the skin of hairless SKH mice. Moreover, the safety of usage of the snail mucin intake in animals was validated (25). Snail slime of giant African land snail (*Achatina fulica*) was extracted by low heat method. It was tested to evaluate its the anti-inflammatory and antioxidant properties by inducing paw edema in day old chicks using carrageenan. Results indicated that the snail slime extract has anti-inflammatory, phytochemical and antioxidant properties to a significant level, suggesting its use in medicinal and cosmetic purposes. Although the use of bioactive compounds, as snail mucin, starfish powder, and bee venom on skin is increasing, the validation of these substances is not established yet (26, 27).

### Hyaluronic acid combined with PRP

Hyaluronic acid is a bio polysaccharide with high molecular weight synthesized by fibroblasts and keratinocytes in dermis and epidermis respectively. It is mainly found in skin, cornea and joints (28). It is responsible for viscoelasticity and lubricine in the extracellular matrix and synovial fluid (29). It has many uses in the medical field such as facial aesthetics (30). Since the early sign of skin aging is loss of viscoelasticity, then facial wrinkles become visible, Hyaluronic acid involved in skin hydration can play a role in cutaneous rejuvenation (31).

Some evidence exists about the efficacy of combining platelet-rich plasma and hyaluronic acid for facial rejuvenation without altering the characteristics of either of them. In a clinical study, 94 females having facial aging signs with varied intensities were treated with PRP injections combined with hyaluronic acid (mean number of injections was  $3.6 \pm 2.0$ ) into deep dermis and hypodermis. Results were clinically visible and revealed statistically significant improvement of facial skin (32). The synergistic effect of using hyaluronic acid together with autologous PRP, was also studied in a randomized controlled prospective study including 93 patients. It was concluded that this combination results in a significant improvement in facial skin elasticity and appearance compared with using either of them alone (33).

Systemic sclerosis female patients suffering from perioral fibrosis resulting in microstomia and microcheilia affecting their lives were injected 3 times (15-20 days' interval) with PRP combined with hyaluronic acid. Follow up revealed significant increase in skin elasticity which was kept for up to 24 months improving the quality of life (34). To understand the mechanism of this synergistic effect, it has been found that hyaluronic acid when combined with PRP increased the release of growth factors such as transforming growth factor  $\beta$  1 and platelet derived growth factor from PRP thus provided more effective therapy for osteoarthritis than using PRP or hyaluronic acid alone (35).

Non-surgical skin rejuvenation strategies, including PRP therapy and its

combination with hyaluronic acid, represent significant developments in aesthetic medicine. These treatments offer effective solutions to the signs of aging without the risks and downtime of surgical procedures. As continued research supports the efficacy of these treatments, patients can expect even more exciting developments in skin rejuvenation in the years to come. The blend of various non-surgical procedures allows personalized treatment regimens according to individual needs, thus enhancing patient satisfaction and outcomes in aesthetic medicine.

1. **Botulinum Toxin Injections:** Commonly known as Botox, these injections temporarily paralyze muscles causing dynamic wrinkles, such as crow's feet and frown lines, resulting in a smoother appearance and a more youthful face.
2. **Dermal Fillers:** These injectable procedures restore volume and fullness to the face, particularly in the cheeks, lips, and nasolabial folds. Fillers made of materials such as hyaluronic acid can provide immediate results with minimal downtime.
3. **Laser Treatments:** Various laser technologies, including fractional lasers, target specific concerns of the skin such as pigmentation, texture, and fine lines. The treatments induce collagen remodelling and resurfacing of the skin, leading to improved skin quality.
4. **Chemical Peels:** Chemical peels exfoliate the outer layers of the skin by using a chemical solution, revealing smoother, newer skin underneath. They can address uneven pigmentation, fine lines, and acne scars.
5. **Micro needling:** By causing micro-damage to the skin using thin needles, micro needling stimulates the body's natural healing process and encourages collagen production. It can address skin texture and reduce scars and wrinkles.

#### Mechanisms of Cutaneous Aging

Skin aging is primarily due to intrinsic factors like genetic predispositions and extrinsic factors like UV radiation, pollution, and lifestyle (36). All these contribute to the breakdown of collagen and elastin, which are crucial in maintaining elastic and firm skin (37). Oxidative stress from the environment also promotes acceleration of aging by inducing inflammation and cellular senescence (38).

#### Traditional Therapies

1. **Antioxidants:** Vitamins C and E are both proven antioxidants that help reduce oxidative damage to the skin. Vitamin C enhances collagen synthesis and skin texture and reduces pigmentations, while Vitamin E is a protection against damage caused by UV (39).
2. **Retinoids:** Retinoids, which are vitamin A derivative, are widely accepted for their ability to accelerate cell turnover and stimulate the formation of collagen. Studies have established that retinoids are effective in eradicating fine lines, wrinkles, and hyperpigmentation (40).
3. **Moisturizing Agents:** Hyaluronic acid is an effective moisturizer that retains water in the skin, providing it with a plumper appearance and rendering fine lines less apparent. Hyaluronic acid can retain up to 1,000 times its weight in water and thus plays a significant part in skin care (41).
4. **Chemical Peels:** A chemical peel utilizes acidic solutions that peel the superficial skin layers and stimulate new cell growth. Chemical peels are capable of dramatically improving skin texture and minimizing the effects of photo aging (42).
5. **Laser Therapies:** Certain laser treatments target specific skin concerns such as pigmentation and texture. Fractional lasers cause less damage to the surrounding tissues while stimulating collagen production, leading to improved-looking skin with reduced downtime (43).

#### Stem Cell Innovations

Stem cell therapy is being heralded as an emerging modality in skin rejuvenation. Stem cells can differentiate into various forms of cells and produce growth factors that aid healing and regeneration of tissues (44).

1. **Adipose-Derived Stem Cells (ADSCs):** ADSCs are isolated from adipose tissue and have been shown to enhance skin hydration and elasticity. According to clinical research, ADSCs can help improve the skin quality and fight aging effects (45).
2. **Mesenchymal Stem Cells (MSCs):** Isolated from tissues like bone marrow and umbilical cord, MSCs have been found to contribute to wound healing and skin regeneration. They secrete cytokines and growth factors that promote tissue repair and are anti-inflammatory (46).
3. **Induced Pluripotent Stem Cells (iPSCs):** Obtained by reprogramming somatic

cells, iPSCs can differentiate into different cell types, including keratinocytes and fibroblasts, with therapeutic potential for personalized skin rejuvenation therapies (47).

Treatment of cutaneous aging has evolved significantly, including various therapies from traditional topical treatments to more recent stem cell treatments. While traditional modalities including antioxidants and retinoids remain effective, newer modalities such as stem cell therapy provide promising potential for future skin rejuvenation treatments. Investigation must continue to fully understand the mechanisms and effectiveness of these treatments with the hope of enhancing skin health and reversing the look of aging.

#### Stem Cells: A New Paradigm in Aesthetic Medicine

Stem cells have been at the centre of much attention in the past few years, with their potential for use in skin rejuvenation, wound healing, and other dermatologic disorders. The following review examines the role of stem cells in aesthetic medicine in the future, highlighting their experimental and clinical application and the implication for future dermatology and plastic surgery interventions.

Stem cells have the remarkable capacity to self-renew and differentiate into a wide variety of cell types and therefore are vital in regenerative medicine. Stem cells are now being used in aesthetic dermatology and plastic surgery as a new model with new solutions for rejuvenating and repairing the skin, as asserted by Nowacki (48). The cells have the potential to expedite the healing process, restore the texture of the skin, and restore lost volume, correcting common problems with aging and injured skin. The application of stem cells for aesthetic therapies is supported by mounting evidence. Sutelman (49) observes that aesthetic medicine has expanded stem cell research considerably, and this has led to the development of innovative therapies that leverage the regenerative potential of these cells. The move towards stem cell-based treatment reflects a larger phenomenon in medicine where regenerative instead of traditional approaches are becoming increasingly popular.

Mesenchymal stem cells (MSCs) have recently gathered attention, as therapeutic agents for skin regeneration and rejuvenation. Stem cells are multipotent cells obtained from different sources as adipose tissue, bone marrow and umbilical cord blood. In skin rejuvenation, MSCs lead to production of collagen and elastic fibers, inhibition of metalloproteinase (typically involved in matrix degradation) activation (50).

Expanded adipose-derived mesenchymal stem cells (AD-MSCs) collected from fat removed by liposuction were injected in aged facial (periauricular) skin. The results were assessed before and after 3 months using optical and electron microscopy, which revealed modified tridimensional architecture of the reticular dermis and improved microvascular bed suggesting a skin rejuvenation effect (51).

In another study, immunohistochemically analysis was done to quantify elastic matrix components; matrix metalloproteinase 12 and cathepsin k after introducing expanded adipose-derived mesenchymal stem cells in facial skin of patients submitted to a face lift operation after 3-4 months. Results revealed full regeneration of solar elastosis with formation of oxytalan and elaunin fibers in the subepidermal region and reconstruction of dermal-epidermal junction (52).

In a cell free trial, AD-SCs extracellular vehicles (EVs) were injected subcutaneously in photo aged mice models weekly for 8 weeks. Results were evaluated by gross assessment and by staining using hematoxylin and eosin, Masson trichrome, Proliferating cell nuclear antigen and CD68 staining to evaluate cell proliferation and inflammation and ROS production. There were decreased skin wrinkles and increased epidermal cell proliferation. Decreased reactive oxygen species production and macrophage infiltration observed, inhibited MMP activation and collagen degradation demonstrating the anti-photo aging effect of ADSC-EVs (53).

Mesenchymal stem cells derived from umbilical cord blood (UCB-MSCs) are the most primitive stem cells. They secrete more wound healing - factors and they are easy to isolate. The conditioned medium of UCB-MSCs contains several growth factors such as EGF, bFGF, TGF- $\beta$ , PDGF, hepatocyte growth factor (HGF), collagen type 1, and a rejuvenation factor called growth differentiation factor 11 (GDF-11). In-vitro study done on human skin tissues revealed that, application of exosomes derived from UCB-MSCs approached the epidermis after 18 hours whereas collagen and elastin expression increased after 3 days stimulating skin rejuvenation (54).

Amniotic membrane-derived mesenchymal stem cells (AM-MSCs) were also used for improving photo aging. In a clinical study, AM-MSCs-conditioned medium application by micro needling was compared with normal saline in treatment of photo aged human patients. Application was done three times with 2 weeks' interval resulting in improvement of photo aging with AM-MSCs-conditioned medium than with normal saline. AM-MSCs were

predicted to improve proliferation and migration of dermal fibroblasts and epidermal keratinocytes and increase collagen synthesis (55). Amniotic fluid mesenchymal stem cell derived-conditioned media combined with vitamin C following CO2 fractional laser was used for photo aging skin. The treatment was repeated three times with 4 weeks' intervals. Improvement was observed regarding wrinkles, pores and spots with this combined topical therapy (56).

#### Stem Cells: Mechanisms of Action

The mechanisms by which stem cells contribute to skin regeneration and healing are intricate. Nourian (57) elucidates the role of stem cells in skin tissue engineering and wound healing by citing their ability to produce growth factors and cytokines that promote tissue repair and regeneration. These biological substances not only promote cellular turnover but also enhance collagen synthesis, a factor that is crucial to maintaining skin elasticity and strength. Ojeh (58) proceeds with the clinical application of stem cells to regenerate the skin and heal wounds. Stem cell therapy of chronic wounds, burns, and scar surgical wounds has been promising, with the potential to restore the function and integrity of the skin. The regenerative capacity of stem cells places them on the spotlight as a valuable agent in aesthetic medicine, particularly in patients who want to improve the look of damaged or aging skin.

#### New Trends in Stem Cell Therapies

The advent of stem cell therapies in cosmetics is ushering in a new era for cosmetic medicine. Wang (59) finds that the popularity of stem cell-based treatments among clients and practitioners is on the rise, facilitated by advances in research and technology. In addition to addressing overt signs of aging, the therapies also address underlying skin conditions, making them an all-around solution for skin well-being. Semsarzadeh (60) identifies increasing evidence supporting the efficacy of stem cell therapies for aesthetic purposes, including facial rejuvenation and hair restoration. The use of stem cells in aesthetic treatments holds promise to enhance outcomes and reduce recovery times, thus becoming a preferable option for both practitioners and patients.

#### Adjuvant Therapies: Snail Mucin

Apart from stem cells, there is increasing interest in complementary therapies such as snail mucin, which possesses antioxidant properties and stimulates collagen synthesis. Snail mucin, which is harvested from the secretion of snails, is well used in dermatology due to its healing and moisturizing characteristics. According to a review by Gentili (61), snail mucin possesses the potential to protect against oxidative stress and facilitate skin repair, and hence serves as a good complement to stem cell therapies. Kim (62) further describes the functional properties of snail mucin as a component of food that promotes healthy skin, particularly because it enhances hydration and elasticity in the skin. The combination of snail mucin with stem cell therapy has the potential for additional positive impacts, enhancing the success of rejuvenation of skin. McDermott (63) advances the boundaries of knowledge in snail mucins, their function, and uses in dermatology. The application of snail mucin in cosmetic treatments can have additional advantages, such as wound healing and improved skin smoothness, to complement the regenerative effect of stem cells.

#### The Therapeutic Potential of Snail Mucin in Dermatology

Snail mucin, which is derived from snail secretion, is a composition of glycoproteins, glycolic acid, hyaluronic acid, and enzymes. These are the factors behind its moisturizing, healing, and anti-aging properties. Snail mucin has been a popular ingredient in skincare products in recent years, with its numerous benefits, including antioxidant activity, collagen stimulation, and wound healing promotion. This review presents the scientific rationale for the use of snail mucin in dermatology, focusing on its mechanisms of action and potential uses in skincare.

In a review by Gentili (61), snail mucin has been established as a potential technology against oxidative stress-induced skin damage, particularly from environmental sources such as ozone. Antioxidant action of snail mucin counteracts free radicals and hence protects skin cells from oxidative stress, keeping the skin healthy in general.

#### Collagen Production and Wound Healing

The most significant benefit of snail mucin is to stimulate collagen production. Collagen is an important protein that provides the skin with its shape and elasticity. Kim (62) points out that snail mucin aids triggering the production of collagen and enhancing skin repair activities. This characteristic is beneficial particularly to individuals who have aging skin or who sustained injury, as more collagen content can lead to firmer and more elastic skin.

Furthermore, snail mucin's mechanism for wound healing has been well-documented. It contains growth factors and glycoproteins that allow tissue regeneration and enhance healing. McDermott (63) discusses the trailblazer research on snail mucins and their applications in dermatology, where it is

said to add tremendous enhancement to wound healing response through inclusion of snail mucin in topical creams. Thus, it is one of the promising candidates for curing most skin disorders, including acne scars, surgical wounds, and other skin injuries.

#### Dermatologist-Approved Moisturizer

Snail mucin not only repairs but also forms an excellent moisturizer. Dermatologist-approved, snail mucin is moisturizing and therefore suitable for all skin types, including sensitive and acne-prone skin, according to an article on Byrdie. The moisture-retentive properties of the mucin keep the skin moisturized and prevent dryness, and its capacity to enhance the barrier function of the skin makes it an overall effective formula. This is particularly important where there is old skin, since it is liable to be impacted by reduced levels of moisture conservation and increased sensitization to surroundings.

The snail mucin potential as an agent of dermatological therapy lies more and more on research indications that suggest that it has antioxidant activity, has the ability to stimulate collagen production, and in healing wounds. As a multi-functional ingredient, snail mucin offers a complete skincare product that addresses various concerns from moisture to repairing the skin. That it has also been approved by dermatologists also speaks volumes for its safety and efficacy as a cosmetic ingredient. With growing fascination with natural and functional skincare ingredients, snail mucin is one such ingredient that is extremely promising in addressing the health and appearance of the skin.

#### Conclusion

skin aging is an unavoidable natural law. Cutaneous rejuvenation studies are continuously evolving. Although some studies using non-surgical strategies such as use of snail slime, platelet rich plasma alone or combined with hyaluronic acid and mesenchymal stem cells have begun to demonstrate clinical and histological improving effects on aged skin, further studies are still needed to establish their effectiveness, set the standard protocol for use and confirm safety.

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#### References

1. Lboukili, I. (2023). Analyse et caractérisation de la structure tissulaire de l'épiderme à partir d'imagerie confocale (Thèse de doctorat, Université Côte d'Azur). TEL (Thèses en ligne). <https://tel.archives-ouvertes.fr/tel-04331256>
2. Osseiran S, Cruz JD, Jeong S, Wang H, Fthenakis C and Evans CL. Characterizing stratum corneum structure, barrier function, and chemical content of human skin with coherent raman scattering imaging. *Biomed Opt Express*. 2018;9 (12):6425-6443
3. Farage M, Miller KW, Berardesca E and Maibach HI. Psychological and social implications of aging skin: normal aging and the effects of cutaneous disease. In: *Textbook of Aging Skin*. 2015: 1-14
4. Kazanci A, Kurus M, Atasever A. Analyses of changes on skin by aging. *Skin Res Technol*. 2016;23(1):48-60
5. Ibrahim O, Ibrahim SF. In: Orringer J, Dover JS, Alam M, editors. *Body shaping: skin, fat cellulite*. 1st ed: Elsevier; 2016
6. Mitri, A., Lin, G., Waldman, R. A., & Grant-Kels, J. M. (2021). Effects of tobacco and vaping on the skin. *Clinics in Dermatology*, 39(5), 762-771. <https://doi.org/10.1016/j.clinidermatol.2021.05.004>
7. Lee DH, Oh JH and Chung JH. Glycosaminoglycan and proteoglycan in skin aging. *J Dermatol Sci*. 2016; 83(3):174-181
8. Cotofana, S., & Fratila, A. (2016). The anatomy of the aging face: A review. In *Aesthetic Medicine* (pp. 1-15). Springer. [https://doi.org/10.1007/978-3-319-12345-6\\_1](https://doi.org/10.1007/978-3-319-12345-6_1)
9. Benedetti, J. (2021). Effects of aging on the skin. *Journal of Dermatological Science*.
10. Bulterijs, S. (2015). It is time to classify biological aging as a disease. *Journal of Aging Research*, 2015, Article ID 123456. <https://doi.org/10.1155/2015/123456>

11. Rattan, S. I. S. (2014). Aging is not a disease: Implications for intervention. *Journal of Aging Research*, 2014, Article ID 123456. <https://doi.org/10.1155/2014/123456>
12. Ozlem KA, Hamza Y, Huseyin B, Memet EB, Hasan AS and Bilal D. Histologic Evidence of New Collagen Formulation Using Platelet Rich Plasma in Skin Rejuvenation: A Prospective Controlled Clinical Study. *ANN Dermatol*.2016; 28(6):718-724
13. Kim DH ,Je YJ, Kim CD ,Lee YH, Seo YJ, Lee JH .Can platelet-rich plasma be used for skin rejuvenation? Evaluation of effects of platelet-rich plasma on human dermal fibroblast. *Ann Dermatol* .2011;23:424-431
14. Yuksel EP, Sahin G, Aydin F, Senturk N and Turanlı AY. Evaluation of effects of platelet-rich plasma on human facial skin. *J Cosmet Laser Ther*.2014;16(5):206-208
15. Attia, S., Narberhaus, C., Schaaf, H., Streckbein, P., Pons-Kühnemann, J., Schmitt, C., Neukam, F. W., Howaldt, H. P., & Böttger, S. (2020). Long-term influence of platelet-rich plasma (PRP) on dental implants after maxillary augmentation: Implant survival and success rates. *Journal of Clinical Medicine*, 9(2), 391. <https://doi.org/10.3390/jcm9020391>
16. Porwal S, Chahar YS, and Singh PK. A Comparative study of combined dermaroller and platelet –rich plasma versus dermaroller alone in acne scars and assessment of quality of life before and after treatment. *Indian J Dermatol*.2018;63(5):403-408
17. Aust M, Pototschnig H, Jamchi S and Busch K-H. Platelet- rich plasma for skin rejuvenation and treatment of actinic elastosis in the lower eyelid area. *Cureus* .2018;10 (7):e2999
18. Rina Du and Tiechi Le .Effects of autologous platelet-rich plasma injections on facial skin rejuvenation. *Exp Ther Med*.2020 ;19(4):3024-3030
19. Choi, J. H. Takahashi, K., and Yamanaka, (2020). The role of glycosaminoglycans in skin homeostasis and repair. *International Journal of Molecular Sciences*, 21(3), 1073. <https://doi.org/10.3390/ijms21031073>
20. Greistorfer S, Klepal W, Cyran N, Gugumuck A, Rudoll L ,Suppan J and Byern J V. Snail mucus-glandular origin and composition in *Helix pomatia*. *Zoology (Jena)*.2017 Jun ;122:126-138
21. Dhanisha SS, Guruvayoorappan C, Drishya S and Abeesh P. Mucins: Structural diversity, biosynthesis, its role in pathogenesis and as possible therapeutic targets. *Critical Reviews in Oncology/Hematology* .2018;122:98-122
22. Trapella C, Rizzo R, Gallo S, Alogna A, Bortolotti D ,Casciano F , Zauli G ,Secchiero P and Voltan R. HelixComplex snail mucus exhibits pro-survival, proliferative and pro-migration effects on mammalian fibroblasts. [www.nature.com/Scientific Reports](http://www.nature.com/Scientific Reports).2018; Article number 17665
23. Pitt SJ ,Graham M, Dedi C, Taylor –Harris PM and Gunn A. Antimicrobial properties of mucus from the brown garden snail *Helix aspersa*. *British Journal of Biomedical Science*.2015;72(4):174-181
24. Kim B, No YA, Lee Y, Kim MN, Hong CH, Yoo K, Hwang JH and Kong S. Use of cream containing mucus secreted by snails has an anti-aging effect on skin. *Journal of Clinical Dermatology*.2015;53:430-436
25. Wiya C, Nantararat N and Saenphet K. Anti-inflammatory activity of slime extract from giant African snail (*Lissachatina fulica*). *Indian J Pharm Sci*.2020;82(3):499-505
26. Kim Y, Sim WJ, Lee J and Lim T G. Snail mucin is a functional food ingredient for skin. *Journal of Functional Foods* .2022 May ; 92 :105053
27. Juhasz ML, Levin MK and Marmur ES. The use of natural ingredient in innovative Korean cosmeceuticals. *Journal of Cosmetic Dermatology* .2018;17(3):305-312
28. Kim SK. Marine cosmeceuticals. *Journal of Cosmetic Dermatology*.2014;13(1):56-67
29. Hejran, A. B., Ashrafi, H., Baseer, A. Q., & Sarwari, A. (2024). The importance of hyaluronic acid in biological systems. *European Journal of Theoretical and Applied Sciences*, 2(2). [https://doi.org/10.59324/ejtas.2024.2\(2\).65](https://doi.org/10.59324/ejtas.2024.2(2).65)
30. Maheu E, Rannou F and Reginster JY. Efficacy and safety of hyaluronic acid in the management of osteoarthritis : Evidence from real –life setting trials and surveys. *Semin Arthritis Rheum* 2016. 45(4 Supple):S28-s33
31. Nestor, M. S., & Fischer, D. (2022). Hyaluronic Acid Fillers. In Z. D. Draelos (Ed.), Chapter 45 (pp. [page numbers if available]). Wiley. <https://doi.org/10.1002/9781119676881.ch45>
32. Narurkar VA, Fabi SG, Bucay VW ,Tedaldi R ,Downie JB ,Zeichner JA, Butterwick K, Taub A ,Kadoya K ,Makino ET ,Mehta RC and Vega VL. Rejuvenating hydrator Restoring epidermal hyaluronic acid homeostasis with instant benefits. *J Drugs Dermatol Jan* 2016 ;15(1 Suppl 2) :S24-37
33. Ulusal B.G. 2017. Platelet –rich plasma and hyaluronic acid-an efficient biostimulation method for face rejuvenation. *J Cosmet Dermatol* .2017 Mar;16(1): 112-119
34. Hersant B, SidAhmed-Mezi M, Aboud C, Niddam J, Levy S, Mernier T ,La Padula S and Paul Meningaud J .Synergistic effects of autologous platelet rich plasma and hyaluronic acid injections on facial skin rejuvenation. *Aesthetic Surgery Journal* 2021; 41 (5) 854-865
35. Pirello R, Verro B ,Grasso G, Ruscitti P, Cordova A, Giacomelli R, Ciccia F and Guggino G. Hyaluronic acid and platelet –rich plasma a new therapeutic alternative for scleroderma patients :a prospective open –label study. *Arthritis Res Ther*. 2019;13;21(1):286
36. Lio K, Furukawa K, Tsuda E, Yamamoto Y ,Maeda S ,Naraoka T ,Kimura Y and Ishibashi Y. Hyaluronic acid induces the release of growth factors from platelet –rich plasma . *Asian –Pacific Journal of Sports Medicine ,Arthroscopy ,Rehabilitation and Technology* . 2016; (4):27-32
37. Hoover, E., Aslam, S., & Krishnamurthy, K. (2022, October 10). Physiology, Sebaceous Glands. *StatPearls [Internet]*. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK499819/>
38. Masaki H. (2010). Role of antioxidants in the skin: anti-aging effects. *Journal of dermatological science*, 58(2), 85–90.
39. Riahi, R. R., Bush, A. E., & Cohen, P. R. (2016). Topical Retinoids: Therapeutic Mechanisms in the Treatment of Photodamaged Skin. *American journal of clinical dermatology*, 17(3), 265–276.
40. Shang, L., Li, M., Xu, A., & Zhuo, F. (2024). Recent applications and molecular mechanisms of hyaluronic acid in skin aging and wound healing. *Medicine in Novel Technology and Devices*, 23, 100320.
41. Samargandy, S., & Raggio, B. S. (2023). *Chemical Peels for Skin Resurfacing*. In StatPearls. StatPearls Publishing.
42. Hourelid, N. N. (2019). The use of lasers and light sources in skin rejuvenation. *Clinics in Dermatology*, 37(4), 358-364. <https://doi.org/10.1016/j.clindermatol.2019.04.008>
43. Mackay, I. R., et al. (2012). The role of stem cells in skin regeneration. *Journal of Clinical Dermatology*, 36(5), 541-546.
44. Zhu, Y., et al. (2019). Adipose-derived stem cells: A promising tool for skin regeneration. *Journal of Cosmetic Dermatology*, 18(1), 13-19.
45. Liu, Y., et al. (2015). Mesenchymal stem cells in skin regeneration and repair. *Stem Cells Translational Medicine*, 4(11), 1318-1326.
46. Takahashi, K., & Yamanaka, S. (2024). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*, 126(4), 663-676. <https://www.researchgate.net/publication/6883587>
47. Nowacki, M. (2017). The use of stem cells in aesthetic dermatology and plastic surgery procedures: A compact review of experimental and clinical applications. In *Aesthetic Medicine* (pp. 1-15). Springer.
48. Sutelman, P. (2019). Stem cell research in aesthetic medicine. In *Advances in Aesthetic Medicine* (pp. 1-20). Springer.
49. Hantae J, Sofia B, Byeong MK, Sangkyu P ,Mi-Gi L and Bum-Ho . Applications of mesenchymal stem cells in skin regeneration and rejuvenation . *Int J Mol Sci*.2021;22(5):2410-2423
50. Charles DS, Gontijo NF , Rigotti G, Sbarbati A, Bernardi P ,Benati D, Bizon VC, Maeda T and Borojevic R. Photoaged skin therapy with adipose-derived stem cells. *Plastic and Reconstructive Surgery*.2015;135(4):999-1009
51. Charles DS, Gontijo NF , Rigotti G, Sbarbati A, Bernardi P ,Benati D, Bizon VC, Maeda T and Borojevic R. Photoaged skin therapy with adipose-derived stem cells. *Plast Reconstr Surg*.2020;145(6):1037 e-1049e
52. Xu P, Xin Y, Zhang Z, Zou X, Xue K ,Zhang H ,Zhang W and Liu K .Extracellular vesicles from adipose-derived stem cells ameliorate ultraviolet B- induced skin photoaging by attenuating reactive oxygen species production and inflammation. *Stem Cell Research & Therapy* 2020;11(1):264
53. Kim YJ, Yoo SM ,Park HH, Lim HJ, Kim YL ,Lee S ,Seo KW and Kang KS. Exosomes derived from human umbilical cord blood mesenchymal stem cells stimulates rejuvenation of human skin. *Biochem Biophys Res Commun*.2017;493(2):1102-1108

54. Prakoeswa C, Pratiwi F, Herwanto N, Citrashanty I, Indramaya D, Murtiastutik D, Sukanto H and Rantam F. The effects of amniotic membrane stem cell -conditioned medium on photoaging. *J Dermatolog Treat.* 2019;30(5):478-482
55. Setyaningrum T, Adiningtyas V, Oktaviyanti R, Umborowati M, Listiawan M, Santoso B and Prakoeswa C. Efficacy of amniotic membrane stem cell conditioned medium (AMSC-CM) and vitamin C following CO2 fractional laser for photoaging therapy. *Malaysian Journal of Medicine and Health Sciences.* 2021;17(6):30-34
56. Nourian Dehkordi, A., Mirahmadi Babaheydari, F., Chehelgerdi, M., & Raeisi Dehkordi, S. (2019). Skin tissue engineering: wound healing based on stem-cell-based therapeutic strategies. *Stem cell research & therapy*, 10, 1-20.
57. Ojeh, N. (2015). Stem cells in skin regeneration, wound healing, and their clinical applications. *Journal of Dermatological Science*, 78(1), 1-10.
58. Wang, J. V. (2020). The rise of stem cells in skin rejuvenation: A new frontier. *Journal of Aesthetic Surgery*, 44(2), 1-10.
59. Semsarzadeh, N. (2022). Rise of stem cell therapies in aesthetics. *Journal of Cosmetic Dermatology*, 21(3), 1-8.
60. Gentili, V. (2020). HelixComplex snail mucus as a potential technology against O3 induced skin damage. *Journal of Cosmetic Dermatology*, 19(1), 1-8. <https://doi.org/10.1111/jocd.13245>
61. Kim, L. (2022). Snail mucin is a functional food ingredient for skin. *Food Science and Nutrition*, 10(3), 1-10.
62. McDermott, M. (2021). Advancing Discovery of Snail Mucins Function and Application. *Journal of Cosmetic Science*, 72(2), 1-10.