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Recent Developments in Using Microneedle Patch Technology as a More Efficient Drug Delivery System for Treating Skin Photoaging

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Abstract: Skin photoaging, resulting from prolonged exposure to ultraviolet (UV) radiation, is characterized by intricate biological changes involving oxidative damage and structural alterations. Despite an increasing demand for effective interventions, the current therapeutic options for treating skin photoaging are limited. We discovered through literature data search on PubMed that recent research has shifted its focus to the application of microneedle patches as an innovative approach to address this concern. Microneedle patches, serving as a novel transdermal delivery system, exhibit the potential to deliver bioactive substances such as cytokines, cellular vesicles, gene fragments and even alive algae to mitigate the effects of skin photoaging. This review aims to provide a comprehensive overview of recent advancements in research about utilizing microneedle patches for the treatment of skin photoaging and potential future directions in leveraging microneedle patches as clinical therapeutic agents for skin rejuvenation. Ultimately, we believe that microneedle patches have a broader application prospect in the fields of medical cosmetology and anti-photoaging.

Keywords: skin photoaging, antioxidants, microneedle patch, transdermal delivery, skin rejuvenation

Introduction

The skin, as the body's largest protective organ, is vulnerable to a myriad of injuries resulting from genetic factors, lifestyle choices, nutrition, solar radiation, and environmental influences.[1,2] Notably, skin photoaging, a prominent manifestation of cutaneous aging, predominantly arises from chronic exposure to UV radiation.[3,4] With the improvement of people's living standard, people pay more and more attention to skin photoaging, and people urgently want to solve the aging caused by ultraviolet.

The aging process manifests in fine lines, wrinkles, pigmentation irregularities, and a reduction in skin elasticity.[4,5] Structural alterations in photoaged skin encompass the breakdown of collagen fibers, abnormal elastic fiber accumulation, and disruption of the epidermal barrier function.[6] Over the past decade, substantial progress has been made in understanding the molecular mechanisms of photoaging in human skin. The recruitment of cellular mechanisms in response to UV radiation-induced damage to skin connective tissue begins with the photochemical generation of reactive oxygen species (ROS).[4,7] UV-induced ROS also directly cause harmful chemical modifications to cellular components, including DNA, proteins, and lipids. The chemical oxidation of cellular components and the activation of cellular mechanisms induced by UV-induced oxidative stress collectively contribute to photoaging.[4,8,9]

Regarding the specific mechanisms, some studies suggest that UV radiation leads to the activation of cell surface cytokines and growth factor receptors.[10–12] In human skin, within 15 minutes after UV exposure (twice the minimal erythema dose), receptors for epidermal growth factor (EGF), interleukin (IL) 1, and tumor necrosis factor α (TNF-α) are activated.[13–15] The functional activation of these receptors requires stimulation of distinct tyrosine kinase activities. The activated kinases also upregulate the expression and functional activation of the nuclear transcription factor AP-1 (composed of Jun and Fos proteins).[16–18] This, in turn, stimulates the transcription of genes for matrix-degrading

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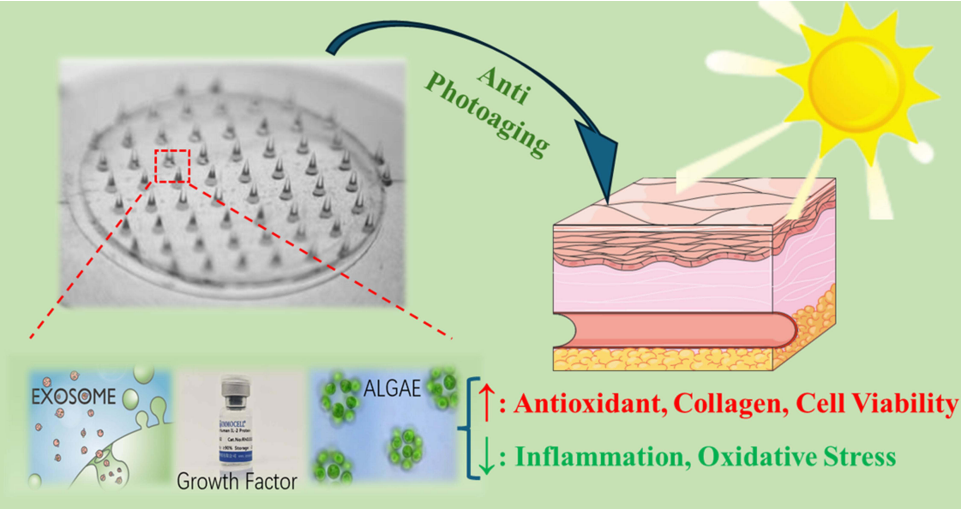
Graphical Abstract



enzymes such as metalloproteinase MMP 1 (collagenase), MMP-3 (stromelysin 1), and MMP-9 (92-kDa gelatinase).[12,19,20] UV-induced MMP-1 initiates the cleavage of fibrillar collagen (type I and III) at a single site within its central triple helix.[21] Therefore, anti-oxidation and promoting epidermal repair are the main two most effective ways to treat skin photoaging, which currently include topical retinoids, antioxidants, and laser therapies, but these methods often yield temporary results and side effects such as redness triggered by retinoids and damage caused by the laser, prompting exploration into innovative therapeutic strategies.[22–26]

Microneedle patch transdermal delivery systems have emerged as innovative tools with diverse applications in medical treatments (Figure 1). These patches utilize micro-sized needles to pierce the skin's outermost layer, creating

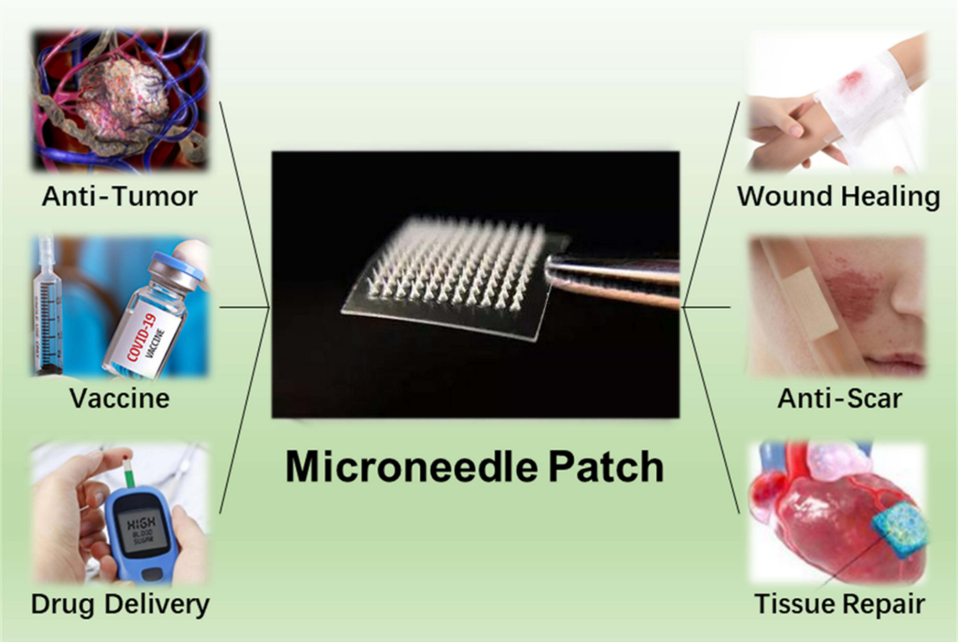


Figure 1 The applications of microneedle patches.

microchannels for the targeted delivery of therapeutic substances.[27–29] The versatility of microneedle patches extends to various medical fields, including skin tumor therapy, wound healing, and scar treatment.[29] Microneedle patches offer a promising approach in the treatment of skin tumors. By incorporating anti-cancer drugs, gene fragments, or other therapeutic agents onto the patch, it enables localized and controlled release directly into the tumor site.[27] This targeted delivery minimizes systemic exposure and enhances the efficacy of the treatment while reducing potential side effects. In wound care, microneedle patches play a crucial role in promoting efficient healing.[28] These patches can deliver growth factors, cytokines, or other bioactive substances directly to the wound site.[28] The controlled and sustained release of these substances accelerates cell migration, proliferation, and tissue regeneration, fostering a conducive environment for optimal wound healing.[29,30] Microneedle patches contribute to scar treatment by facilitating the delivery of therapeutic agents that promote collagen remodeling and reduce excessive scar formation.[29] As research in this field continues to advance, the potential applications of microneedle patches in dermatological treatments are expected to expand, providing innovative solutions for various skin-related conditions.

This review aims to provide a comprehensive overview of the latest research progress in utilizing microneedle patches for skin photoaging treatment with animal experimental models. The focus lies on the innovative use of microneedle patches in delivering various bioactive substances for skin photoaging treatment, ranging from cytokines and stem cell extractions to gene microcapsules and microalgae.

Microneedle Patch, an Ideal Transdermal Delivery System

Microneedle patch technology, as an innovative drug delivery system, has demonstrated immense potential and diverse applications in the field of medical health. In recent years, researchers have propelled the rapid development of microneedle patch technology across various therapeutic domains through innovative design and material selection.

In terms of transdermal drug delivery, microneedle patches leverage their minimally invasive nature to effectively penetrate the skin's surface layer, facilitating rapid drug absorption and release. For instance, the integration of flexible surface acoustic wave technology with microneedle patches has enhanced the transdermal delivery capability of macromolecular drugs.[31] Additionally, a lipid nanocapsule-microneedle array patch loaded with Fenretinide has provided a novel administration method for the chemoprevention of breast cancer, enhancing drug bioavailability by improving local drug distribution.[32] A proof-of-concept study has also successfully fabricated a three-layer dissolving microneedle (TDMN) to enhance the bioavailability and brain delivery of Rivastigmine, a drug for the treatment of Alzheimer's disease.[33]

In the treatment of specific diseases, microneedle patch technology has made significant progress. It has been combined with microneedle patches to improve the therapeutic effects of drugs for common diseases such as cancer,[32,34] Alzheimer's disease,[33] and skin wounds.[35–38] Beyond these conditions, for the issue of insomnia, researchers have developed a traditional Chinese medicine microneedle patch that optimizes microneedle design through finite element analysis, achieving effective drug delivery and improved sleep effects.[39] In the field of obesity treatment, researchers have reported a rapidly adhering, water-soluble nanoparticle microneedle patch composed of a soluble hyaluronic acid microneedle matrix and weakly acidic, degradable Rosiglitazone nanoparticles.[40] This patch has shown significant weight loss effects in a mouse model without affecting skin integrity, offering a suitable weight loss method for working populations. In the treatment of gout, a milestone study has developed a new dissolvable microneedle system encapsulating ethosomal formulations of Colchicine and Iguratimod for the treatment of recurrent gout.[41] In diabetes management, a bilayer hydrogel microneedle patch based on polyvinyl alcohol and carboxymethyl chitosan has enabled rapid detection of blood glucose levels through in situ colorimetric analysis.[42] Additionally, a painless, soft microneedle sensing patch has been developed to achieve on-site, accurate, and continuous glucose monitoring through a high mechanical strength microneedle base and thin-layer fluorescent hydrogel sensor. This patch utilizes a Förster Resonance Energy Transfer (FRET)-based hydrogel sensor, prepared through a simple photopolymerization reaction, characterized by reversibility, high selectivity, and signal stability against photobleaching. Research results indicate that this microneedle sensor can continuously monitor hypoglycemia, normoglycemia, and hyperglycemia on a porcine skin model for up to 6 hours, providing a powerful tool for continuous diabetes monitoring.[43]

Some microneedle patches have adopted biomimetic designs or more complex responsive therapies. For example, a microneedle patch inspired by the mouthparts of mosquitoes has been developed for local anesthesia in ophthalmic

surgery. This patch, composed of polyvinylpyrrolidone (PVP) and hyaluronic acid (HA), can rapidly dissolve and release Lidocaine, achieving effective ocular anesthesia.[44] Another study designed a novel double-barbed microneedle for the treatment of tendinopathy. This microneedle is loaded with nanocapsules containing the JAK/STAT inhibitor WP1066, promoting the self-renewal, migration, and stemness of tenocyte stem/progenitor cells (TSPCs), thereby improving symptoms of tendinopathy.[45] A study has also designed a new core-shell microneedle (CSMN) patch for the sequential delivery of Tannic Acid-Magnesium (TA-Mg) complex and extracellular vesicles from Lactobacillus druckerii (LDEVs). When applied to the site of infection, this CSMN@TA-Mg/LDEV patch first releases TA-Mg to combat pathogen overload and reduce reactive oxygen species (ROS), facilitating the transition to the proliferative phase. Subsequently, the sustained release of LDEVs enhances the activity of keratinocytes and fibroblasts, promotes vascularization, and regulates collagen deposition.[37]

These research findings not only reflect the high innovation and adaptability of microneedle patch technology but also provide new solutions for clinical treatment. With the continuous advancement in fields such as material science, bioengineering, and nanotechnology, microneedle patch technology is expected to play an increasingly important role in the medical health field in the future.

Microneedle Patch for Skin Photoaging Treatment

People have applied substances to the skin for therapeutic effects for thousands of years. Transdermal drug delivery plays an important role in medical practice, but its potential as an alternative to oral and subcutaneous administration has not been fully realized. In the clinical application of low-dose, lipophilic, and low-concentration drugs, the surface application of transdermal drug delivery systems has steadily increased.[46] However, in delivering biological macromolecules and vaccines such as insulin, parathyroid hormone, and influenza vaccine, there is yet to be an effective transdermal delivery method due to the large molecular size. One of the biggest challenges for transdermal delivery is the limited number of drugs that can be administered through this route. Under current delivery methods, successful transdermal drugs typically have a molecular weight of only a few hundred Daltons, with an octanol-water partition coefficient favoring lipids, and require daily doses of milligrams or less. Transdermal delivery of hydrophilic drugs, peptides and large molecules (such as DNA or small interfering RNA) presents special challenges.[47] As a result, microneedle technology has begun to attract the attention of researchers, who are trying to use this technology to achieve high-efficiency transdermal delivery of these difficult-to-deliver drugs.

Currently, the precaution or treatment of skin photoaging involves not only daily sun protection and the use of skincare products such as vitamin A derivatives, specifically retinol-based products, but also clinical cosmetic procedures. These include laser or radiofrequency treatments,[48] photodynamic therapy,[49] and the transdermal delivery of bioactive substances such as platelet-rich plasma (PRP) using microneedle rollers,[50] aiming to promote the repair of skin photoaging. Scholars are continually exploring more effective and convenient methods for the repair of skin photoaging, such as microneedle patches.

Microneedle Patches Deliver Extracellular Vesicles (EVs)

To further optimize drug delivery outcomes, researchers have explored the use of hydrogels in the preparation of microneedle patches. The team led by Xiuli Wang investigated the delivery of adipose-derived stem cell-derived extracellular vesicles (ADSC-EVs) to the skin using roller microneedles (MNs).[51] ADSCs-EVs have demonstrated immunomodulatory and anti-photoaging effects; however, the skin barrier prevents their absorption through the skin.[51–53] Therefore, attempts have been made to deliver EVs subcutaneously through MNs roller, which create tiny injuries initiating the wound healing process and also have a neocollagenesis effect.[51] SKH-1 mice were used to induce photoaging through chronic exposure to ultraviolet radiation, with different treatments applied on their backs. One side received either MN alone or MN + EVs treatment, while the other side remained untreated.[51] For the side treated with MN alone or MN + EVs, the epidermal thickness decreased, and the skin barrier function improved compared to the untreated side.[51] However, in the MN + EVs group, wrinkles were minimized, collagen density was maximized, and collagen fibers were more organized. On the 3rd day post-treatment, the level of $CD11b^+$ cell infiltration in the MN + EVs group was lower than that in the MN group.[51] These results suggest that MN treatment alone can enhance the

epidermal structure and function of photoaging skin and combining it with ADSCs-EVs accelerates the recovery from MN-induced inflammation and improves collagen content.[51] However, due to some usage restrictions and operational techniques associated with microneedle rollers, long-term use is not convenient. As a result, scholars have started exploring the use of microneedle patches to load EVs, and EVs can be artificially constructed as carriers for nucleic acids, including mRNA, siRNA, etc., for drug delivery.[54–56] To address the challenge of collagen's large molecular weight, some researchers turned to gene regulation akin to mRNA therapy. Lee et al combined EVs encapsulating mRNA encoding extracellular matrix α1 type-I collagen (COL1A1) with microneedle patches to treat skin photoaging in mice (Figure 2).[57] Through cellular nanoporation (CNP) technology, they constructed EVs carrying mRNA plasmids capable of expressing specific collagen proteins.[57] These COL1A1-EVs can efficiently transfect fibroblasts and promote the expression of collagen proteins.[57] When injected alone, it can effectively improve skin photoaging. However, when loaded onto microneedle patches, they can achieve a longer drug release time and more uniform drug release, resulting in a more pronounced therapeutic effect.[57]

Microneedle Patches Deliver Protein

In another approach, researchers focused on the extracellular matrix components of adipose tissue, purifying adipose collagen fragments (ACF) through physical methods. ACF is used as a dermal filler for filling skin depressions, it can release large amounts of adipokines such as adiponectin, transforming growth factor-β, fibroblast growth factor, and vascular endothelial growth factor.[58] These adipokines are involved in many biological processes, such as reducing oxidative stress,[59] improving fibroblast vitality,[60] and stimulating collagen synthesis and angiogenesis.[61] And research has demonstrated that ACF exhibit therapeutic effects on skin photoaging in a mouse model. However, skin aging is a continuous and irreversible physiological phenomenon, and this treatment requires repeated preparation processes and injection procedures, which may be time-consuming and painful.[62] The invasiveness and discomfort associated with the procedure greatly limit its clinical application and patient compliance. Therefore, they have developed a long-acting ACF-MN patch for transdermal drug delivery.[62] ACF-MN patches possess excellent skin puncture performance and can release ACF components slowly (Figure 3a).[62] Their results suggest that implantation of the microtrauma-mediated ACF-MN system could be utilized as a potential candidate for preventing skin photoaging with no risk of needle stick injury or

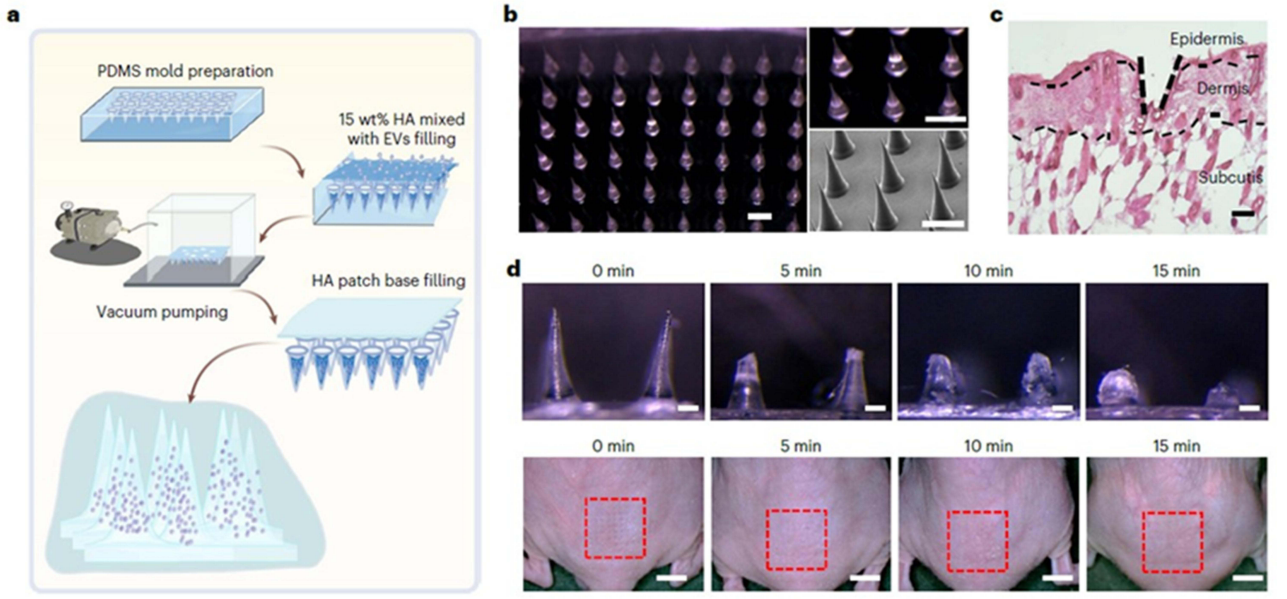


Figure 2 (**a**) A diagrammatic representation of the microneedle fabrication process is provided. (**b**) Visual representations of the microneedle array are captured through both optical and scanning electron microscopy. Scale bar, 500 μm. (**c**) A histological section of the mouse skin, stained with H&E, illustrates the penetration by a microneedle. Scale bar, 100 μm. (**d**) The upper part of the illustration tracks the dissolution of HA EV microneedle tips upon contact with the skin. Scale bar, 200 μm. The lower part depicts the skin's post-treatment recovery, exhibiting minimal irritation. Scale bars, 5 mm. Reproduced with permission of Springer Nature. You Y, Tian Y, Yang Z, et al. Intradermally delivered mRNA-encapsulating extracellular vesicles for collagen-replacement therapy. *Nat Biomed Eng*. 2023;7:887–900.[57]

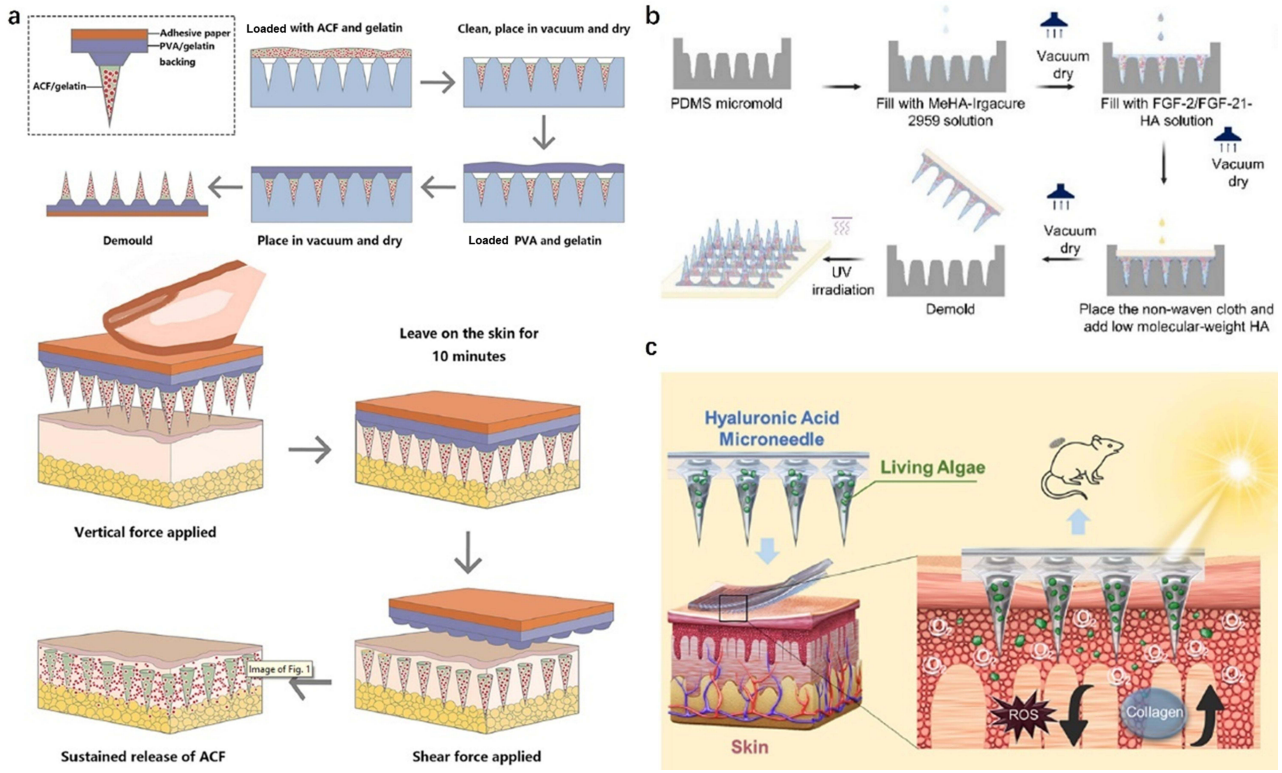


Figure 3 (**a**) Schematic of skin photoaging therapy through a detachable ACF-MN patch system. Used with permission of Elsevier Science & Technology Journals, from Long-acting microneedle patch loaded with adipose collagen fragment for preventing the skin photoaging in mice, Jin X, Zhang X, Li Y, et al, Vol 135, Copyright 2022; permission conveyed through Copyright Clearance Center, Inc.[62] (**b**) Fabrication and characterization of the HA-based dissolving FGF-2/FGF-21 MN patch. Reproduced with permission from Yang G, Hu S, Jiang H, Cheng K. Peelable microneedle patches deliver fibroblast growth factors to repair skin photoaging damage. *Nanotheranostics*. 2023;7(4):380–392.[63] (**c**) Microalgae MN supplies oxygen for antiphotoaging treatment. Reproduced with the permission from Wang Z, Kwong CHT, Zhao H, et al. Microalgae microneedle supplies oxygen for antiphotoaging treatment. *ACS Appl Bio Mater.* 2023;6(9):3463–347. Copyright 2023 American Chemical Society.[64]

cross-infection and low pain.[62] Therefore, this type of patch can be regarded as a novel, ACF-releasing MN patch and may be applied for skin rejuvenation applications in the clinic.

In addition to extracellular matrix proteins, some cytokine proteins can also be loaded into MN patches.[65,66] Researchers from China have also explored the incorporation of cytokines into microneedle patch systems. For instance, Ke Cheng et al loaded FGF-2 and FGF-21 into microneedle patches made from hyaluronic acid (HA) hydrogel, observing significant improvement after 4 weeks of treatment.[63] The fibroblast growth factor (FGF) family encompasses proteins that are structurally similar to heparin-binding proteins and play diverse roles, especially in wound healing and angiogenesis.[63] The FGF-2/FGF-21-loaded microneedle (FGF-2/FGF-21 MN) patch (Figure 3b) exhibited a consistent structure and suitable mechanical properties, facilitating easy insertion and penetration into mouse skin.[63] Within 10 minutes of application, the patch released approximately 38.50 ± 13.38% of the loaded drug. Notably, the FGF-2/FGF-21 microneedles demonstrated significant improvements in UV-induced acute skin inflammation and reduced mouse skin wrinkles within a span of two weeks.[63]

Microneedle Patch Deliver Single-Cell Organisms (Microalgae)

Beyond conventional bioactive substances, microneedle patches have shown potential in delivering single-cell organisms such as microalgae for skin photoaging treatment. Previous studies have indicated that dissolved oxygen can reverse photoaged skin; however, the treatment is often limited by the availability of equipment (eg, hyperbaric oxygen).[67] Insufficient diffusion of oxygen into the skin also restricts its therapeutic efficacy. Here, researchers developed a microneedle patch to deliver living microalgae Chlorella (GY-H60) to the deeper layers of mice skin for efficient oxygenation and reversal of photoaging (Figure 3c).[64] The continuous release of oxygen from microalgae in the skin through photosynthesis reversed the inflammatory microenvironment, reduced reactive oxygen species levels in photo-damaged mice skin, promoted collagen regeneration, and reduced wrinkles.[64]

Table 1 Recent Developments of Microneedle Patches for Skin Photoaging Treatment

Hydrogel	Agent	Effect	Year	Ref.
ADSC-EVs MN	Adipose-derived stem cell-derived extracellular vesicles (ADSC-EVs)	Improving epidermal structure and function of photoaging skin. (improving the content of collagen)	2021	[51]
COL1A1-EVs-MN	mRNA encoding for extracellular-matrix α1 type-I collagen (COL1A1); hyaluronic acid (HA)	Collagen protein-replacement therapy	2023	[57]
ACF-MN	Adipose collagen fragments (ACF); gelatin	Preventing ROS accumulation and inducing antioxidase production; inducing neovascularization and reduce apoptosis	2022	[62]
FGF-2/FGF-21 MN	FGF-2 and FGF-21; HA	Reversing the UVBinduced cell senescence.	2023	[63]
Microalgae-MN	Chlorella (GY-H60); HA	Antioxidant and anti-inflammatory, enhancing collagen regeneration	2023	[64]
DA-MNP (clinical trial)	HA; acetyl octapeptide-3, L-ascorbic acid 2-glucoside, and sodium cyclic lysophosphatidic acid	Manufactured via DEN® technology and improving eye wrinkles, reducing trans-epidermal water loss (TEWL), enhancing skin elasticity and lifting	2024	[68]

In summary, microneedle systems, as outlined in Table 1, offer diverse substances to skin photoaging problems, addressing inflammation, oxidative stress, and cell aging induced by UV. Notably, hyaluronic acid (HA) emerges as a commonly used polymer hydrogel material for microneedle production.

Recent Clinical Study of Microneedle Patch for Skin Aging Treatment

The concept of microneedles was proposed in the 1970s,[69] but it was not until the 1990s that the microelectronics industry provided the microfabrication tools necessary to create these small structures, allowing for experimental validation. Since the first study on microneedle transdermal drug delivery in 1998,[70] most research has focused on metal needle manufacturing techniques for developing microneedle heads for drug applications. Clinically, metal microneedle injectors or microneedle rollers are more commonly used, while the application of microneedle patches remains limited. However, there was a clinical trial about microneedle patch for anti-aging recently, the study evaluated a novel dissolving microneedle patch (DA-MNP), which has been verified for its skin puncture ability, safety, and efficacy through clinical research.[68] The DA-MNP contains a hyaluronic acid polymer backbone, acetyl octapeptide-3, L-ascorbic acid 2-glucoside, and sodium cyclic lysophosphatidic acid, and is manufactured using DEN® technology. Compared to the placebo MNP, the DA-MNP treatment group demonstrated more effective anti-aging effects in improving eye wrinkles, reducing trans-epidermal water loss (TEWL), enhancing skin elasticity and lifting, and exhibited no adverse reactions.[68] Some companies with certain technical capabilities have begun applying microneedle technology to develop cosmetic patches and have already launched some products. As research on microneedle technology advances and findings are translated into practical applications, the use of microneedle patches is expected to expand significantly.

Discussion and the Future Perspectives

Microneedle patches have shown tremendous potential in the treatment of skin photoaging. Current research indicates that microneedle patches can enhance the transdermal delivery efficiency of cytokines, exosomes, genes, and more.[71] We have summarized various types of microneedle patches for treating skin photoaging. Among these patches, we believe that microneedle patches delivering exosomes and bioactive proteins hold the most promise for the treatment of skin photoaging. Currently, stem cell exosomes and bioactive proteins are widely used in clinical trials across various medical specialties.[72] Further research and validation are needed for the use of microneedles to deliver mRNA for photoaging treatment, as the clinical application of gene therapy is still in its early stages. As for algae microneedle patch, it is used extensively in research, but its clinical applications remain relatively limited.

In the future, with ongoing technological advancements, the application prospects of microneedle patches in the treatment of skin photoaging remain broad. Researchers can further optimize the design of microneedle patches to enhance drug delivery effectiveness and develop patches targeting different symptoms of photoaging. Moreover, microneedle patches have the potential to serve as carriers for personalized treatment, allowing customized treatment plans based on individual patient conditions. Overall, microneedle patches, as an innovative treatment modality, pave the way for addressing skin photoaging through more precise and convenient drug delivery. With the potential to become

a crucial tool in the field of dermatology, microneedle patches offer the prospect of more effective and personalized treatment experiences for patients.

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Disclosure

There are no conflicts of interest to declare.

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