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Review Article

INNOVATIVE APPROACHES TO COMBAT SKIN AGING: ADVANCES IN WRINKLE AND SAGGING TREATMENTS

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ABSTRACT

Recent developments in dermatological science have greatly changed the concept of skin aging and, more particularly, wrinkling and sagging. Based on previous studies, this review summarizes the current findings regarding molecular mechanisms in skin aging: oxidative stress, glycation, and cellular senescence. Among the more recent topical innovative treatments are next-generation retinoids, advanced peptides, and exosomes derived from stem cells, promising new clinical treatments to improve skin elasticity and other signs of aging. Advances in minimally invasive procedures, dermal fillers and combined microneedling-radiofrequency treatments have shown greater efficacy with less downtime to achieve skin rejuvenation. Other emerging technologies related to personalized skin grafts via 3D bioprinting and nano-delivery systems may provide even new approaches for the regeneration of skin and delivery of anti-aging compounds with more precise delivery. Future directions involve very individualized treatments based on genomics, specific biomarkers, application of artificial intelligence in treatment planning and follow-up. These developments promise great new approaches; however, longer-term studies in terms of safety and efficacy are also needed to validate these approaches fully in diverse populations. The review brings into view the rapid pace of anti-aging skincare improvement into more complex, effective, and personalized treatments, holding a lot of promise for revolutionizing dermatology and aesthetic medicine.

Keywords: Anti-aging formulations, Skin aging, Nanotechnology in skincare, Artificial intelligence in dermatology, Personalized skincare

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INTRODUCTION

Skin aging is a multifactorial process based on slow progressive changes in structural and functional properties of the dermis and epidermis. It manifests itself through wrinkles and sagging as well as elasticity loss with well-defined effects on the aesthetic component and physiological functioning of the skin [1]. Aging skin etiology may be divided into two main interacting processes: intrinsic or chronological aging and extrinsic or environmental aging [2].

This process, intrinsic aging, is biologically and genetically predetermined. It manifests over time, mainly characterized through cellular senescence; it reduces proliferative capacity and lower metabolic activity [3]. Telomere shortening, mitochondrial dysfunction, and accumulation of senescent cells have been identified as major molecular hallmarks of intrinsic aging [4]. The studies explained that all of these processes result in slow dermal degradation of collagen and elastin, which causes fine wrinkles with low skin elasticity [5]. According to Tigges *et al.*, intrinsic aging occurs due to a reduction in the number and activity of the fibroblasts, which are major cells that ensure collagen and elastin synthesis in the dermis [6]. The two extrinsic factors of aging include photoaging, unlike intrinsic aging; this is majorly influenced by environmental factors: primarily UV radiation [7].

Other extrinsic factors include pollution, smoking, and inadequate nutrition. The degree of upregulation of MMPs quickens the breaking down of proteins in ECM, primarily collagen and elastin [8]. This results in deep wrinkles, skin laxity, and abnormal pigmentation [9]. Additionally, it have elaborated that air-borne particles may penetrate the skin and cause oxidative stress, thus resulting in premature aging of the skin [10].

Over the last centuries, tremendous advancement has been made in the molecular mechanisms that determine both intrinsic and extrinsic aging. This has opened up ground-breaking new approaches toward novel anti-aging, covering.

Antioxidant and antiaging formulation: There has been development of new antioxidant formulations as well as delivery systems in order to counteract oxidative stress, which is one of the main reasons for both intrinsic as well as extrinsic aging [11]. This nanoencapsulation system of antioxidants is more penetrative and potent than a traditional formulation.

Cellular senescence modulation: New senolytic therapies involve the elimination of senescent cells, which reverses some of the age-related changes occurring in the skin found topical application of a small-molecule senolytic agent improves the appearance and functions of the skin in aged mice [12]. Skin barrier repair: Devised advanced moisturizers and skin-identical lipids to be used in the enhancement of barrier function of the skin, which naturally declines with aging. In their study, they found that such formulations resulted in a significant improvement in hydration of the skin and reduction in TEWL in aging skin.

Induction of collagen and elastin: The next-generation peptides, growth factors, and energy-based devices promise to enhance the synthesis of these critical extracellular matrix proteins. Findings of new hexapeptide invention also revealed significant improvement in skin elasticity and wrinkle-resolving properties in human volunteers.

Leveraging of stem cell technology: As discussed, the potential of exosomes derived from various sources of stem cells in skin regeneration and rejuvenation. It was found that exosomes from adipose-derived stem cells can enhance collagen synthesis and skin. Antioxidant and antiaging formulation: There has been development of new antioxidant formulations and delivery systems to counteract oxidative stress, which is one of the main reasons for both intrinsic and extrinsic aging. This nanoencapsulation system of antioxidants is more penetrative and potent than a traditional formulation.

With the population growing ever older and the demand for effective anti-aging solutions continuing to rise, the work in this field has become very intensive. According to a report by Grand View Research in 2021, the worldwide anti-aging market size will reach USD 119.6 billion by 2030, therefore showing great economic and societal impact of this field.

The review is aimed at an integrative approach to move forward with anti-aging techniques targeted specifically at wrinkles and skin sagging. Novel approaches in topical treatments, minimally invasive procedures, and emerging technologies are likely to be effective tools for combating these visible signs of aging. This review will synthesize recent scientific findings for insight into contemporary findings on anti-aging research and future directions.

The articles for the current review were chosen from specialized databases (range of years: 2014-2024) such as Elsevier, Pubmed, and Cambridge using the keywords Anti-aging formulations, Skin Aging, Nanotechnology in Skincare, Artificial Intelligence in Dermatology, Personalized Skincare. Other options include Springer and Wiley articles, information from the Internet, and online published articles from The Lancet Respiratory Medicine, Medscape, and StatPearls.

Molecular mechanism of skin aging

The molecular basis of skin aging involves a complex interplay of various biological processes. Intrinsic aging, driven by genetic factors, and extrinsic aging, caused by environmental stressors like UV radiation, both contribute to the progressive deterioration of skin structure and function. At the cellular level, oxidative stress plays a pivotal role, leading to the accumulation of Reactive Oxygen Species (ROS) that damage cellular components, including DNA, proteins, and lipids. This oxidative damage triggers a cascade of events, including telomere shortening, which limits cellular replication capacity and leads to senescence Additionally, glycation of structural proteins like collagen and elastin results in the formation of Advanced Glycation End Products (AGEs), compromising the extracellular matrix's integrity [13]. Epigenetic modifications, such as DNA methylation and histone modifications, also contribute to age-related changes in gene expression profiles. Furthermore, chronic low-grade inflammation, termed "inflammaging," perpetuates tissue damage and accelerates the aging process. Recent research has also highlighted the role of mitochondrial dysfunction in skin aging, as impaired energy metabolism and increased ROS production further exacerbate cellular damage Understanding these intricate molecular mechanisms provides a foundation for developing targeted anti-aging interventions and more effective skincare strategies [14].

Oxidative stress and free radical damage

Oxidative stress, caused by an imbalance between free radical production and antioxidant defenses, is a key factor in skin aging. Free radicals, such as Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), can damage cellular components, including lipids, proteins, and DNA, leading to premature aging and various skin disorders. Recent research has demonstrated that UV radiation, pollution, and lifestyle factors contribute significantly to oxidative stress in the skin [15]. The highlighted role of mitochondrial dysfunction in generating excess ROS, accelerating skin aging. To combat these effects, researchers have focused on developing more potent antioxidants and innovative delivery systems. The efficacy of nanoencapsulated vitamin C in penetrating deeper skin layers and providing enhanced protection against oxidative damage. Additionally, the use of natural compounds such as polyphenols from green tea and resveratrol from grapes has shown promising results in neutralizing free radicals and promoting skin health [16]. A comprehensive review emphasized the importance of a multi-faceted approach, combining topical antioxidants, oral supplements, and lifestyle modifications to effectively manage oxidative stress in the skin.

Glycation and advanced glycation end products (AGEs)

Glycation can be cited among the essential processes associated with the aging of skin, more so with the breakdown of structural proteins such as collagen and elastin. Nonglycative cross-linking between reducing sugars and proteins can result in the aging process characterized by extensive cross-links formation, significantly altering the mechanical properties of the skin with decreases elasticity and increase stiffness [17]. In addition to their role in compromising structural integrity, accumulation of AGEs can induce oxidative stress and inflammation, which in turn accelerates aging [18]. Current studies on the complex ways in which AGEs induce skin aging include their role in enhancing cellular senescence and degradation of the extracellular matrix in the skin.

With an effective anti-glycation agent now the focus of constant research and development thrust in skincare. Other promising compounds include natural extracts such as Ginkgo biloba and green tea polyphenols, where recent evidence shows that these inhibit AGE formation and reduce their potential toxicity. Several synthetic compounds, including aminoguanidine and pyridoxamine, are being tested as AGE breakers that break cross-links or inhibitors that prevent the formation of AGEs [19]. On the other hand, topical use of antioxidants like vitamins C and E has been viewed as a way of fighting against oxidative stress from AGEs [20]. However, practical applications of the developed formulation in the products for skin care prove difficult and entail different issues among them poor penetration and stability of the active ingredient throughout the shelf life of cosmetics [21].

However, clinical trials have recently commenced investigating the ability of anti-glycation therapies to be effective in humans and some of them have demonstrated promising results, including increased skin elasticity and decreased wrinkle formation [22]. However, more controlled, long-term studies need to be performed to determine the full capacity of such treatments to prevent and reverse AGE-related dermatological damage. As the mechanism of glycation in aging continues to be unraveled, new possibilities for targeted interventions and personalized approaches to skincare are opened up. The integration of strategies to counteract the effects of glycation with other anti-aging strategies, such as photoprotection and proper hydration of the skin, could well represent the best of both worlds in managing aged skin and appearance [23].

Cellular senescence

Cellular senescence is an important mechanism of skin aging, during which arrested cells that undergo clear morphological and functional changes accumulate. Both types of cells, namely fibroblasts and keratinocytes, are senescent cells displaying an overall aging phenotype [24]. Senescent cells secrete a complex mixture of factors that have been called the Senescence-Associated Secretory Phenotype (SASP) [25], including proinflammatory cytokines and chemokines, growth factors, and matrix-degrading enzymes [26]. This SASP can induce senescence in adjacent cells, leading to a cascade effect that hastens tissue aging [27]. Recent studies also indicated that the presence of senescent fibroblasts in the dermis allows for decreased collagen production, increased activity of the matrix metalloproteinase, extracellular matrix degradation, and loss of skin elasticity [28]. The field of therapies designed to selectively eliminate senescent cells is an emerging area for targeting some aspects of skin aging [29]. Depletion of senescent cells has been demonstrated to enhance several features of aging phenotypes, including in skin, in preclinical models [30]. Indeed, removal of p16Ink4a-positive senescent cells was shown to promote delays in aging-related disorders and to increase healthspan in mice [31]. Topical administration of a senolytic drug combination has dramatically decreased the number of senescent cells and enhanced wound healing in aged mice [32].

Topical treatments

Next-generation retinoids

Topical formulations: Long recognized as anti-aging active agents, retinoids have been well established as a pharmacological treatment. Application is often avoided due to side effects, such as irritation and photosensitivity. New-generation retinoids are under development to prolong the duration of effectiveness of these compounds without any loss of potency: Trifarotene is a fourth-generation retinoid, specifically targeting the Retinoic Acid Receptor- γ (RAR-γ), which is dominant in the epidermis. Based on a randomized, vehicle-controlled study, trifarotene 50 μg/g cream highly improved facial and truncal acne with a favorable tolerability profile [33]. In as much as this study focused on acne, it is through its selectivity that trifarotene might have future anti-aging uses but with reduced irritation. Retinyl retinoate is a new hybrid retinoid that has shown promising photo-aging stability with decreased irritation. Study was conducted on randomized, double-blind, vehicle-controlled, split-face study comparing retinyl retinoate and retinol. They demonstrated that retinyl retinoate significantly improved wrinkles and hyperpigmentation after 12 w with effects comparable to or better than retinol and fewer adverse effects [34].

Bakuchiol is not a 'true' retinoid but has been proven to have retinol-like action with no adverse events related to retinoids. Dhaliwal *et al.* performed a randomized, double-blind 12 w trial comparing 0.5% bakuchiol cream to 0.5% retinol cream. Results: both compounds significantly reduced wrinkle surface area and hyperpigmentation, and users of bakuchiol experienced less facial scaling and stinging.

The application of encapsulation technologies may also enhance retinoid delivery and irritation. Study was conducted to evaluate a new 0.05% retinol product stabilized by a cyclic sugar-derived matrix [35]. This formulation showed improvement in facial wrinkles, skin evenness, and overall appearance after 12 w. Minimal irritation was reported. These advances in the field of retinoid science are very significant strides in topical anti-aging therapy. More importantly, however, better-powered, longer-duration clinical trials will be needed to establish with greater certainty the efficacy and safety profiles of these newer compounds vis-à-vis traditional retinoids.

Topical treatments retinoids are long-known effective antiaging compounds; however, their clinical use is mostly restricted by their side effects, most importantly irritation and photosensitivity. Next-generation retinoids are being developed that address these shortcomings while hopefully maintaining or improving efficacy.

The fourth-generation retinoid, trifarotene, selectively acts on the receptor-γ of retinoic acid predominant in the epidermis [36]. A randomized, vehicle-controlled study of 22 patients showed that the trifarotene 50 μg/g cream led to significant improvement in facial and truncal acne with a favorable tolerability profile. This study is more related to acne, but considering the selective mechanism of action of trifarotene, anti-aging applications are quite plausible with lesser irritation.

New hybrid retinoids, such as retinyl retinoate, have been promising in the treatment of photoaging with improved stability and irritation. Randomized, double-blind, vehicle-controlled, splitface study that compared retinyl retinoate and retinol. The authors found at the end of 12 w that retinyl retinoate significantly improved wrinkles and hyperpigmentation with effects equal to or superior to retinol, with fewer side effects.

Bakuchiol, though not a natural retinoid, has been of interest due to its retinol-like actions but without typical retinoid-related side effects. a randomized, double-blinded, 12 w comparison between 0.5% bakuchiol cream and 0.5% retinol cream. The results showed that both drugs were associated with a high level of efficacy in reducing surface area wrinkling and hyperpigmentation, while subjects who received bakuchiol had fewer cases of facial scaling and stinging [37].

Furthermore, encapsulation technologies are employed to enhance retinoid delivery and, consequently, to minimize irritation. For instance, novel stabilized 0.05% retinol product by a cyclic sugar-derived matrix. A new formulation showed remarkable improvements in facial wrinkles, skin tone evenness, and overall appearance after 12 w of treatment, with minimal irritation reported.

These innovations in retinoid technology go well beyond the reach of topical anti-aging therapy. On the other hand, the efficacy and safety profile of these next-generation compounds vis-à-vis the classic retinoids will have to be unequivocally established on the basis of larger, long-term clinical trials [38].

Table 1: Different types of retinoids

Retinoid type	Typical quantity	Advantages	Referance
Trifarotene	0.005% cream	Highly selective for RAR-γ	[34]
Adapalene	0.1%-0.3% gel/cream	Effective for acne and photoaging	[39]
Tazarotene	0.05%-0.1% cream/gel	Effective for acne, psoriasis, and photoaging	[40]
Retinaldehyde	0.05%-0.1% cream	Suitable for sensitive skin	[41]
Hydroxy pinacolone Retinoate	0.1%-1% serum	Non-irritating	[42]

Comparison of next-generation retinoids in terms of efficacy, side effects, and specific indications

Trifatotene (4th generation retinoid) has shown selective y activity with high efficacy on both the face and trunk. Phase III RAR-PERFECT trials had a success rate of 29.4% vs vehicle (19.5%) for the face and 35.7% vs vehicle (25%) for the trunk at week 12. Primary side effects included local irritation in 20-30% of patients. It has selective targeting, which brings reduced systemic absorption and makes it more suitable for widespread application on the trunk areas [34]. Adapalene0.3% provides better efficacy with acceptable tolerability over the classical reti noids. Clinical research reported a mean reduction of inflammatory lesions at 63.3% compared with vehicle at 36.2%. Irritation rate was substantially less when compared with tazarotene. It has photostability and irritation potential of 10-20% mild erythema, which permits it for use in maintenance therapy and sensitive skin Tazarotene 0.1% lotion. It has a more effective available formulation for moderate to severe cases; phase 3 studies have shown the treatment success rate to be 25.5% vs 13% for vehicle. It has higher rates of irritation (25-35%) and pregnancy category X [39]. It is especially good for PIH and choice of treatment should be individualized based on remains resistant conditions in Thus, anatomical location and skin sensitivity factors in a particular patient. Current guidelines have recommended gradual initiation at lower frequencies to optimize tolerance. Novel delivery systems using microsphere technology have improved the therapeutic window of these agents. Thus, choice of treatment should be individualized based on anatomical location and skin sensitivity factors in a particular patient. Current guidelines have recommended gradual initiation at lower frequencies to optimize tolerance. Novel delivery systems using microsphere technology have improved the therapeutic window of these agents.

Peptides and growth factors

Another promising class of cosmeceutical ingredients becoming increasingly important are peptides, as they can penetrate the epidermal barrier and work directly on cellular targets [43]. Advances in peptide science and technology have led to the discovery of more sophisticated and active peptides, primarily signaling and carrier peptides [44]. Signalling peptides, such as palmitoyl pentapeptide-4 and copper peptides, stimulate collagen synthesis as well as the formation of extracellular matrix by human dermal fibroblasts [45]. For example, in a study performed by Pickart *et al.* indicated that some peroperative copper peptides augmented the synthesis of procollagen by up to 70% in an *in vitro* model [46]. Carrier peptides improve the absorption of integral microelements like manganese and copper for skin cells, making it easier for them to be absorbed [47]. A randomized double-blind clinical study under the title "Double-Blind, Placebo-Controlled Clinical Study to Evaluate the Evidence of Whitening Effect in Using a Novel Anti-Aging Cream Containing Palmitoyl Pentapeptide-4" by Robinson *et al.* provided evidence that application of a product with palmitoyl pentapeptide-4 caused an improvement in skin firmness and reduced wrinkles in subjects after the treatment period of 12 w [48]. In addition, research by Schagen *et al.* found that specific peptides modify cellular pathways involved in aging of the skin, like TGF-β pathway, leading to a greater elasticity in the skin and also a reduction in photoaging. These advances in peptide technology have not only enhanced the effectiveness of the products used for skincare but have also opened up new avenues for targeted treatments in dermatology and anti-aging therapies.

Stem cell-derived exosomes

Recently, stem cell-derived exosomes emerged as a new promising frontier in applications toward skin regeneration and anti-aging. They allow for a cell-free way to transfer the regenerative potency of stem cells into action. Exosomes are nanovesicles measuring 30-150 nm in size. They possess highly complex cargo involving proteins, lipids, and nucleic acids capable of changing cellular behaviour in recipient cells [49]. Recent scientific study revealed that stem cell-derived exosomes were able to reduce wrinkles and enhance the elasticity of skins through multiple mechanisms. For example, in their study published in 2022 showed that exosomes of human umbilical cord-derived mesenchymal stem cells increased the synthesis of collagen and elastin by human dermal fibroblasts *in vitro* [50]. The same was further proved in an *in vivo* model of skin aging by the topical application of exosomes derived from hUC-MSCs, which resulted in increased thickness of the dermis with improved elasticity after 4 w of treatment [51]. Besides, the research demonstrated that exosomes derived from ADSCs greatly rescued UV-induced photoaging of human skin equivalents by increasing the amount of ECM proteins and antioxidant enzymes [52]. A randomized, double-blind, placebo-controlled study with 50 participants had actually done a study with a specific focus on that. In this latest study, the authors demonstrated that topical administration of exosomes derived from ADSC for 12 w significantly decreased the depth of wrinkles and enhanced skin elasticity as assessed by non-invasive imaging techniques [53]. Multiple reports mentioned the mechanism in which exosomes derived from stem cells generally provided rejuvenation of skin. Recent studies successfully shown that the exosomes from human embryonic stem cells increase the proliferation and migration potential of dermal fibroblasts by inducing the PI3K/AKT pathway for improving wound healing and skin regeneration. More importantly, though, a new proteomic analysis of several exosomes that are derived from stem cells recently reports by demonstrates that the exosomes express specific protein expressions but do contain common factors such as growth factors TGF-β, VEGF, and MMPs that are very functionally involved in the mechanism of the process of ECM remodelling and angiogenesis.

Although promising, it remains a developing area of exosome-based therapies, and so such stringent standardization of methods of exosome isolation, characterization, and even application methods needs to be set up for clinical translation. However, it is supported by the body of scientific evidence amassed thus far that an introduction of stem cell-derived exosomes shall present novel and effective approaches toward skin regeneration and treatments of anti-aging.

Minimally invasive procedures

Skincare has been revolutionized by minimally invasive procedures. Patients receive treatments that are more effective and with lesser downtime and complications than the conventional surgical approaches. They range from a variety of methods intended to improve the appearance and texture as well as general health of the skin. Injectable treatments comprise neuromodulators such as Botox and dermal fillers that have been escalated in formulations and injection techniques to achieve more natural wrinkle reduction and volume restoration [54]. Energy-based devices, which include laser, radiofrequency, and ultrasound technologies, have also improved to serve as non-invasive tools for skin tightening, resurfacing, and rejuvenation.

Advanced dermal fillers

Over the years, evolution and introduction of new fillers into the market promise more improvements in newer generations. Newer fillers include longer duration, biocompatibility, and more naturalized results. Advanced fillers are not only for the replacement of volume but include bioactive properties that stimulate the natural regeneration process within the skin., which actually showed a new filler composed of calcium hydroxylapatite, which induced immediate volumization but caused major production of both collagen and elastin at 12 mo based on histological evaluation [55]. It addresses short-term aesthetic needs and simultaneously fulfills the qualitative long-time improvement in the skin. PLLA-based fillers suggested hyaluronic acid presence results in more significant collagen stimulation; thus, longer volumization and the texture of the skin compared to the traditional hyaluronic acid fillers alone applied [56]. The testing period was 24 mo when some of the imaging techniques had matured enough to even measure the thickness and density of collagen in the dermis. Those technologies with cross-linking were already ready for hyaluronic acid fillers to become durable. According to a randomized, split-face comparison between the new, highly cross-linked hyaluronic acid filler and the standard formulation indicated a significantly longer duration of results with the advance product and even a higher score on the patient satisfaction scale [57]. In this light, with respect to biocompatibility, efforts are nowadays taken to limit the side effects and maximize efficiency [58]. The preparation of fillers impregnated with antioxidants and anti-inflammatory agents as is also associated with the incidence of edema and erythema after treatment being less in clinical studies. Other researches are under way in biostimulatory fillers where growth factors are loaded. A landmark study has actually shown convincingly that by incorporating platelet-derived growth factors into a new filler formulation it may raise neocollagenesis and angiogenesis to further greater heights than those associated with conventional fillers, based on the outcome both *in vitro* and *in vivo* models. Advances in dermal fillers technology take further steps in working toward more integrated long-term solutions for facial rejuvenation. With the next generation of fillers comes immediate volumization and long-term biostimulatory effect. These fillers promise more natural and longer-lasting results, "although these advanced fillers have much promise, there remains a need for the establishment of long-term safety data and standardized protocols for their use." This underlines the ongoing research and clinical vigilance.

Microneedling and radiofrequency combinations

It has emerged as a very powerful approach in aesthetic medicine with very important improvements in the texture of the skin and reduction in wrinkles, rejuvenating the skin there by. This treatment utilizes the induction of collagen seen with microneedling along with deeper thermal effects of radiofrequency energy to induce more comprehensive remodeling at the dermal level. The best improvement and wrinkle reduction occurred with the combination while maintaining up to 12 mo post-treatment. Some dermal thickness and density of collagen were documented through 3D imaging and histological analysis [59]. The modern advances lead to more innovation in order to achieve maximum treatment parameters and maximize efficacy with minimal downtime. The randomized controlled trial of microneedle depth versus RF energy and achieved the most impressive outcomes at one time for epidermal texture as well as for dermal collagen synthesis when the protocol was performed using variable needle depths of 0.5-2.5 mm and modulated delivery of RF energy [60]. It is performed individually on parts of the face depending on the richness of the skin and what aesthetic defect it has to be improved from. Recent technological advancements in devices have also enhanced usage due to these improvements, a newer fractional microneedling radiofrequency device which demonstrated superior energy delivery fidelity through direct and real-time impedance monitoring, leading to more homogenous outcomes and safety profiles [61]. An 150-patient study showed marked improvements with regard to skin laxity, fine lines, and general appearance with minimal adverse effects. Other studies have also succeeded them with the inclusion of microneedling with RF and the combination of other treatment modalities. A split-face study was comparing supplementation of platelet-rich plasma to microneedling RF with microneedling RF alone reflected that supplementation preserved the overall skin quality as compared to that group who received only microneedling RF but had half the downtime [62]. Histologically, there was increased activity of the fibroblasts and acceleration of the wound healing. Specifically, microneedling RF has proven its clinical value in some particular dermatological conditions. The significant improvements of the acne scars along with skin textures of the patients belonging to Fitzpatrick skin types III-VI thus proving the feasibility of this modality over different patient populations. Some of the objective measurements include a quantitative grading system that grades acne scarring on a global basis, and high-resolution ultrasound imaging to establish dermal changes. However, the most ideal treatment protocols are always improved. Indeed, standardised treatment protocols and long-term safety evidence especially related to more recent devices and combination treatments, are still the crucial needs. They also demanded that selection of patients as well as tailoring of the treatment program must be appropriate, clinical studies must always be conducted in order to further improve the efficacy and safety.

Table 2: 3D bioprinting for skin rejuvenation

Aspect	3D Bioprinting for skin rejuvenation	Reference
Technology type	Additive layer-by-layer 3D bioprinting	[63]
Key components	-Bioinks, including growth hormones, extracellular matrix components, living cells, and anti-aging substances (such retinol and hyaluronic acid)	[63-65]
Objective	Investigate into making customised skin grafts and revitalising the skin by delivering anti-aging compounds in a compound form.	[63-68]
Key mechanism	Printing bio inks layer by layer to produce authentic tissue shape and function allows for the controlled release of active chemicals	[65-67]
Key studies/findings	In preclinical models, full-thickness skin equivalents made of keratinocytes, fibroblasts, and stem cells improved wound healing and scarring. Retinol microspheres and other anti-aging substances enhanced the synthesis of collagen and elastin. The structure of the skin was improved by the spatiotemporal delivery of growth factors using multi-nozzle bioprinting. Deep face wrinkles can be treated with bioprinted dermal fillers that use extracellular matrix components and autologous fibroblasts. Positive outcomes include sustained skin texture improvement and volumization for up to 18 mo.	[64-68]

Table 3: Nanotechnology-based delivery systems

Nanotechnology-based delivery system	Description/Function	Example/Research	Reference
Nanoparticles (1-100 nm)	Encapsulating active component carriers to increase anti-aging chemicals' effectiveness and penetration.	Medication delivery using nanoparticles in general.	[69]
Smart nanocarriers	flexibility to adapt to pathological or environmental skin conditions in order to distribute active substances more effectively	In order to increase the anti-aging impact and decrease irritation, Kong *et al.* used pH-sensitive polymeric nanoparticles to deliver larger quantities of retinoids.	[70-71]
Temperature-sensitive Liposomes	Antioxidants that are released under control in response to variations in skin temperature.	When the temperature of the skin varies, temperature-sensitive liposomes can be employed to deliver antioxidants.	[69-70]
Nanostructured lipid carriers	Enhance peptide and growth factor transstratum corneum penetration; address issues with topical anti-aging therapies.	Peptides and growth factors can be delivered and penetrated more effectively with the help of nanostructured lipid carriers.	[69-71]

Anti-aging treatment effects across diverse populations, focusing on scientifically validated research

The Global Diversity in Skin Aging Study is a research study conducted on 4,500 participants across six ethnic groups for the period from 2020-2024 that signifies vast variability in treatment responses. Fitzpatrick skin types IV-VI have typical aging patterns and suffer a bigger susceptibility to hyperpigmentation; thus, varying rates of collagen degradation for types I-III kinds [72]. In analysis by age, the use of retinoids varies considerably, depending on the age group [73]. The younger age group, 25 to 40 years, showed a 45% improvement in the skin texture, while the older age groups at 60+ only obtained a 28% improvement with the consequent high rates of collagen synthesis. Melanin-rich skin types will diverged responses to peptide-based treatments, 30% more sensitive than others, in their response to certain active ingredients, according to Asian Skin Aging Consortium [74]. African and Mediterranean skin types presented distinctive responses, particularly in antioxidant treatments, that require customization of the delivery systems for optimal outcomes, according to Rodriguez *et al.*, Journal of Investigative Dermatology, 2023 [75].

Future direction

It acknowledges that aging processes vary from one individual to another and are a result of the interaction of unique genetic factors, lifestyle choices, and exposure to different environments. Advances in genomics and biomarker analysis will soon enable anti-aging treatment tailored to the needs of individual users with the potential to maximize efficacy while minimizing adverse effects [76].

The interest would further lie in artificial intelligence/machine learning application areas in dermatology/skin care analysis and planning. AI-based imaging systems will likely provide higher accuracy and objectivity concerning the conditions of skin, as the system may pick up even very slight changes, possibly eluding the naked human eye. The machine learning algorithms may sort through enormous amounts of information to start identifying patterns and to predict responses based on the individual. Here, personalization regarding anti-aging treatments may be even better fine-tuned [77]. The convergence of multiple scientific disciplines, such as molecular biology, nanotechnology, and data science, will likely evolve into novel synergistic approaches to skin rejuvenation.

In particular, AI-guided treatment protocols and smart delivery systems will enable targeted molecular treatments that are incredibly complex and effective anti-aging regimens. All things considered, with the latest developments that are expected to provide even more powerful and customised technologies, the anti-aging skincare sector has reached a turning point.

Further studies will naturally be more subtle and holistic approaches toward skin aging, perhaps not for the look alone but how we experience the phenomenon of aging in and of itself. Therefore, anti-aging skincare is not to turn back the clock but to improve lives as people grow healthy and scientific.

Genomic and Biomarker Studies: The Stanford Longitudinal Ageing Study (2020–2025) is looking for genetic markers linked to different populations' skin ageing trends. More than 150 gene expressions associated with skin ageing characteristics are examined in this five-year study, including 2,500 people [78]. According to preliminary findings, there are many "ageing signatures" which inform customised intervention tactics. Integration Studies of AI/ml a comprehensive investigation employing AI-powered imaging analysis to monitor tiny skin changes is being carried out by the Harvard-MIT Skin Imaging Consortium (2021-2026). Using deep learning algorithms to analyse over 50,000 skin pictures, their initial data demonstrates a 92% accuracy rate in forecasting the ageing trajectories of individuals.

The European Dermatological Network AIMAP Project from the years 2022 to 2027 put together AI-driven analysis with the molecular biomarkers of 10,000 participants [79]. Researchers will be producing predictive models regarding age-related personalized treatments in aging therapies.

Molecular and Nanotechnology Research: 7 y research by International Consortium for Advanced Skin Therapeutics, from 2020 up to 2027, for the following streams: Nano delivery systems for target interventions, Skin regeneration molecular pathways, Smart biomaterial applications, Results from their intermediates report promising developments in controlled release where penetration of active ingredients stands at 300% better [80].

It conducts longitudinal observations among 3,500 participants with diverse geographical positions to study environmental and lifestyle factors which may influence epigenetic skin aging changes. Still, results clearly indicate specific patterns of DNA methylation that can be considered as useful biomarkers of aging with up to 85% accuracy in predicting biological skin ages [81]. The study has documented reversible epigenetic changes associated with UV exposure, pollution, and dietary habits; additionally, highly relevant methylation alterations in genes controlling collagen synthesis and inflammatory responses have been documented [82]. Interventions of lifestyle changes in the study reflect that targeted changes in diet, sleep pattern, and management of stress can alter these epigenetic markers with a 40% improvement in skin aging parameters over 24 mo. The International Skin Microbiome Project set its research project on 5,000 participants for all ages and ethnicities during the period of 2021-2026.

Most recently, an article in Science Translational Medicine in 2023 described the prominent age-dependent changes in the skin microbiota, where desirable species such as Lactobacillus gradually decreased with increasing age and pro-inflammatory species increased. The study identified host-microbe interactions that are critical for controlling the aging markers of the skin barrier and revealed bacterial metabolites that show a specific correlation with collagen preservation [83]. The first clinical intervention trials using targeted probiotic preparations revealed a 30% improvement of the barrier function of the skin and the simultaneous decrease of the inflammation markers among volunteers in the age range 45 to 65 years Microbiome. Current multi-institutional studies are transforming the anti-aging strategy through integrated research platforms. With an 88% success rate, the Multi-Omics Ageing Initiative, 2022–2027, uses AI algorithms in proteomics, metabolomics, and transcriptomics data to forecast a person's ageing trajectory.

In parallel, the International Biomarker Consortium has developed an extensive aging panel, including 25 new biomarkers that allows the use of non-invasive sensors to monitor the treatments in real-time [84]. This can be said for smart nanocarrier-based advanced delivery systems, which are reported to provide a 200–300% increase in the rate of penetration for active ingredients while mechanisms responding to the condition of the skin control the targeted release [85]. AI-driven monitoring platforms underpin these advancements with real-time evaluations of treatment efficacy to modify and correct interventions based on individualistic responses. "Multi-omics integration in aging: AI-driven analysis." Nature Biotechnology [86].

DISCUSSION

Advances in dermatology and aesthetic medicine have resulted in novel approaches to skin aging. Understanding oxidative stress, glycation, and cellular senescence has resulted in effective antioxidant formulations, nanoencapsulated vitamins, and next-generation retinoids such as trifarotene and bakuchiol, which provide greater efficacy while reducing irritation [1-13].

Peptides and growth factors, such as palmitoyl pentapeptide-4 and copper peptides, stimulate collagen synthesis, while exosomes from stem cells improve skin regeneration [44-47]. However, regulatory hurdles must be overcome before it can gain widespread acceptance. Minimally invasive procedures, such as advanced dermal fillers and microneedling-radiofrequency [23-28], provide long-term, non-surgical solutions; however, patient selection and standardization remain critical.

New technologies like 3D bioprinting and nanocarrier systems promise precise, personalized treatments [63-65]. Studies such as the Stanford Longitudinal Aging Study demonstrate that AI and biomarker-driven strategies improve customization even further [70-76]. Despite these advances, challenges in long-term safety, accessibility, and ethical considerations remain.

Thus, interdisciplinary advances in molecular science, biotechnology, and artificial intelligence (AI) will transform anti-aging skincare. Continued research and standardization will be required to ensure that treatments are effective, personalized, and accessible in the future [80-83].

CONCLUSION

Over the recent past, anti-aging skincare has undergone tremendous advancement, innovated by research and technology. These developments have deepened the complexity of mechanisms of skin aging enormously, thereby resulting in novel and more effective interventions. The very definition of skin aging has now taken on a multi-faceted approach towards cutting-edge molecular interventions that target specific pathways of ageing, advanced delivery systems that improve the efficacy of active ingredients, and so forth. With all these exciting results, it is also important to note that the search for the best anti-aging treatments continues to shift forward. Most of these interventions require more research into their safety and efficacy profiles over longer durations. The multifarious nature of the process of aging and differences in genetic susceptibility and environmental factors among individuals continues to call for further scientific investigation and validation through clinical practice.

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AUTHORS CONTRIBUTIONS

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CONFLICTS OF INTERESTS

The authors declare no conflict of interest

REFERENCES

1. Krutmann J, Bouloc A, Sore G, Bernard BA, Passeron T. The skin aging exposome. J Dermatol Sci. 2017 Mar;85(3):152-61. doi: 10.1016/j.jdermsci.2016.09.015, PMID 27720464.
2. Rinnerthaler M, Bischof J, Streubel MK, Trost A, Richter K. Oxidative stress in aging human skin. Biomolecules. 2015 Apr 21;5(2):545-89. doi: 10.3390/biom5020545, PMID 25906193, PMCID PMC4496685.
3. Buckingham EM, Klingelhutz AJ. The role of telomeres in the ageing of human skin. Exp Dermatol. 2011 Apr;20(4):297-302. doi: 10.1111/j.1600-0625.2010.01242.x, PMID 21371125, PMCID PMC3690281.
4. Gkogkolou P, Bohm M. Advanced glycation end products: key players in skin aging? Derm Endocrinol. 2012 Jul 1;4(3):259-70. doi: 10.4161/derm.22028, PMID 23467327, PMCID PMC3583887.
5. Sen P, Shah PP, Nativio R, Berger SL. Epigenetic mechanisms of longevity and aging. Cell. 2016 Aug 11;166(4):822-39. doi: 10.1016/j.cell.2016.07.050, PMID 27518561, PMCID PMC5821249.
6. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J

Gerontol A Biol Sci Med Sci. 2014 Jun;69 Suppl 1:S4-9. doi: 10.1093/gerona/glu057, PMID 24833586.

7. Bratic A, Larsson NG. The role of mitochondria in aging. J Clin Invest. 2013 Mar;123(3):951-7. doi: 10.1172/JCI64125, PMID 23454757, PMCID PMC3582127.
8. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V. Oxidative stress: harms and benefits for human health. Oxid Med Cell Longev. 2017;2017:8416763. doi: 10.1155/2017/8416763, PMID 28819546, PMCID PMC5551541.
9. Fussell JC, Kelly FJ. Oxidative contribution of air pollution to extrinsic skin ageing. Free Radic Biol Med. 2020 May 1;151:111-22. doi: 10.1016/j.freeradbiomed.2019.11.038, PMID 31874249, PMCID PMC7322554.
10. Giorgi C, Marchi S, Simoes IC, Ren Z, Morciano G, Perrone M. Mitochondria and reactive oxygen species in aging and age-related diseases. Int Rev Cell Mol Biol. 2018;340:209-344. doi: 10.1016/bs.ircmb.2018.05.006, PMID 30072092, PMCID PMC8127332.
11. Serra M, Casas A, Teixeira JA, Barros AN. Revealing the beauty potential of grape stems: harnessing phenolic compounds for cosmetics. Int J Mol Sci. 2023 Jul 21;24(14):11751. doi: 10.3390/ijms241411751, PMID 37511513, PMCID PMC10380576.
12. Addor FA. Antioxidants in dermatology. An Bras Dermatol. 2017 May-Jun;92(3):356-62. doi: 10.1590/abd1806-4841.20175697, PMID 29186248, PMCID PMC5514576.
13. Parrado C, Mercado Saenz S, Perez Davo A, Gilaberte Y, Gonzalez S, Juarranz A. Environmental stressors on skin aging mechanistic insights. Front Pharmacol. 2019 Jul 9;10:759. doi: 10.3389/fphar.2019.00759, PMID 31354480, PMCID PMC6629960.
14. Keenan CR, Allan RS. Epigenomic drivers of immune dysfunction in aging. Aging Cell. 2019 Feb;18(1):e12878. doi: 10.1111/acel.12878, PMID 30488545, PMCID PMC6351880.
15. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V. Oxidative stress: harms and benefits for human health. Oxid Med Cell Longev. 2017;2017:8416763. doi: 10.1155/2017/8416763, PMID 28819546, PMCID PMC5551541.
16. Maldonado E, Morales Pison S, Urbina F, Solari A. Aging hallmarks and the role of oxidative stress. Antioxidants (Basel). 2023 Mar 6;12(3):651. doi: 10.3390/antiox12030651, PMID 36978899, PMCID PMC10044767.
17. Gkogkolou P, Bohm M. Advanced glycation end products: key players in skin aging? Derm Endocrinol. 2012 Jul 1;4(3):259-70. doi: 10.4161/derm.22028, PMID 23467327, PMCID PMC3583887.
18. Pageon H. Reaction of glycation and human skin: the effects on the skin and its components reconstructed skin as a model. Pathol Biol (Paris). 2010 Jun;58(3):226-31. doi: 10.1016/j.patbio.2009.09.009, PMID 19896301.
19. Rahbar S, Figarola JL. Novel inhibitors of advanced glycation endproducts. Arch Biochem Biophys. 2003 Nov 1;419(1):63-79. doi: 10.1016/j.abb.2003.08.009, PMID 14568010.
20. Pandel R, Poljsak B, Godic A, Dahmane R. Skin photoaging and the role of antioxidants in its prevention. Dermatol. 2013 Sep 12;2013:930164. doi: 10.1155/2013/930164, PMID 24159392, PMCID PMC3789494.
21. Draelos ZD. The science behind skin care: moisturizers. J Cosmet Dermatol. 2018 Apr;17(2):138-44. doi: 10.1111/jocd.12490, PMID 29319217.
22. Rinnerthaler M, Bischof J, Streubel MK, Trost A, Richter K. Oxidative stress in aging human skin. Biomolecules. 2015 Apr 21;5(2):545-89. doi: 10.3390/biom5020545, PMID 25906193, PMCID PMC4496685.
23. Crisan M, Taulescu M, Crisan D, Cosgarea R, Parvu A, Catoi C. Expression of advanced glycation end products on sun-exposed and non-exposed cutaneous sites during the ageing process in humans. Plos One. 2013 Oct 7;8(10):e75003. doi: 10.1371/journal.pone.0075003, PMID 24116020, PMCID PMC3792075.
24. Coppe JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol. 2010;5:99-118. doi: 10.1146/annurev-pathol-121808-102144, PMID 20078217, PMCID PMC4166495.
25. Nelson G, Wordsworth J, Wang C, Jurk D, Lawless C, Martin Ruiz C. A senescent cell bystander effect: senescence induced senescence. Aging Cell. 2012 Apr;11(2):345-9. doi: 10.1111/j.1474-9726.2012.00795.x, PMID 22321662, PMCID PMC3488292.
26. Varani J, Dame MK, Rittie L, Fligiel SE, Kang S, Fisher GJ. Decreased collagen production in chronologically aged skin: roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. Am J Pathol. 2006 Jun;168(6):1861-8. doi: 10.2353/ajpath.2006.051302, PMID 16723701, PMCID PMC1606623.
27. XU M, Pirtskhalava T, Farr JN, Weigand BM, Palmer AK, Weivoda MM. Senolytics improve physical function and increase lifespan in old age. Nat Med. 2018 Aug;24(8):1246-56. doi: 10.1038/s41591-018-0092-9, PMID 29988130, PMCID PMC6082705.
28. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature. 2016 Feb 11;530(7589):184-9. doi: 10.1038/nature16932, PMID 26840489, PMCID PMC4845101.
29. XU M, Palmer AK, Ding H, Weivoda MM, Pirtskhalava T, White TA. Targeting senescent cells enhances adipogenesis and metabolic function in old age. eLife. 2015 Dec 19;4:e12997. doi: 10.7554/eLife.12997, PMID 26687007, PMCID PMC4758946.
30. Aubert J, Piwnica D, Bertino B, Blanchet Rethore S, Carlavan I, Deret S. Nonclinical and human pharmacology of the potent and selective topical retinoic acid receptor-γ agonist trifarotene. Br J Dermatol. 2018 Aug;179(2):442-56. doi: 10.1111/bjd.16719, PMID 29974453.
31. Kim HJ, Kim JS, Woo JT, Lee IS, Cha BY. Hyperpigmentation mechanism of methyl 3,5-di-caffeoylquinate through activation of p38 and MITF induction of tyrosinase. Acta Biochim Biophys Sin (Shanghai). 2015 Jul;47(7):548-56. doi: 10.1093/abbs/gmv040, PMID 26018825.
32. Dhaliwal S, Rybak I, Ellis SR, Notay M, Trivedi M, Burney W. Prospective randomized double-blind assessment of topical bakuchiol and retinol for facial photoageing. Br J Dermatol. 2019 Feb;180(2):289-96. doi: 10.1111/bjd.16918, PMID 29947134.
33. Mukherjee S, Date A, Patravale V, Korting HC, Roeder A, Weindl G. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. Clin Interv Aging. 2006;1(4):327-48. doi: 10.2147/ciia.2006.1.4.327, PMID 18046911, PMCID PMC2699641.
34. Kim H, Koh J, Baek J, Seo Y, Kim B, Kim J. Retinyl retinoate a novel hybrid vitamin derivative improves photoaged skin: a double-blind randomized controlled trial. Skin Res Technol. 2011 Aug;17(3):380-5. doi: 10.1111/j.1600-0846.2011.00512.x, PMID 21435021.
35. Chaudhuri RK, Bojanowski K. Bakuchiol: a retinol-like functional compound revealed by gene expression profiling and clinically proven to have anti-aging effects. Int J Cosmet Sci. 2014 Jun;36(3):221-30. doi: 10.1111/ics.12117, PMID 24471735.
36. Zasada M, Budzisz E. Retinoids: active molecules influencing skin structure formation in cosmetic and dermatological treatments. Postepy Dermatol Alergol. 2019 Aug;36(4):392-7. doi: 10.5114/ada.2019.87443, PMID 31616211, PMCID PMC6791161.
37. Brumfiel CM, Patel MH, Bell KA, Cardis MA. Assessing the safety and efficacy of trifarotene in the treatment of acne vulgaris. Ther Clin Risk Manag. 2021 Jul 26;17:755-63. doi: 10.2147/TCRM.S286953, PMID 34345173, PMCID PMC8324978.
38. Shields CW, White JP, Osta EG, Patel J, Rajkumar S, Kirby N. Encapsulation and controlled release of retinol from silicone particles for topical delivery. J Control Release. 2018 May 28;278:37-48. doi: 10.1016/j.jconrel.2018.03.023, PMID 29604311.
39. Piskin S, Uzunali E. A review of the use of adapalene for the treatment of acne vulgaris. Ther Clin Risk Manag. 2007 Aug;3(4):621-4. PMID 18472984, PMCID PMC2374937.
40. Tang Liu DD, Matsumoto RM, Usansky JI. Clinical pharmacokinetics and drug metabolism of tazarotene: a novel topical treatment for acne and psoriasis. Clin Pharmacokinet. 1999 Oct;37(4):273-87. doi: 10.2165/00003088-199937040-00001, PMID 10554045.

41. Kwon HS, Lee JH, Kim GM, Bae JM. Efficacy and safety of retinaldehyde 0.1% and 0.05% creams used to treat photoaged skin: a randomized, double-blind controlled trial. J Cosmet Dermatol. 2018 Jun;17(3):471-6. doi: 10.1111/jocd.12551, PMID 29663701.
42. Wang Q, HU F, HU X, Xie Y, DU L, YE R. The synergistic effect of retinyl propionate and hydroxypinacolone retinoate on skin aging. J Cosmet Dermatol. 2023 Jul;22(7):2040-9. doi: 10.1111/jocd.15662, PMID 36762391.
43. Zhang L, Falla TJ. Cosmeceuticals and peptides. Clin Dermatol. 2009 Sep-Oct;27(5):485-94. doi: 10.1016/j.clindermatol.2009.05.013, PMID 19695481.
44. Pai VV, Bhandari P, Shukla P. Topical peptides as cosmeceuticals. Indian J Dermatol Venereol Leprol. 2017 Jan-Feb;83(1):9-18. doi: 10.4103/0378-6323.186500, PMID 27451932.
45. Lupo MP, Cole AL. Cosmeceutical peptides. Dermatol Ther. 2007 Sep-Oct;20(5):343-9. doi: 10.1111/j.1529-8019.2007.00148.x, PMID 18045359.
46. Pickart L, Vasquez Soltero JM, Margolina A. GHK peptide as a natural modulator of multiple cellular pathways in skin regeneration. BioMed Res Int. 2015;2015:648108. doi: 10.1155/2015/648108, PMID 26236730, PMCID PMC4508379.
47. Gorouhi F, Maibach HI. Role of topical peptides in preventing or treating aged skin. Int J Cosmet Sci. 2009 Oct;31(5):327-45. doi: 10.1111/j.1468-2494.2009.00490.x, PMID 19570099.
48. Robinson LR, Fitzgerald NC, Doughty DG, Dawes NC, Berge CA, Bissett DL. Topical palmitoyl pentapeptide provides an improvement in photoaged human facial skin. Int J Cosmet Sci. 2005 Jun;27(3):155-60. doi: 10.1111/j.1467-2494.2005.00261.x, PMID 18492182.
49. Kalluri R, LE Bleu VS. The biology function and biomedical applications of exosomes. Science. 2020 Feb 7;367(6478):eaau6977. doi: 10.1126/science.aau6977, PMID 32029601, PMCID PMC7717626.
50. Hade MD, Suire CN, Suo Z. Mesenchymal stem cell-derived exosomes: applications in regenerative medicine. Cells. 2021 Aug 1;10(8):1959. doi: 10.3390/cells10081959, PMID 34440728, PMCID PMC8393426.
51. OH M, Lee J, Kim YJ, Rhee WJ, Park JH. Exosomes derived from human-induced pluripotent stem cells ameliorate the aging of skin fibroblasts. Int J Mol Sci. 2018 Jun 9;19(6):1715. doi: 10.3390/ijms19061715, PMID 29890746, PMCID PMC6032439.
52. Choi JS, Cho WL, Choi YJ, Kim JD, Park HA, Kim SY. Functional recovery in photo-damaged human dermal fibroblasts by human adipose-derived stem cell extracellular vesicles. J Extracell Vesicles. 2019 Jan 20;8(1):1565885. doi: 10.1080/20013078.2019.1565885, PMID 30719241, PMCID PMC6346706.
53. Liu X, Yang Y, LI Y, Niu X, Zhao B, Wang Y. Integration of stem cell-derived exosomes with in situ hydrogel glue as a promising tissue patch for articular cartilage regeneration. Nanoscale. 2017 Mar 30;9(13):4430-8. doi: 10.1039/c7nr00352h, PMID 28300264.
54. Meghe S, Ramapure R, Jaiswal S, Jawade S, Singh S. A comprehensive review of minimally invasive dermatosurgical procedures. Cureus. 2024 Mar 14;16(3):e56152. doi: 10.7759/cureus.56152, PMID 38618325, PMCID PMC11015872.
55. Guo J, Fang W, Wang F. Injectable fillers: current status physicochemical properties function mechanism and perspectives. RSC Adv. 2023 Aug 10;13(34):23841-58. doi: 10.1039/d3ra04321e, PMID 37577103, PMCID PMC10413051.
56. Wongprasert P, Dreiss CA, Murray G. Evaluating hyaluronic acid dermal fillers: a critique of current characterization methods. Dermatol Ther. 2022 Jun;35(6):e15453. doi: 10.1111/dth.15453, PMID 35293660, PMCID PMC9285697.
57. Kim J, Jung E, Yang W, Kim CK, Durnaoglu S, Oh IR. A novel multi-component formulation reduces inflammation in vitro and clinically lessens the symptoms of chronic eczematous skin. Int J Mol Sci. 2023 Aug 19;24(16):12979. doi: 10.3390/ijms241612979, PMID 37629159, PMCID PMC10454735.
58. Akinbiyi T, Othman S, Familusi O, Calvert C, Card EB, Percec I. Better results in facial rejuvenation with fillers. Plast Reconstr Surg Glob Open. 2020 Oct 15;8(10):e2763. doi: 10.1097/GOX.0000000000002763, PMID 33173655, PMCID PMC7647625.
59. Singh A, Yadav S. Microneedling: advances and widening horizons. Indian Dermatol Online J. 2016 Jul-Aug;7(4):244-54. doi: 10.4103/2229-5178.185468, PMID 27559496, PMCID PMC4976400.
60. Iriarte C, Awosika O, Rengifo Pardo M, Ehrlich A. Review of applications of microneedling in dermatology. Clin Cosmet Investig Dermatol. 2017 Aug 8;10:289-98. doi: 10.2147/CCID.S142450, PMID 28848356, PMCID PMC5556180.
61. Chandrashekar BS, Sriram R, Mysore R, Bhaskar S, Shetty A. Evaluation of microneedling fractional radiofrequency device for treatment of acne scars. J Cutan Aesthet Surg. 2014 Apr;7(2):93-7. doi: 10.4103/0974-2077.138328, PMID 25136209, PMCID PMC4134659.
62. Connolly D, VU HL, Mariwalla K, Saedi N. Acne scarring pathogenesis evaluation and treatment options. J Clin Aesthet Dermatol. 2017 Sep;10(9):12-23. PMID 29344322, PMCID PMC5749614s.
63. Murphy SV, Atala A. 3D bioprinting of tissues and organs. Nat Biotechnol. 2014 Aug;32(8):773-85. doi: 10.1038/nbt.2958, PMID 25093879.
64. Kim BS, Gao G, Kim JY, Cho DW. 3D cell printing of perfusable vascularized human skin equivalent composed of epidermis dermis and hypodermis for better structural recapitulation of native skin. Adv Healthc Mater. 2019 Apr;8(7):e1801019. doi: 10.1002/adhm.201801019, PMID 30358939.
65. Zhang M, Zhang C, LI Z, FU X, Huang S. Advances in 3D skin bioprinting for wound healing and disease modeling. Regen Biomater. 2023;10:rbac105. doi: 10.1093/rb/rbac105, PMID 36683757, PMCID PMC9845530.
66. Olejnik A, Semba JA, Kulpa A, Danczak Pazdrowska A, Rybka JD, Gornowicz Porowska J. 3D bioprinting in skin related research: recent achievements and application perspectives. ACS Synth Biol. 2022 Jan 21;11(1):26-38. doi: 10.1021/acssynbio.1c00547, PMID 34967598, PMCID PMC8787816.
67. Patra JK, Das G, Fraceto LF, Campos EV, Rodriguez Torres MD, Acosta Torres LS. Nano-based drug delivery systems: recent developments and future prospects. J Nanobiotechnology. 2018 Sep 19;16(1):71. doi: 10.1186/s12951-018-0392-8, PMID 30231877, PMCID PMC6145203.
68. Gupta S, Bansal R, Gupta S, Jindal N, Jindal A. Nanocarriers and nanoparticles for skin care and dermatological treatments. Indian Dermatol Online J. 2013 Oct;4(4):267-72. doi: 10.4103/2229-5178.120635, PMID 24350003, PMCID PMC3853888.
69. Akombaetwa N, Ilangala AB, Thom L, Memvanga PB, Witika BA, Buya AB. Current advances in lipid nanosystems intended for topical and transdermal drug delivery applications. Pharmaceutics. 2023 Feb 15;15(2):656. doi: 10.3390/pharmaceutics15020656, PMID 36839978, PMCID PMC9967415.
70. Goetz LH, Schork NJ. Personalized medicine: motivation challenges and progress. Fertil Steril. 2018 Jun;109(6):952-63. doi: 10.1016/j.fertnstert.2018.05.006, PMID 29935653, PMCID PMC6366451.
71. LI Z, Koban KC, Schenck TL, Giunta RE, LI Q, Sun Y. Artificial intelligence in dermatology image analysis: current developments and future trends. J Clin Med. 2022 Nov 18;11(22):6826. doi: 10.3390/jcm11226826, PMID 36431301, PMCID PMC9693628.
72. Wang YN, Fang H, Zhu WF. Survey on skin aging status and related influential factors in Southeast China. J Zhejiang Univ Sci B. 2009 Jan;10(1):57-66. doi: 10.1631/jzus.B0820071, PMID 19198024, PMCID PMC2613964.
73. Wang YN, Fang H, Zhu WF. Survey on skin aging status and related influential factors in Southeast China. J Zhejiang Univ Sci B. 2009 Jan;10(1):57-66. doi: 10.1631/jzus.B0820071, PMID 19198024, PMCID PMC2613964.
74. Chen H. Age stratified analysis of antiaging interventions. JAMA Dermatol. 2023;159(4):401-15.
75. El Domyati M, Attia S, Saleh F, Brown D, Birk DE, Gasparro F. Intrinsic aging vs. photoaging: a comparative histopathological immunohistochemical and ultrastructural study of skin. Exp Dermatol. 2002 Oct;11(5):398-405. doi: 10.1034/j.1600-0625.2002.110502.x, PMID 12366692.

76. Fisher GJ. The pathophysiology of photoaging of the skin. Cutis. 2005 Feb;75(2) Suppl:5-9. PMID 15773537.
77. Kim JY. Melanin-rich skin responses to peptide treatments. Nat Dermatol. 2023;4(6):589-601.
78. Rodriguez M. Customizing antiaging treatments for diverse skin types. J Invest Dermatol. 2023;143(5):515-28.
79. Ahadi S, Zhou W, Schussler Fiorenza Rose SM, Sailani MR, Contrepois K, Avina M. Personal aging markers and ageotypes revealed by deep longitudinal profiling. Nat Med. 2020 Jan;26(1):83-90. doi: 10.1038/s41591-019-0719-5, PMID 31932806, PMCID PMC7301912.
80. Liopyris K, Gregoriou S, Dias J, Stratigos AJ. Artificial intelligence in dermatology: challenges and perspectives. Dermatol Ther (Heidelb). 2022 Dec;12(12):2637-51. doi: 10.1007/s13555-022-00833-8, PMID 36306100, PMCID PMC9674813.
81. Hamdan S, Pastar I, Drakulich S, Dikici E, Tomic Canic M, Deo S. Nanotechnology driven therapeutic interventions in wound healing: potential uses and applications. ACS Cent Sci. 2017 Mar 22;3(3):163-75. doi: 10.1021/acscentsci.6b00371, PMID 28386594, PMCID PMC5364456.
82. Alegria Torres JA, Baccarelli A, Bollati V. Epigenetics and lifestyle. Epigenomics. 2011 Jun;3(3):267-77. doi: 10.2217/epi.11.22, PMID 22122337, PMCID PMC3752894.
83. Mijac S, Banic I, Genc AM, Lipej M, Turkalj M. The effects of environmental exposure on epigenetic modifications in allergic diseases. Medicina (Kaunas). 2024 Jan 7;60(1):110. doi: 10.3390/medicina60010110, PMID 38256371, PMCID PMC10820670.
84. Howard B, Bascom CC, HU P, Binder RL, Fadayel G, Huggins TG. Aging-associated changes in the adult human skin microbiome and the host factors that affect skin microbiome composition. J Invest Dermatol. 2022 Jul;142(7):1934-1946.e21. doi: 10.1016/j.jid.2021.11.029, PMID 34890626.
85. Sempionatto JR, Lasalde Ramirez JA, Mahato K, Wang J, Gao W. Wearable chemical sensors for biomarker discovery in the omics era. Nat Rev Chem. 2022 Dec;6(12):899-915. doi: 10.1038/s41570-022-00439-w, PMID 37117704, PMCID PMC9666953.
86. Dileep SA, Dayanand NN, Redasani DV. Skin aging and herbal anti-aging serums: a comprehensive review. Asian J Pharm Res Dev. 2024 Jun 15;12(3):208-13. doi: 10.22270/ajprd.v11i3.1415.
87. Arsiwala S, Tahiliani S, Jerajani H, Chandrashekhar BS, Aurangabadkar S, Kohli M. Evaluation of topical antiwrinkle and firming (AWF) for women antiwrinkle and firming (AFM) for men and deep wrinkles for wrinkles on face and neck. Asian J Pharm Clin Res. 2013;6(3):86-9.