SKIN

IN-DEPTH REVIEW

Tissue-Engineered Skin Substitutes for Use in Clinical Dermatological Practice

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ABSTRACT

Skin replacements are essential in dermatology as they serve to connect the gap between conventional wound care and surgical procedures. Due to pioneering innovations from the last century, tissue-engineered skin substitutes have significantly advanced in the field of dermatology, offering new hope for patients with complex wound healing needs. Whilst before, skin grafting was performed to act as an intermediary to promote skin healing, it has now evolved to also mimic skin structure and function. To our knowledge, there have not been any summaries on the use of tissue-engineered in dermatology. Therefore, we conducted a scoping review to summarize research papers which performed human clinical trials and follow-up work using synthetic lab-made skin with a clear clinical application from the last 30 years.

INTRODUCTION

The skin, the body's largest organ, is a sophisticated and versatile tissue that serves as the primary defence against environmental harm, regulates body temperature, and detects external sensory stimuli. In addition to its protective role, the skin is also involved in many other physiological processes, such as modulating immune response, vitamin D synthesis, and facilitating wound healing.[1] Burns, trauma, illnesses and surgical treatments may all compromise skin quality and quantity, leading to significant physiological and psychological impacts.[2] These challenges highlight the need for effective skin substitutes in the field of dermatology.

Historically, the endeavour to repair and restore injured skin dates back to early civilizations with grafting techniques being documented in both India and Egypt around 600 B.C.[3] The 19th and 20th centuries witnessed notable breakthroughs in reconstructive surgery with the introduction of full-thickness and split-thickness grafts.[4] Full-thickness grafts transfer the epidermis and dermis to a well-vascularized donor site for better cosmetic effects and durability. Split-thickness grafts heal faster but lack function since they include only the epidermis and a piece of the dermis. Despite advances, tissue rejection, donor tissue scarcity, and graft site problems such inadequate blood circulation, loss of sensation, and increased discomfort necessitated the development of artificial skin replacements.[5]

The combination of tissue engineering with cellular and molecular biology has led to significant advancements in the creation of artificial skin replacements. These laboratory-designed synthetic alternatives replicate the structural and functional characteristics of skin. In the past three decades, with a particular emphasis on the last ten years, there has been immense progress in biomaterials, scaffold design, and cellular technologies. All of these facilitate the development of advanced skin substitutes that provide better integration with the recipient's tissue, improved blood vessel formation, and enhanced functional and aesthetic results.[6] Furthermore, the transition from acellular matrices to sophisticated bi-layered live cellular structures signifies a noteworthy achievement in dermatology. These emerging technologies, such as 3D bioprinting and the incorporation of stem cells, offer extraordinary opportunities for skin regeneration, positioning modern artificial skin alternatives as not just a temporary fix but as a prospective replacement for natural skin that can fully restore both appearance and functionality.[7]

This review will analyze laboratory-made synthetic skin substitutes, particularly those with proven clinical usage, that have undergone human clinical trials and additional research by the same or different experts to assess long-term efficacy and safety. The analysis covered 2014–2024 studies over the past 30 years. This review will cover artificial skin replacement types, materials, manufacture, and mechanics. It will also discuss medical uses, advantages, cons, and limits. Finally, the review evaluates skin substitution clinical trial results and patient satisfaction.

MATERIALS AND METHODS

This scoping review consolidates the literature on laboratory-created artificial skin replacements from the past three decades, focusing on the last ten years to capture the current advances. The study prioritizes studies that effectively mimic normal skin, demonstrate clinical applications, include follow-up research, and involve human clinical trials.

We searched PubMed, Scopus, Web of Science, and Google Scholar for "synthetic skin substitutes," "tissue-engineered skin," "clinical trials," "human studies," "biomimetic skin," and "wound healing."

Inclusion conditions were strict. We omitted papers on autografts, allografts, xenografts, harvested skin, or animal models without human trials. To ensure uniformity, selected studies collected data using a standardized form. The extracted data included study authors, year of publication, journal, and synthetic skin substitution features (type, materials, and fabrication methods). Clinicians recorded clinical applications, mechanisms of action (integration with host tissue, promotion of angiogenesis, and wound contraction and scar reduction), clinical trial outcomes (effectiveness, safety, and patient outcomes), and follow-up work. A comprehensive overview of artificial skin replacements' accomplishments, medical uses, and prospects was created from data. Comparative clinical trials and patient satisfaction evaluations evaluated alternative treatments.

We evaluated the selected studies (**Table 1**) based on design strength, sample size, follow-up time to establish long-term effectiveness and safety, and end measure

relevance. A narrative synthesis technique summarized important findings, identified common themes, and discussed strengths and weaknesses. Comparing synthetic skin substitutes' efficacy and safety required quantitative clinical study data.

Table 1. Summary of tissue-engineered skin substitutes discussed in the scoping review, including scaffold composition, clinical indications, key findings, and relevant references. This table highlights the applications of various substitutes in treating conditions such as burns, ulcers, and genetic skin disorders, as well as the clinical outcomes and benefits observed in different studies.

Tissue-Engineered Substitute	Scaffold Composition	Indications	Findings	References
Integra	Dual-layered membrane: silicone (top), bovine tendon collagen, and chondroitin-6-sulphate (bottom)	Burn scar removal	Demonstrated improved scar pliability and pigmentation in burn patients compared to traditional methods	Yannas & Burke (1980), Mittal & Kahn (2024)
Dermagraft	Bioabsorbable polyglactin mesh scaffold with human fibroblasts	Diabetic foot ulcers	Stimulated granulation tissue formation and wound closure, 50% improvement in wound closure compared to standard care	Gentzkow (1996), Marston et al. (2003)
Apligraf	Bovine collagen structure containing human keratinocytes and fibroblasts	Venous and diabetic ulcers	Promoted epithelial tissue regrowth and reduced infection risk, significantly accelerated wound healing	Falanga & Sabolinski (1998)
Biobrane	Silicone film, nylon fabric, and porcine collagen	Partial-thickness burns, donor site wounds	Facilitated faster healing, decreased hospital length of stay, particularly in pediatric patients	Greenwood (2010), Lesher et al. (2011)
Epicel	Patient-cultivated keratinocytes	Extensive burn lesions	Reduced donor site morbidity and hospital stay duration in burn patients	O'Connor et al. (1981), Fagan et al. (2024)
BLCC (Bioengineered Living Cell Construct)	Neonatal fibroblasts and keratinocytes in a bovine collagen matrix	Chronic non-healing venous leg ulcers	Healed non-healing tissue, reduced wound area, shifted non-healing tissue to healing status	Brem et al. (2007)

Silk Fibroin/Nanosilver Scaffolds	Silk fibroin and nanosilver	Burn wound healing	Enhanced cell proliferation, re-epithelialization, and reduced inflammation	Meinel et al. (2007), Farroha et al. (2013)
hESCs (Human Embryonic Stem Cells)	Cultured human embryonic stem cells (hESCs)	Epidermolysis bullosa (EB)	Promoted long-term regeneration, reduced blister formation, and integrated with surrounding tissue	Hirsch et al. (2017), Nourian Dehkordi et al. (2019)

RESULTS AND DISCUSSION

Burns, persistent wounds, and other dermatological conditions require skin substitutes. Three types of skin substitutes exist: synthetic, biosynthetic and composite, and lab-grown or tissue-engineered.

Artificial skin improves consistency, accessibility, and health. They function like native skin with biocompatible materials. Integra's dual-layered membrane uses silicone on top and permeable bovine tendon collagen and chondroitin-6-sulphate on the bottom. Collagen facilitates cell mobility and tiny blood vessel formation, making it ideal for burn scar removal.[8] Dermagraft induces cutaneous collagen synthesis and organization using bioabsorbable polyglactin mesh scaffolds and human fibroblasts. Dermagraft's skin regeneration helps diabetic foot ulcers.[9]

Biosynthetic and composite materials combine natural and synthetic elements, blending biological properties with synthetic durability. The first FDA-approved product for treating venous and diabetic foot ulcers was Apligraf, a two-layered bovine collagen structure containing human keratinocytes and fibroblasts. The presence of keratinocytes and fibroblasts restores the epidermis and dermis, enhancing wound healing and minimizing infection risk.[10] Silicone film, nylon fabric, and porcine collagen make Biobrane a valuable material in treating partial-thickness burns and donor site wounds, aiding natural healing by adhering to the wound bed.[11]

Using cells, scaffolds, and growth hormones, lab-grown or tissue-engineered skin substitutes mimic natural skin. Epicel, made from patient-cultivated keratinocytes, can cover extensive burn lesions and reduce the need for numerous grafts.[12] Organogenesis recreates skin with fibroblasts and keratinocytes, aiding venous ulcers and improving wound healing and skin health.[12] Silk fibroin/nanosilver scaffolds and bioengineered living cell constructs (BLCC) show promise. Silk fibroin and nanosilver scaffolds are biocompatible and antimicrobial, facilitating cell proliferation, adhesion, re-epithelialization, and inflammatory suppression in burn wound healing.[13] BLCC, which uses neonatal fibroblasts and keratinocytes from human foreskin and bovine collagen matrix, heals non-healing tissue, reducing wound area and treating chronic non-healing venous leg ulcers.[14] Electrospun silk fibroin nanofibers facilitate cell development in a biocompatible framework, promoting epithelial renewal and healing of chronic wounds and burns.[13]

Materials and Methods Used in Tissue Engineering

As shown in **Figure 1**, the creation of tissue-engineered skin substitutes relies on the complex interaction between scaffolding

materials, cellular components, and growth factors, which together enable the development of skin replacements that replicate the structural and functional characteristics of genuine skin.

Scaffolding materials serve as the fundamental framework for cell adhesion, proliferation, and differentiation. Natural scaffolds like collagen and hyaluronic acid are widely esteemed for their biocompatibility

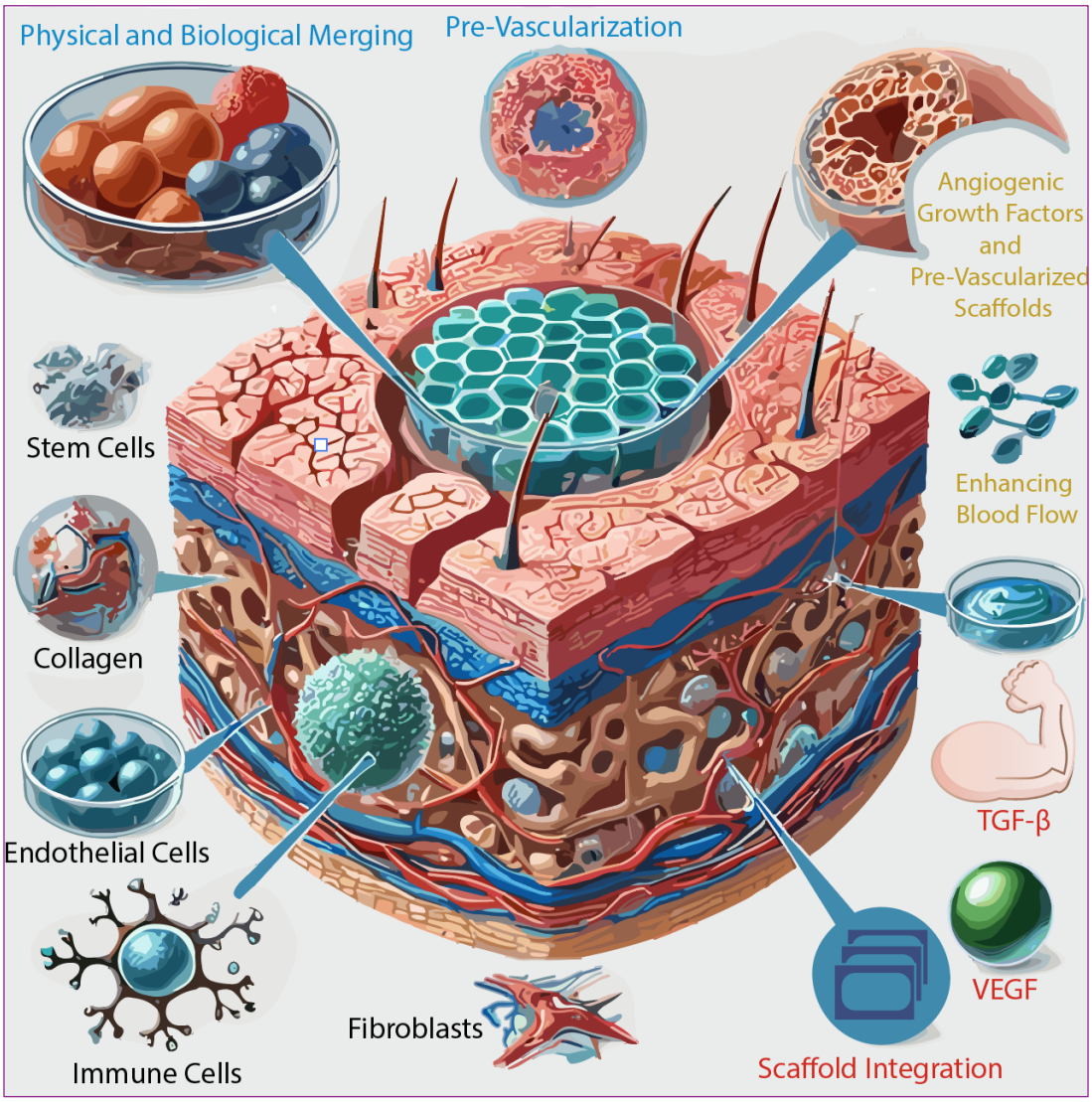

Figure 1. Tissue-engineered skin substitutes are created using scaffolds (e.g., collagen, PLA, PCL), cellular components (MSCs, iPSCs, fibroblasts, keratinocytes), and growth factors (TGF-β, VEGF) to mimic skin structure and function. Scaffolds support cell adhesion, while cells aid regeneration, and growth factors drive proliferation and vascularization, improving host integration.

and capacity to enhance vital cellular processes necessary for tissue regeneration. Collagen, for example, facilitates the attachment and proliferation of cells while also integrating well with surrounding tissue to improve the overall healing process.[8] Whereas synthetic scaffolds, such as polylactic acid (PLA) and polycaprolactone

(PCL), offer customizable mechanical qualities, such as precise rates of deterioration and mechanical strengths, making them ideal for broad-spectrum applications in skin restoration.[13]
Additionally, cellular components, which vary based on the specific application and desired result, are equally vital for the functionality of skin substitutes. Stem cells, namely mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs), are valued for their regenerative abilities and their potential to differentiate into other cell types, such as keratinocytes and fibroblasts, improving tissue regeneration while minimizing scarring.[13] Fibroblasts contribute to the creation of the extracellular matrix, offering physical support and chemical signals for other cells. Keratinocytes, the predominant cell type in the epidermis, are vital in repairing the skin's barrier function.[15]

Growth factors and signaling molecules are crucial in cell proliferation, differentiation, and tissue regeneration. Growth factors, such as transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF), are often added to tissue-engineered skin substitutes to improve their treatment efficacy.[16] TGF-β regulates essential wound healing, such as cell migration and the creation of the extracellular matrix.[9] Whereas VEGF stimulates angiogenesis, the process of creating new blood vessels, by delivering nutrients and oxygen to the healing tissue. [16] Controlled release of these growth factors from the scaffold can establish an optimal environment, by re-epithelization and regulating inflammatory response, for tissue regeneration, thus enhancing the integration, appearance, and functionality of the skin substitute.[10]

The successful integration of tissue-engineered skin replacements with the host tissue is crucial for their effectiveness. This encompasses both the physical connection of the scaffold to the wound bed and the seamless biological merging of the replacement with adjacent tissues. Cellular migration, proliferation, and matrix deposition assist in this process, ensuring that the replacement functions as part of the host tissue.[14] Incorporating endothelial cells into the scaffold to create pre-existing vascular networks, a technique known as pre-vascularization, has also been demonstrated to greatly improve the integration and viability of the skin substitute.[13]

Facilitating angiogenesis is essential for the extended viability and effectiveness of tissue-engineered skin substitutes. Angiogenesis provides ample blood flow to regenerated tissue, delivering nutrients, removing waste, and sustaining cellular functions. Methods to enhance angiogenesis involve the integration of angiogenic growth factors, such as VEGF, and using pre-vascularized scaffolds to expedite blood vessel formation post-implantation.[16]

Clinical Applications

Tissue-engineered skin substitutes have greatly transformed the treatment of several dermatological disorders, providing substantial progress in clinical results for patients with intricate wound healing requirements. (**Figure 2**) These uses range from severe burn injuries to chronic ulcers and rare skin disorders, demonstrating versatility and effectiveness.

In burn treatment, tissue-engineered skin substitutes offer both temporary and permanent coverage, improving wound healing outcomes, reducing the requirement for autografts, and minimizing donor site complications. Autologous keratinocytes expanded in vitro, such as Epicel, have demonstrated favorable outcomes in

promoting wound closure and decreasing the need for grafting treatments.[12] Epicel has been shown to reduce donor site morbidity and hospital stay duration in burn patients.[17] Synthetic and biosynthetic alternatives like Integra have moreover improved the cosmetic and functional recuperation of burn patients by reducing scarring.[8] In a recent study, Integra-treated patients have shown to have improved scar pliability and pigmentation compared to conventional treatments.[18]

For chronic ulcers, such as diabetic, venous, and pressure ulcers, these substitutes offer substantial benefits. Chronic wounds are challenging due to underlying pathophysiological abnormalities that hinder the healing process. Dermagraft and similar products, composed of a scaffold that can be absorbed by the body and contains human fibroblasts, have proven to be successful in stimulating the production of granulation tissue and closing wounds in individuals with diabetic foot ulcers.[9] In a 12-week clinical

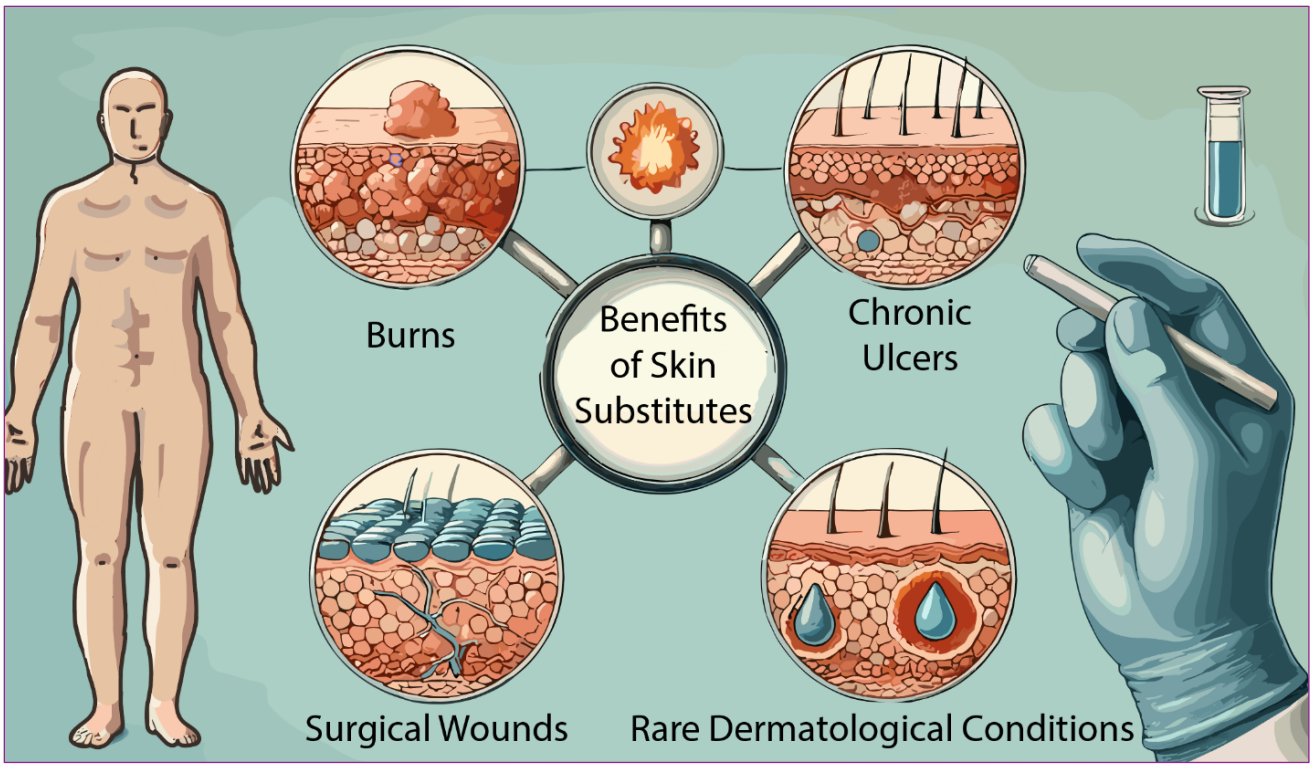

Figure 2. This figure illustrates the diverse clinical applications of tissue-engineered skin substitutes, highlighting their role in managing burns, chronic ulcers, surgical wounds, and rare dermatological conditions. Skin substitutes provide an innovative approach to improving wound healing, reducing scarring, and minimizing complications associated with traditional grafting techniques. The benefits include enhanced integration with host tissue, faster wound closure, and better functional and cosmetic outcomes for patients with complex wound healing needs.

trial, Dermagraft had a demonstrated 50% improvement in wound closure compared to standard care.[19] Apligraf, a bilayered construct consisting of bovine collagen combined with human keratinocytes and fibroblasts, has been shown to effectively cure venous ulcers by promoting the regrowth of epithelial tissue and decreasing the likelihood of infection.[17] These replacements target the persistent inflammation and inadequate blood vessel formation that are typical of these wounds,

resulting in a notable improvement in healing speed and a decrease in the likelihood of sequelae.

Tissue-engineered skin substitutes are an efficient method for managing post-surgical wounds, especially those that occur after intensive reconstructive procedures. Products like Biobrane provide temporary coverage and facilitate natural healing, beneficial for donor-site wounds and partial-thickness injuries from surgery (Greenwood et al., 2010; Farroha et al., 2013).[11,20] Biobrane has been reported to result in faster healing and may also decrease hospital length of stay for pediatric patients requiring inpatient admission.[21]

Some uncommon dermatological conditions, such as epidermolysis bullosa (EB), a genetic disorder characterized by delicate skin that forms blisters easily, have also experienced enhancements through the use of improved skin replacements. Application of cultured human embryonic stem cells (hESCs) directly to wounds has demonstrated promise in promoting long-term regeneration and enhancing skin integrity in patients with Epidermolysis Bullosa (EB). A study on hESCs found that grafted cells were able to integrate with surrounding tissues, promoting healthy skin regeneration and reducing blister formation in EB patients.[22,23] The capacity of these alternatives to assimilate with the surrounding tissue and stimulate the regrowth of cells presents a hopeful therapeutic approach for illnesses that now have limited therapy alternatives.

Advantages of Tissue-Engineered Skin Substitutes

Complex skin injuries and disorders require tissue-engineered skin substitutes because they outperform standard wound treatment. Advanced biomaterials and cellular technologies enable adjustable and effective skin regeneration.

The reduction of donor sites is a major benefit. Traditional skin grafting involves removing skin from many body parts, producing more wounds and difficulties. Tissue-engineered alternatives from tiny biopsies or synthetic materials reduce donor site needs and patient morbidity.[13]
Also, these alternatives are frequently less immunogenic. Patient-derived autologous skin substitutes minimize immunological rejection and improve integration and durability.[12] Modified allogeneic and xenogeneic substitutes lower antigenicity to reduce rejection and speed healing. Xenogeneic scaffolds have demonstrated reduced rejection rates compared to allogeneic substitutes in clinical settings.[24]

Tissue-engineered skin substitutes are customizable, scalable, and heal better than traditional procedures. **Figure 3** illustrates these advantages, as well as challenges such as high production costs and scalability issues. It also shows a cross-section of an engineered skin substitute that combines technological and biological advancements to meet clinical needs. Three-dimensional bioprinting and scaffold engineering provide personalized skin substitutes based on wound size, depth, and location.[13] These technologies also allow rapid mass production, which is beneficial for treating severe burns or traumatic injuries.

Common alternatives include growth hormones and signaling chemicals like TGF-β and VEGF, which promote cell growth, angiogenesis, and tissue repair. Scaffolds allow regulated chemical release, making wound healing optimum.[16] Improved wound contraction and scar reduction are further benefits. Tissue-engineered replacements regulate healing, regrowing epithelial tissue

and reducing fibrosis and scarring. This is crucial for people with major wounds or reconstructive surgery since it increases psychological well-being.[10]

Successful integration with host tissue makes the substitute a functional component of the patient's skin, preserving structural integrity and healing. Prevascularization and biocompatible scaffolds improve integration, eliminating further treatment.[14]

Challenges and Limitations

Although there has been notable progress in the development of tissue-engineered skin substitutes, there are still several obstacles and constraints that need to be addressed.

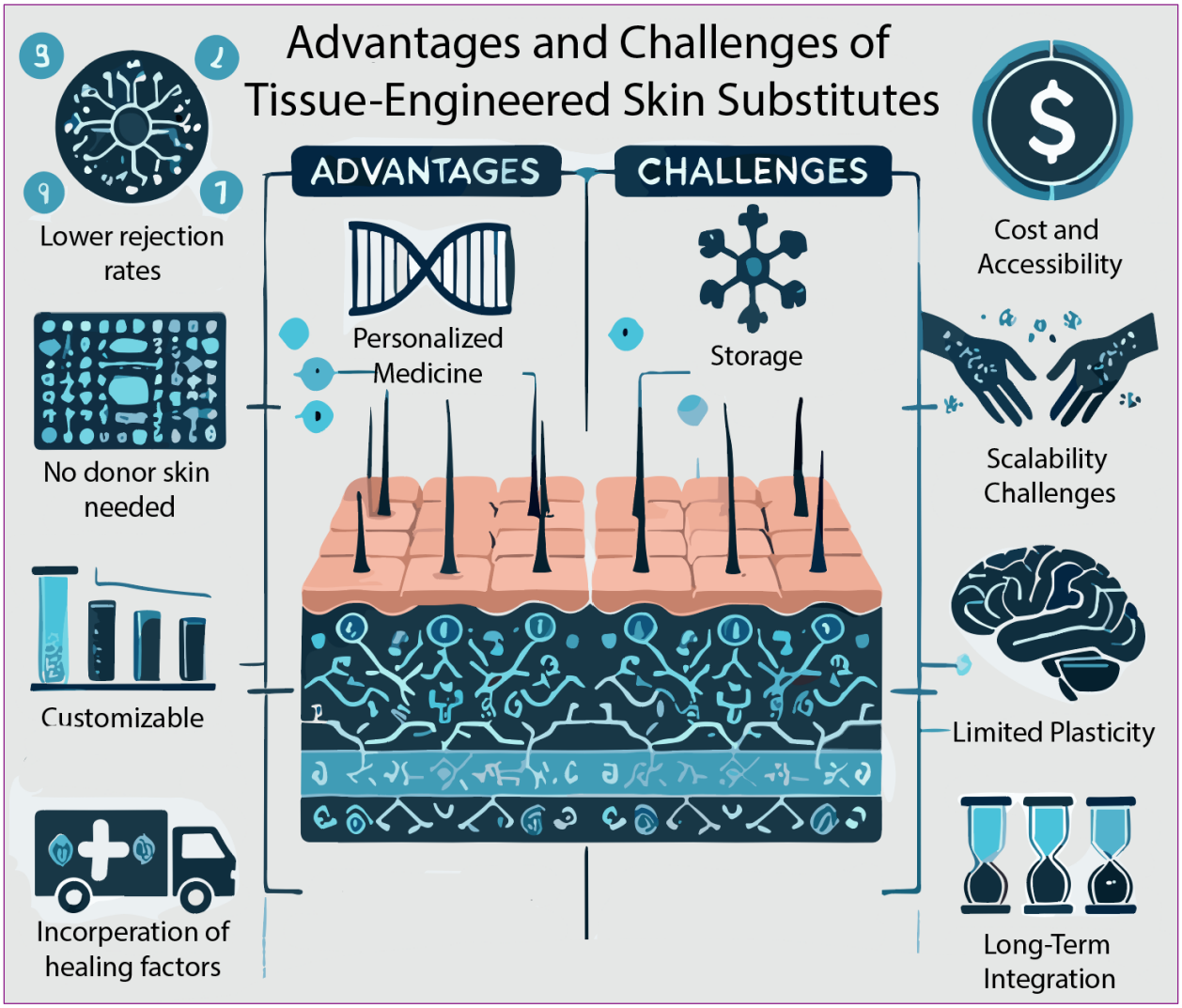

Figure 3. The illustration highlights the benefits and challenges of tissue-engineered skin substitutes. Advantages include lower rejection rates, no need for donor skin, customization, personalized medicine, and incorporation of healing factors. Challenges encompass high production costs, limited accessibility, storage difficulties, scalability issues, limited elasticity, and the need for improved long-term integration with host tissue. The central schematic illustrates a cross-section of engineered skin, emphasizing the blend of technological and biological advancements to meet clinical needs.

Preservation and storage are major logistical hurdles, as many substitutes require strict storage conditions like cryopreservation to uphold viability and functionality.[25] These factors can make it more difficult for the products to be distributed and accessible, particularly in resource-limited settings.[26]

Long-term effectiveness and safety also pose concerns. Although short-term results are promising, extensive longitudinal studies are needed to evaluate the durability and integration of the skin substitutes.[27] The investigation of potential dangers, such as immunological reactions, infections, and mechanical failure of the scaffold materials, is necessary.[28,29]

Cost and accessibility also offer substantial obstacles. The creation of these new therapies frequently entails intricate technology and substantial production expenses, rendering them less attainable for patients residing in low-income locations.[30] Moreover, the reimbursement rules for these items exhibit significant variation, which has a direct impact on their affordability and the extent of their adoption.[31]

Comparative Analysis

Conducting comparative studies on various tissue-engineered skin substitutes is crucial for assessing their relative effectiveness, safety, and impact on patient outcomes. These investigations usually entail conducting direct comparisons of different products in clinical trials, with a specific focus on important measurements like as rates of wound healing, infection control, scar formation, and patient satisfaction. For example, Apligraf and Dermagraft have been evaluated in the context of treating chronic wounds. Both products have demonstrated considerable advantages, but they differ in terms of how they are used and the specific results they provide.[9,10]

Clinicians can make well-informed selections about the most effective treatment options for their patients by comprehending the performance of various alternatives in different clinical situations. Moreover, these comparison evaluations can pinpoint distinct benefits and drawbacks of each product, providing guidance for future enhancements and advancements in tissue engineering.[14]

CONCLUSION

Customized skin replacements with personal cells are promising. Stem cell and 3D bioprinting provide individualized grafts, enhancing compatibility and lowering immunological rejection. Individualized methods will become more widespread as technology becomes more affordable and accessible. By adding appendages and sensory components, tissue-engineered skin substitutes can include hair follicles, sweat glands, and sense neurons, enhancing functionality. Tissue-engineered skin substitutes are a dermatological and regenerative medicine breakthrough. Their ability to solve complex wound healing issues makes them important in modern medicine. Preservation, long-term effectiveness, and cost remain issues, but research and technology are addressing them.

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