Review Article

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Research progress in 3D bioprinting of skin: Challenges and opportunities

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Abstract: This article investigates 3D bioprinting as an exciting solution to the problem of skin regeneration, emphasizing the possibility of eliminating the drawbacks of standard grafts. It covers the anatomy and functions of the skin and the need for synthetic skin for medical purposes. Existing substitutes are analysed, thereby exposing their drawbacks and constraints. This article discusses the concepts underpinning 3D bioprinting, bioinks used for the fabrication of the skin, and the manufacture of skin tissue constructs of several layers. The major issues are associated with vascularization and mechanical stability, while the forthcoming improvement of the integration of biomaterials, automation, and optimization based on AI will enable enhanced functionality and clinical applications. Skin 3D bioprinting offers a new perspective for the development of customizable and engineered skin grafts.

Keywords: artificial skin, autograft, bioprinting, 3D bioprinting, additive manufacturing

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1 Introduction

The skin, which is the largest organ of the human body, works as a major part of the body to keep off harmful exterior attacks and acts in thermoregulation, sensory reception, and immune defence [1]. Although the skin is extremely strong, it is still vulnerable to damage and traumas like burns, trauma, and chronic diseases that can cause physical inconvenience, mental suffering, and social disabilities [2]. Some body burns are so disastrous that they go beyond the natural healing process, forcing the doctors to intervene with artificial procedures, which revamp their functions to bring back the pretty looks they had before the injury.

It is worth mentioning that the desire to create artificial skin to solve this problem has caused the most extensive progress in both fields of tissue engineering and regenerative medicine [2]. The common substitutes, such as skin grafts and synthetic materials, have certain limitations, such as immunogenicity, limited availability, and poor assimilation, with host tissues. Therefore, these constraints have emerged as a critical need for more sophisticated and user-designed alternatives [3].

Nowadays, effective 3D bioprinting has been considered as essential factor due to its potential of resolving relevant shortcomings through precise generation of skin structures [4]. The process is achieved by using biological materials, cells, and growth factors, which help in the duplication of the skin's complexity, including its multilayered structure and functionality [5]. There are some challenges associated with the 3D-printed artificial skin. These challenges are related to the ethical and regulatory bodies. As the cells used in bioprinting are always donated by some donor, the consent of the donor is mandatory. The

long-term effect of artificial skin on the human body is still unknown and has to be investigated by the researchers. Another challenge is the regulatory body because of the categorization of skin. The 3D-printed skin comes in between the medical device and the tissue graft. Therefore, it poses a challenge to the FDA as to which category the 3D skin may get approval, and accordingly, guidelines may be developed.

The review consists of a detailed discussion of the composition and role of the skin, artificial skin's necessity, and substitutes that have already been found [6]. It also examines the development of 3D bioprinting technology, host responses to bioengineered skin, and the problems of the clinical application of such consequences. Along with this, the possible ways of the field's improvement are set forth, with 3D bioprinting being proposed as the most hopeful solution.

This review adequately covers the most recent developments in biomaterials, AI-driven optimization, and vascularization techniques for 3D bioprinting. The study goes beyond the previous approaches and addresses the ethical and regulatory challenges of clinical translation. Additionally, it takes a critical look at the limitations of autografts, allografts, and acellular dermal matrices (ADMs), such as immune rejection, donor scarcity, and integration issues.

2 Skin: Anatomy and functions

The skin is the largest and most multifunctional organ of the human organism, which in adults is about 1.5–2 m^2 and represents almost 15% of the body weight. The skin is the first front of defence against external threats, and it is of central importance for the preservation of normal body functions [7]. Figure 1 shows that the skin consists of three basic layers: the epidermis, the dermis, and the hypodermis, and each of them has a unique structure and function.

- ***Epidermis:*** The epidermis is the outermost layer, mainly the keratinocytes arranged in multiple layers. It is not irrigated with blood and it only obtains the nutrients through the dermis by means of diffusion [8]. Basal cells produce melanin, which defends against ultraviolet rays, and Langerhans cells affect the immune system. The stratum corneum, the superficial layer above it, functions as a barrier to microorganisms, water loss, and chemicals [9].
- ***Dermis:*** Under the epidermis is the dermis, a reticular connective tissue layer rich in collagen and elastin fibres. It supplies the skin with the necessary structural support and flexibility [10]. The dermis comprises various components, including blood and lymph vessels, sweat and sebaceous glands, hair bulbs, and sensory nerve ends.

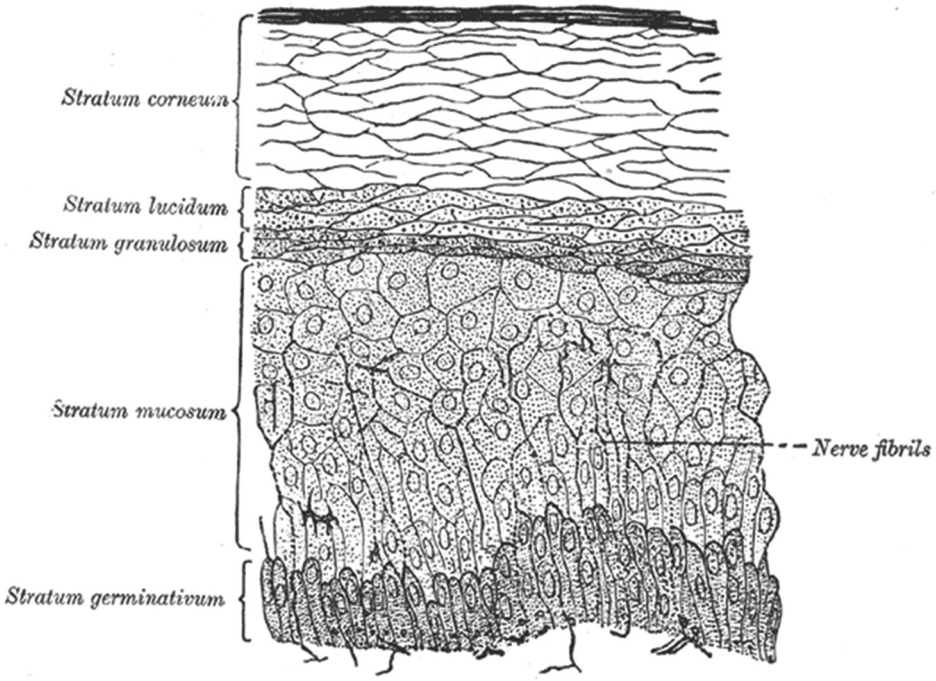

Figure 1: Layers [7].

These elements assist in thermoregulation, sensation, and sebum production, which maintain skin hydration and provide an external barrier against microbial invasion [11].
- ***Hypodermis:*** The hypodermis, also known as the subcutaneous tissue, is mainly comprised of adipose tissue and connective tissue. Seamlessly, it functions as an insulator, padding the body against mechanical injury, a storeroom of energy as fat [12].

2.1 Functions of the skin

The skin serves many critically important functions necessary for life:
- ***Protection:*** Protects against physical damage, infectious agents, environmental factors, and ultraviolet rays [13].
- ***Thermoregulation:*** Figure 2 shows the process of controlling body temperature *via* sweat secretion and altered blood flow in the dermis [14].
- ***Sensation:*** Specialized receptors for pain, pressure, temperature, and touch allow them to communicate with their outer environment [15].
- ***Immune defence:*** The skin resides in immune cells to recognize and respond to pathogens, enabling innate and adaptive immunity [16].
- ***Water retention:*** Decreases the loss of water from the stratum corneum, thus preventing dehydration [17].
- ***Metabolism:*** Synthesizes vitamin D in response to the impact of sunlight, which is necessary for calcium and phosphorus metabolism [18].

Finally, the complex structure and wide-ranging functions of the skin make it an important organ that maintains both the physiologic balance and protects the body from external and internal disturbances.

3 Need for artificial skin

It has emerged as a crucial innovation in contemporary medicine, providing solutions to the problems posed by major skin injuries, chronic ailments, and prenatally occurring malformations [19]. The following are the reasons that define the importance of artificial skin development:
- ***Prevalence of skin injuries and disorders:*** Acute traumatic wounds, burn injuries, chronic ulcers, and skin cancer represent an increasing burden on public health worldwide [20]. Every year, over 11 million people suffer severe burns and need surgical treatment. Natural healing in such situations tends to be slow and incomplete, and complications ensue: infections, scarring, and loss of function [21]. Synthetic skin provides a potentially life-saving approach by speeding up the closure of the wound and lowering the danger that comes with extended healing times.
- ***Limitations of skin grafts:*** A typical care option for severe wounds is skin grafting, but it is limited by a lack of donor sites and risks such as graft rejection, infection, and scarring [22]. Patients with extensive burns or injuries often do not have sufficient healthy skin available for autografts, and allografts or xenografts can elicit immune responses. One of the most crucial steps is wound healing, during which it needs to be covered and protected [19]. Skin grafts can be used for this purpose; however, they are limited by differences in availability and errors, and they depend on donor tissues (Figure 3).
- ***Challenges in wound healing:*** Natural healing processes fail in complex wounds, such as diabetic ulcers and pressure sores, due to inhibited blood supply, persistent inflammation, and microbial invasion. Conventional wound care modalities are inadequate in such situations [23]. Since scaffolds like artificial skin, mimicking the structural and functional properties of nature skin, are crucial for support in cell proliferation, angiogenesis, and regeneration, these concerns are effectively solved [24].
- ***Advancements in tissue engineering:*** Biomedical technology has achieved a fast-forward movement due to the progress in the field of biomaterials and tissue engineering, which has made it possible to create such skin constructs that look like original skin [25]. These constructs could simulate the multilayer structure with the provision of both dermal and epidermal functions. In addition to being a restraint, fake skin also induces cell growth, makes blood vessels, and becomes richer when implanted in the natural tissues of the host, making it the best alternative in skin replacement therapies [26]. Another approach may be the use of extracellular vesicle-loaded hydrogel because of its good biocompatibility, low immunogenicity and no biosafety concern.
- ***Improved aesthetic and functional outcomes:*** The conventional treatments used are often likely to cause ugly scars and loss of sensory functions [27]. The biomimic design of artificial skin prevents scarring and gives back the feeling of touch, and it improves how the person is looking like nowadays. The necessity for the patient to gain self-confidence in this visible injury and to be able to cope with the psychological problems is among the reasons why it is crucial [19].

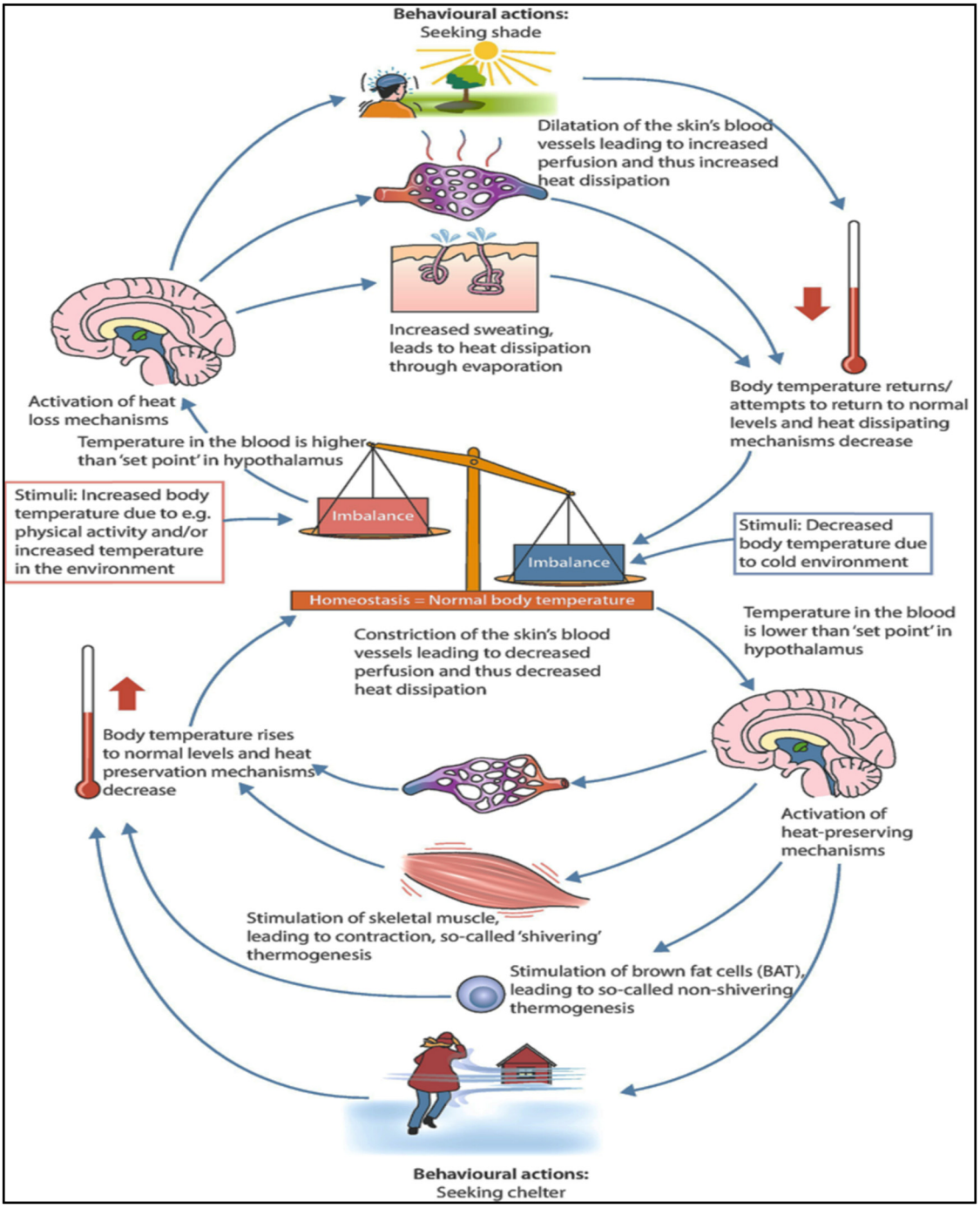

Figure 2: Managing body temperature [14].

- ***Addressing immune rejection:*** The transplantation of natural or synthetic skin substitutes could be met with problems like rejection of foreign tissue and an increase in inflammation [28]. In the case of artificial skin, the problem of rejection is minimized due to the use of biomaterials that cause no immunological reactions and the application of patient-specific cells [29]. Considering the recent improvements made in the fields of bioprinting and stem cell technologies, it is easier than ever before to create skin substitutes that will perfectly match individual immune profiles.
- ***Economic and accessibility challenges:*** Access to donor tissues due to the high cost and limited accessibility in resource-limited settings is a significant challenge. To achieve this, artificial skin, which is made on a big scale, becomes a new and sustainable way of cost-

effectiveness for coping with such issues [30]. Furthermore, synthetic skin can be transported and stored efficiently, making it a realistic option in emergencies and remote areas. In addition, the biotechnology field has embraced less expensive biomaterials and automated printing technologies to cater to 3D bio-printed skins that are increasingly preferred by people [31]. Besides, the relationship between research institutions and biotech firms collaborate on fostering innovations, making them accessible and usable in clinical and cosmetic fields.

- ***Applications in research and testing:*** Artificial skin is crucial to medical research and product testing [32]. It is a pitiable and benign replacement of test animals for the cosmetics industry, pharmaceutical companies, and the skin department of studies. In addition, it acts as a model for the drug trial of skin diseases, testing drug efficacy, and executing novel ways of treatment.
- ***Future prospects in regenerative medicine:*** Artificial skin holds more potential than just wound healing. Cutting-edge technologies such as 3D bioprinting, integration, gene editing, development of fully functional skin replacements that could restore hair, and sweat gland functions mark the beginning of a new era of skin treatment [31]. These innovations were those that had the possibility of changing the ways injuries and disorders of the skin are treated in the coming years.

The development of artificial skin will help to overcome the limitations of currently available treatments for treating severe injuries and chronic wounds. For best results, it is necessary to enhance recovery through improvement of quality of life, which makes it an essential area of research, followed by innovation in regenerative medicine.

4 Current substitutes for skin

A variety of skin replacements that one can use to treat the problems of natural healing and skin grafting is reconfiguration. The substitutes range from biologically derived materials to synthetic constructs, each with specific benefits and challenges [33]. Below is a detailed discussion of the most used skin substitutes:

- ***Autografts:*** Autografts, or skin grafts taken from one's own body, are the gold standard for skin replacement.

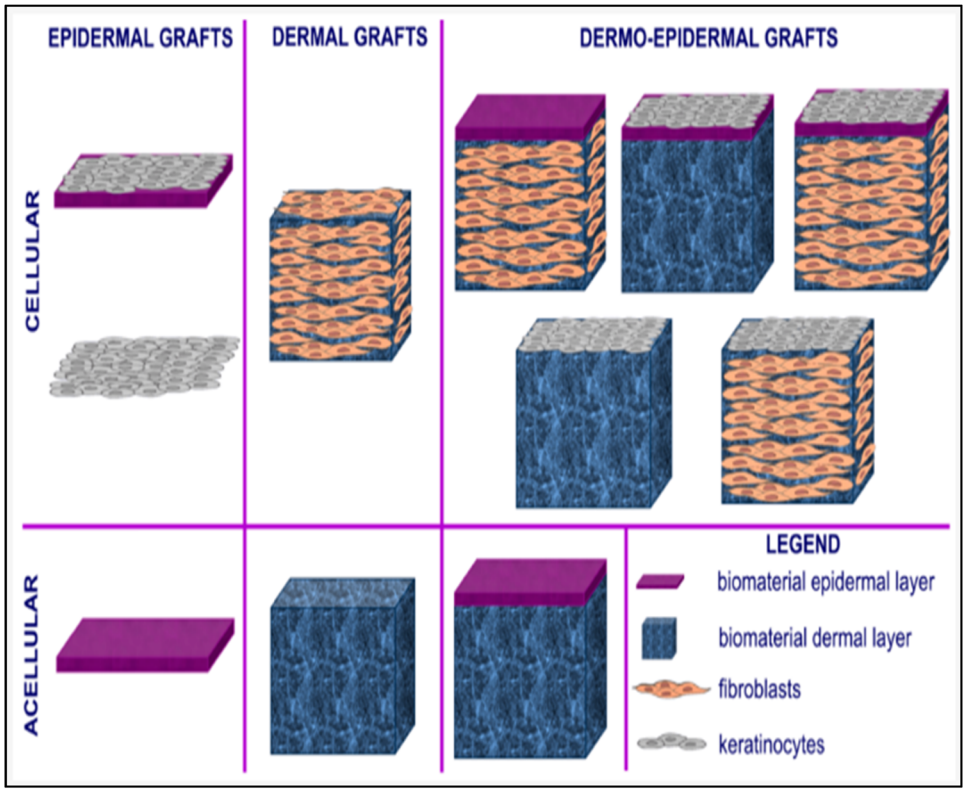

Figure 3: Skin grafts [19].

They include transferring skin from an uninjured site to the injured one [34]. Considered the gold standard, autografts provide great compatibility and low immune rejection. Yet, their use is limited by the availability of donor skin, especially in cases of extensive burn or injury. Furthermore, the harvest of autografts may lead to pain and scarring at the donor site [35]. Skin replacement using autografts represents the existing standard of care because it requires moving natural patient skin from available healthy locations to damaged areas. This grafting technique provides rejection-free restoration, but it becomes ineffective when patients lack adequate donor skin for transplantation, particularly when managing extensive burns or large wounds exceeding available skin reserves. Specifically, extracting autografts produces two separate wounds, which cause elevated discomfort and increase both infection risks and recovery time at all harvested areas. Autografts achieve suboptimal results in replacing native skin's detailed structure together with its complete functional properties despite adequate skin availability. Insufficient skin thickness leads to unfavourable cosmetic results and reduced range of motion over joints since it fails to mimic the original skin structure. The survival of autografts depends on adequate vascular development because poor blood circulation during severe injuries can cause incomplete integration and lead to graft deterioration.

- ***Allografts:*** Allografts, skin transplants from a human donor, usually are cadavers. They act as a makeshift aversion to infection fluid loss and are used to help granulation tissue grow [36]. Allografts act as a temporary solution until autografts or other permanent solutions are available [37]. Nevertheless, their usage is restricted due to the danger of immune rejection, possible disease transmission, and the high cost of tissue banking and processing. The transplanted skin in allograft procedures obtains its origin from genetically different donors and uses cadaver tissue as a temporary wound coverage method; however, these grafts present substantial drawbacks requiring 3D bioprinting solutions. The main drawback of allografts arises from immune rejection because the recipient recognizes transplanted donor tissue as foreign material. Patient rejection prevention through immunosuppressive medications poses risks to the patients who need them because these drugs increase their vulnerability to infections while causing additional medical problems. After patients receive immunosuppressant medication, the donor tissue does not remain permanently as the recipient's body continuously absorbs it. The shortage of donor skin exists because organ donation systems affect access to donor tissue, especially when mass burn injuries occur during crises. The current disease detection systems in donor tissue processing remain inadequate because infectious diseases may still spread between donors. The main purpose of allografts is to function as short-term biological dressings instead of permanent skin replacements, so patients may require further treatment to achieve lasting skin protection.
- ***Xenografts:*** Xenografts, which are from animal organisms (usually pig skin), are used as biological temporary dressings. They help shield the body from infections and dehydration and assist in wound healing [38]. According to Figure 4, xenografts are readily available and relatively inexpensive, making them practical for emergencies. Their characteristic ephemerality, potential immunogenicity, and inability to incorporate into native human tissue preclude their long-term implementation [25].
- ***Synthetic skin substitutes:*** Artificial skin substitutes are constructed either from synthetic polymers, which include silicones like silicone and polyurethane or are designed to mimic the protective membrane of the natural epidermis [39]. This is because these engineered materials are both non-toxic and biocompatible. The main factors that give synthetic substitutes a roadmap to the heart of success are the fact that they can be used anywhere, they have reduced immunogenicity, and they are quite easy to sterilize. Nevertheless, they mainly lack the physiologic stimuli for the whole regeneration of tissue, and by far, the applications are for just some temporary wound cover or cosmetic.
- ***Biological skin substitutes:*** On the other hand, products such as collagen-based scaffolds and de-cellularized dermal matrices are the main species of biological substitutes. Similar to the synthetic ones, they are designed to be biocompatible and to help cell attachment and tissue regeneration [40,41]. Major products in this sector, Integra and Matriderm, are the most used ones in clinical settings. They are effective; however, these substitutes can be very expensive and need very complex surgical techniques for implantation, which makes them not so much available in developing countries (Figure 5). The common practice of using ADMs in skin repair faces major shortcomings that demonstrate the value of implementing advanced 3D bioprinting solutions. ADM materials originate from human or animal tissue by removing all living cells to minimize possible rejection reactions in human bodies. The tissue decellularization process terminates valuable cellular components, which both limit integration into tissues and their

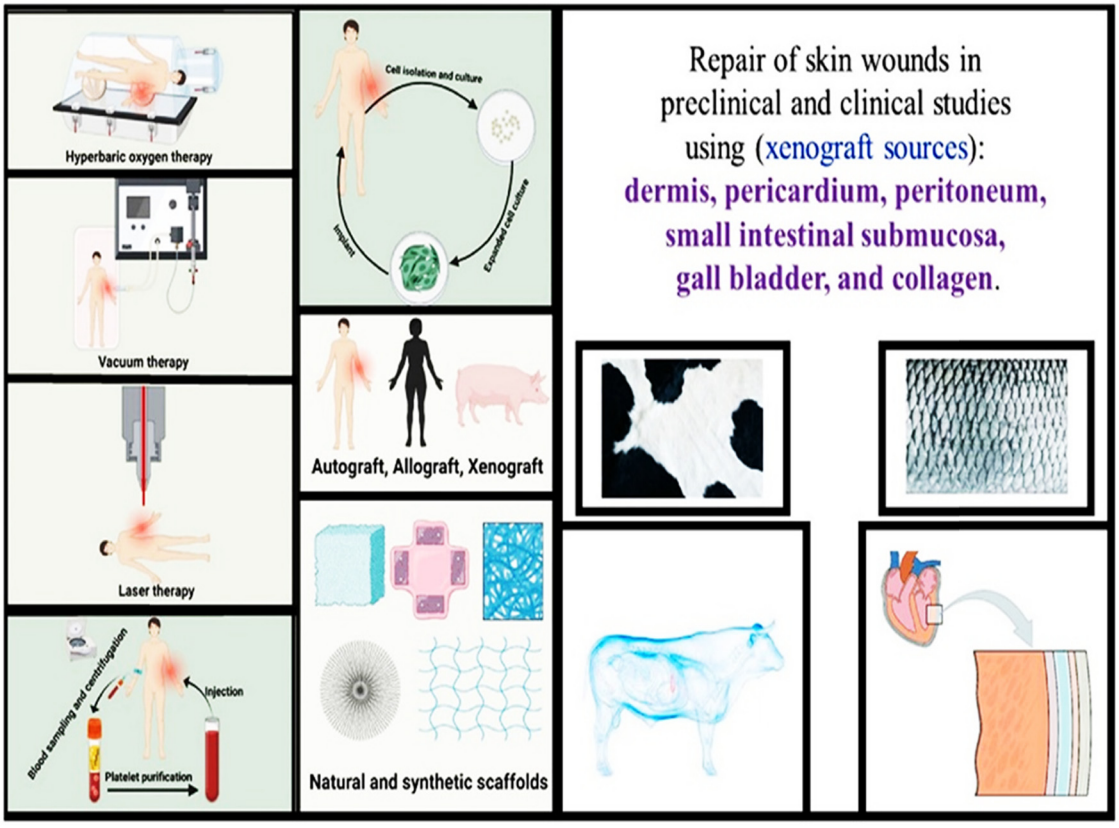

Figure 4: Xenografts [38].

effective functioning. ADM functionality to support swift artery formation diminishes when doctors remove living cells because the healing time lengthens, and procedure success becomes compromised in emergencies. These matrices achieve their functionality from patient body cells that need to populate them, yet the cell population process often shows inconsistent results in patients with poor healing capacity. ADM scaffolds need supplementary treatments such as cell seeding or growth factor applications since they lack fibroblasts, keratinocytes,

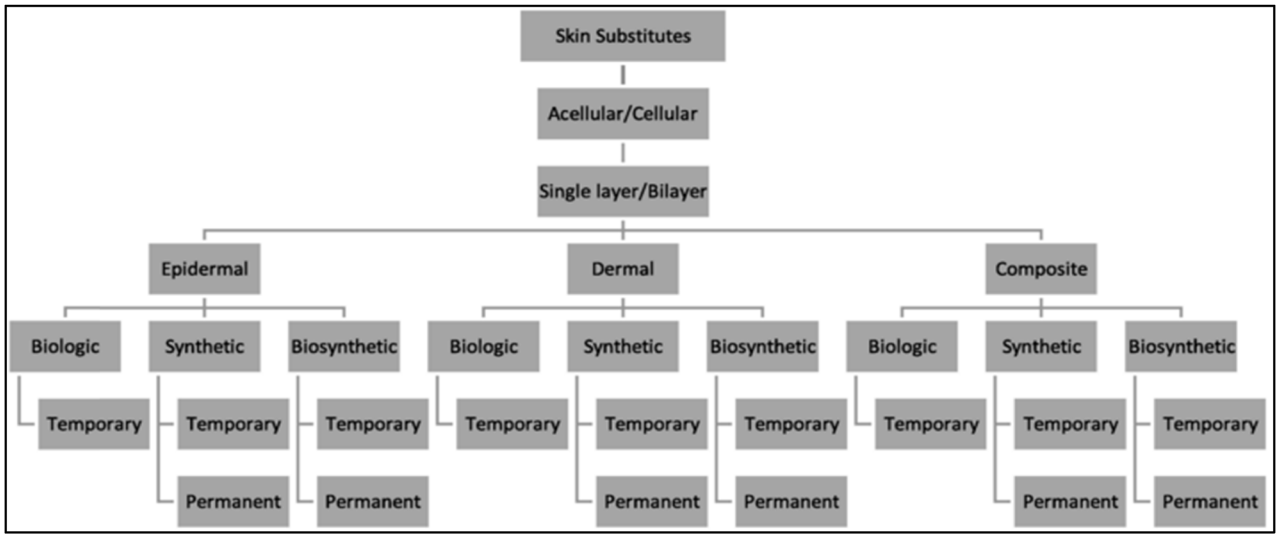

Figure 5: Skin substitutes [40].

and vascular structures, resulting in performance degradation procedure complexity and increased costs. ADM structures fail to match native skin biomechanics, which results in less elastic properties together with an unsatisfactory appearance and an intensified risk of graft failure, specifically in areas under movement.

- ***Composite skin substitutes:*** Composite substitutes are made up of both natural and synthetic materials to copy the qualities of human skin. As an example, Biobrane is a combination of a silicone film bonded to a nylon mesh that is covered with collagen [42]. These substitutes not only guarantee primary wound closure but also provide a matrix for tissue reformation. They act as a zenith; that is they are durable like synthetics and allow also for the biological part to integrate; the drawback is that they are usually difficult to manufacture and expensive.
- ***Hydrogels:*** Hydrogels are created using polymers containing a lot of water that is essential in healing a wound. They can be utilized as an intermediate covering for burns, ulcers, and surgical incisions. Hydrogels can also be used to target the area of the wound with drugs, growth factors, and even stem cells, which would provide better healing outcomes [43]. Although hydrogels are cheap and simple to apply, their mechanical properties and structural stability do not suffice when treating large or deep wounds, rendering them unsuitable as a stand-alone skin substitute [44].
- ***Tissue-engineered skin constructs:*** Apligraf and Dermagraft are dermal substitutes that contain living cells and biomaterials and are deemed laboratory-grown skin equivalents [45]. These products are aimed at replacing natural skin in a way that dermis and epidermal structures are incorporated as well. However, these constructs are still in use, high production cost, poor shelf life, and distribution problems restrict its mass use.
- ***Temporary biological dressings:*** Amniotic membranes and keratin-based films are examples of temporary dressings that are used as a short-term cover for wounds. Particularly, the biological barriers to infection and loss of moisture while assisting in the beginning stages of healing [46]. They are inexpensive and readily available, but because they cannot be used as a long-term remedy, they must be changed or complemented with better substitutes.

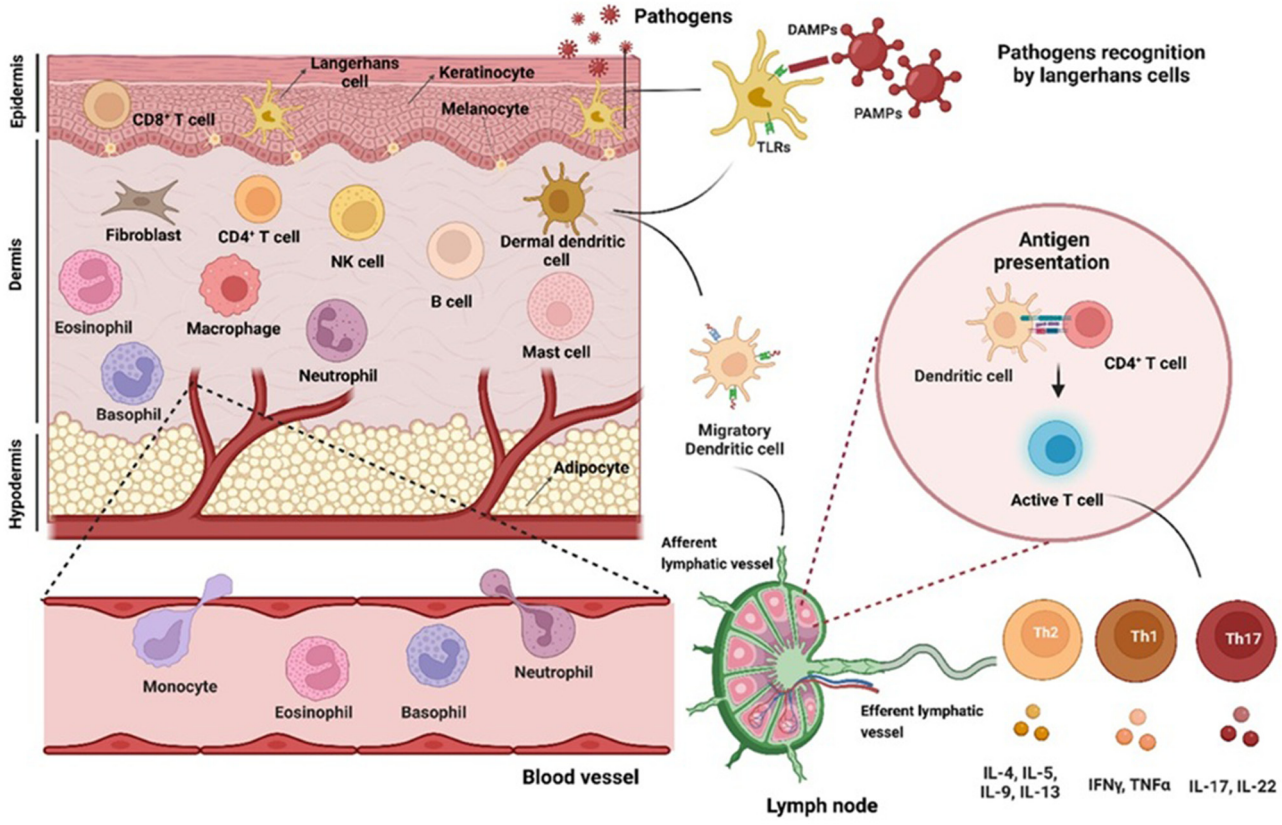

Figure 6: Antigen presentation [48].

3D bioprinting is essential for overcoming the major drawbacks of existing skin substitutes, including autografts, allografts, and ADMs, which frequently fall short in delivering a dependable, functional, and scalable treatment for extensive wounds and burns. Although autografts are the preferred standard, their use is restricted by limited donor sites, the creation of secondary injuries, and their inability to fully replicate natural skin properties. Allografts, while serving as temporary coverings, pose challenges such as immune rejection, risks of disease transmission, and supply constraints. ADMs, despite functioning as biological scaffolds, do not contain living cells or vascular structures, resulting in delayed healing and uneven tissue integration. Conversely, 3D bioprinting allows for the fabrication of customized skin grafts with precise control over cell arrangement, tissue architecture, and vascular networks, greatly enhancing graft viability and performance. By incorporating the patient's cells, bioprinted skin reduces the likelihood of immune rejection, accelerates tissue repair, and improves both aesthetic and functional outcomes. Furthermore, bioprinting supports scalable, on-demand skin production, minimizing reliance on scarce donor tissues and offering a ground-breaking approach for individuals with extensive skin damage. Consequently, 3D bioprinting is poised to revolutionize skin regeneration by providing a more efficient, personalized, and sustainable alternative to conventional skin grafting methods.

5 Host responses to the skin

When skin substitutes or artificial skin is put in place, several responses take place in the host's body in a complex manner. It is important to understand these responses for the purpose of optimizing the integration and functioning of skin substitutes and, at the same time, reducing the number of complications [47]. Responses of the host denote immunological response, the wound environment, and the substitute features. Below is an in-depth discussion of the key aspects of host responses:

- ***Inflammatory responses:*** The inflammatory phase is the first phase that is experienced by the host with respect to a skin substitute. Figure 6 shows that immune cells such as neutrophils and macrophages are still implanted, so they are actively engaged at this stage. These cells secrete cytokines and chemokines, which stimulate a series of responses that are aimed at clearing the debris and curbing possible infection [48].
  - Inflammation is an absolute prerequisite in the process of wound healing; however, in some cases, if inflammation is too pronounced or lasts longer, it can result in problems such as the slow rate of wound healing or even the rejection of the graft. The extent of this response is mainly influenced by the biocompatibility of the substitute.
- ***Immune reaction:*** The human body, as a result, might see the dermal impregnate viscera, such as the grafts or rotating tissue off the neck, as foreign and react to it. They do include the following, depending on their source and the level of immune response seen:
  - ***Autografts*** are immune-privileged since they are made from the tissue of the same individual [49].
  - ***Allografts and xenografts***, because they contain antigens that are non-self, tend to be more prone to immune rejection.
  - Removing cell components, ***synthetic substitutes,*** and decellularized scaffolds lowers the immune response, but due to remaining contaminants or characteristics of the material, they might still cause slight immune responses.
- ***Cellular integration:*** For their proper incorporation, the host cells must infiltrate the substitute for tissue reconstruction. Fibroblasts, keratinocytes, and endothelial cells produce new skin layers and vascular networks.
  - When a biologically derived substitute for the extracellular matrix (ECM) is used, a greater speed of cell adhesion and growth is observed [50].
  - Synthetic substitutes alone might not be reliable enough and may need surface treatments or the addition of biomolecules to boost interactions with cells and improve efficiency.
- ***Vascularisation:*** Angiogenesis, or the formation of new blood vessels, is one of the essential host's responses that will ensure that the skin substitute survives and integrates successfully [51]. If vascularization is not adequate, then due to ischemia, the graft may not be taken.
  - Collagenized matrices are some of the biological substitutes that decrease the ASD risk through the promotion of angiogenesis during the integration phase.
  - Even more vascularization is possible when growth factors such as vascular endothelial growth factor are included in the substitute [52].

The vasculogenic response, ECM synthesis, and tissue remodelling were carefully analysed based on factors such as the co-culture ratio, hydrogel stiffness, and pre-vascularization duration to assess *in vivo* integration with native vasculature. Spheroids co-cultured at a 3:1 ratio of hADSCs to HUVECs within a flexible hydrogel matrix exhibited the highest vasculogenic potential, eventually developing *in vitro* arteriole-scale vasculature with a longitudinal lumen structure and a complex vascular network after extended

culturing. Notably, the pre-vascularized tissue demonstrated successful anastomotic integration with host blood vessels post-transplantation, achieving effective vascularization marked by CD31 and alpha-smooth muscle actin expression, covering a luminal area of 18.6 ± 3.6 μm^2 [53].

One of the biggest challenges in bioprinted skin is establishing a functional vascular network, which is essential for graft survival and integration. Native skin contains an extensive network of blood vessels that supply oxygen and nutrients while eliminating metabolic waste. However, bioprinted skin constructs initially lack these vascular structures, making it difficult for deeper layers of cells to remain viable. Without adequate blood vessel formation, bioprinted grafts are at risk of necrosis, delayed integration with host tissue, and diminished overall performance. To tackle this issue, researchers are investigating multiple approaches, such as incorporating endothelial cells to create vascular structures, utilizing biomaterials that enhance vessel growth, and bioprinting pre-designed microchannels to facilitate blood flow. Progress in bioinks, controlled release of growth factors, and co-printing with supportive cells like pericytes and fibroblasts are also being explored to accelerate vascularization. Addressing this challenge is crucial to ensuring that bioprinted skin becomes a reliable, long-term alternative to conventional skin grafting techniques.

- ***Fibrosis and scar formation:*** This is quite common where the damaged portion of the host is able to heal but the healing is accompanied by an untoward proliferation of collagen and leads to fibrosis or hypertrophic scarring [54].
  - This is also true that they likely came closer to the nature of the skin regarding the biomechanical properties, and these substitutes were expected to induce less scarring.
  - The above goal could be achieved by preventing the occurrence of fibrosis with biomaterials with degrading rates and combining them with anti-fibrotic drugs.
- ***Inflammation-induced rejection:*** Rejection by the host is the major hurdle to overcome in the case of allografts and xenografts [55]. The T cells and antibodies could recognize these foreign substitutes' antigens, which are present and would cause graft failure.
  - However, immunosuppressive treatments run the risk of side effects.
  - A more suitable solution to reject risk factors is offered by decellularized skin substitutes, as they do not contain immunogenic cells.
- ***Chronic wounds and infection:*** The response of the host heavily depends on the wound environment. For instance, the presence of chronic wounds like diabetic ulcers is defined by higher levels of inflammatory markers and poor angiogenesis, which makes the acceptance of substitutes more difficult.
  - In order to reduce the risk of infection, skin substitutes that are synthesized with antimicrobial features, such as the presence of silver nanoparticles or others containing antimicrobial peptides, will be effective.
- ***Biomaterial-specific responses:*** The chosen biomaterial in the case of synthetic and composite substitutes impacts the host reaction considerably and is shown in Figure 7:
  - ***Synthetic polymers:*** Silicones and polyurethanes are durable and biocompatible materials; however, they do not contain biological elements to promote cellular incorporation [56].
  - ***Biological polymers:*** Collagen and hyaluronic acid are effective for adhesion and cellular regeneration; however, they could be quickly degraded or induce a low-grade inflammatory response [57].
  - ***Hybrid materials:*** Composite substitutes possess adequate biological properties and sufficient durability, thereby helping to modulate host responses effectively.

6 3D bioprinting of skin

The 3D bioprinting technology has practical applications in tissue engineering and regenerative medicine. It has overcome the existing problems in developing and implanting usable skin substitutes. Its approach involves the use of biomaterials and living cells to produce structures that imitate the anatomy and function of human skin. 3D bioprinting for the skin along with certain issues and questions that raise interest are next discussed.

6.1 Principles of 3D bioprinting

The CAD design turns into reality with the use of bioprinting techniques as bioinks containing cells [58], biomaterials, and bioactive molecules for skin fabrication are layered. The skin creation process involves the following three phases, as shown in Figure 8:

- ***Before printing***, create bioinks and CAD imaging to design the desired model [59].
- ***During printing:*** Printers are designed to use bioink sprays in levels following the designed image [60].

- ***After printing:*** Moving the constructed image to bioreactors for sustaining temperature, humidity, and nutrients that enhance cell and tissue growth [61].

This accuracy creates foundations for reproducing dermal and epidermal tissues and structures such that the complexity of the natural skin is duplicated.

6.2 Bioinks for skin bioprinting

Bioinks are of great importance in 3D bioprinting because it is connected to the biocompatibility and structural stability of the skin graft.

- ***Natural polymers:*** Compounds such as collagen, gelatine, and hyaluronic acid are frequently utilized because they are like the ECM. As such, these are the best polymers for fostering cell adhesion and growth [62].
- ***Synthetic polymers:*** Polyethylene glycol and polylactic acid do provide some mechanical strength but their bioactivity may be lacking, and so they require blending with natural polymers [63].
- ***Cell-loaded bioinks:*** To build the skin in layers, keratinocytes construct the epidermis, fibroblasts construct the dermis, and melanocytes provide pigmentation. Additionally, growth factors and stem cells may be added to enhance regenerative properties.

Recent discoveries involve bioinks through the reinforcement of de-cellularized extracellular matrix (dECM), which can improve biomimicry and vascularization [64]. In addition, shear-thinning hydrogels and nanocomposite bioinks elevate printability, mechanical strength, and cell viability, while the introduction of oxygen-releasing materials ensures the life of cells during the earliest part of the graft development process [44,64].

6.3 Fabrication of multilayered skin

It becomes quite a daunting task to print a skin correctly because it emerges from multiple differentiated layers of diverse properties.

- Epidermis: It is made up of keratinocytes that form the primary barrier, the outermost layer.

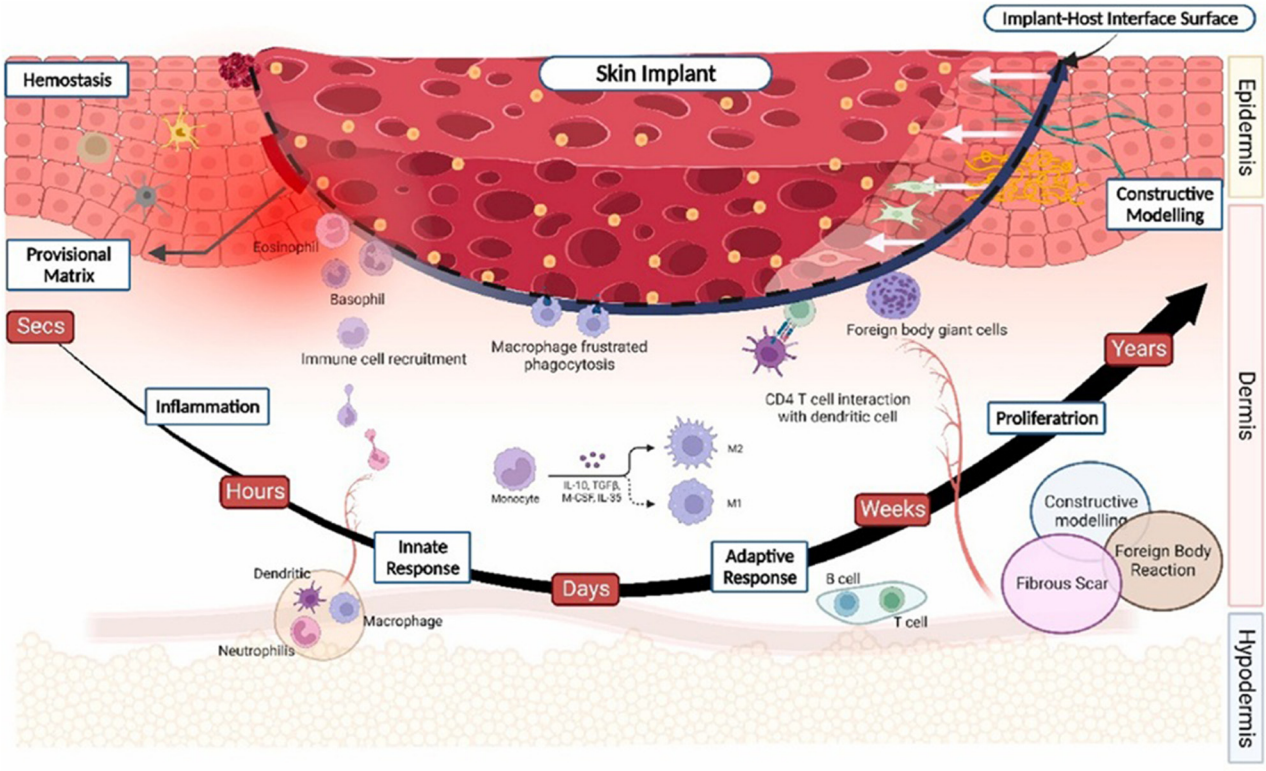

Figure 7: Implementation of the biomaterial in the skin [47].

- Dermis: A thick layer of fibroblasts filled and packed with different types of collagens and cellular matrix proteins that support structures [65]. Here, several protein-based engineered materials are discussed [66]. An effective evaluation at the clinical level provides functional support for tissue repair.
- Vascular networks: Blood vessels can be incorporated within a skin substitute to allow the processes of nourishing and waste removal to take part by 3D bioprinting, thus allowing the incorporation of endothelial cells (Figure 9).

6.4 Techniques in 3D bioprinting for skin

Skin bioprinting is a domain in which many measures have been taken for accuracy and functionality:

- Inkjet bioprinting: The method of creating an epidermal layer by spraying bioink droplets onto a surface [67].
- Extrusion bioprinting: It makes it easy to build denser strips of bioink that can be used as dermis tissues.
- It is laser-assisted bioprinting, which is suitable for enhancing the permeability of bioinks as it uses lasers to position the droplet on the site targeted. This enables high resolution and is advantageous for vascularization [68].

Because of the limitations of each procedure, it becomes ludicrous and costly to deploy a particular procedure when clinical needs differ. According to Table 1, there are different types of bioprinting to be used for 3D bioprinting of skins. A comparison of different techniques has been made depending on resolution, speed, economics, and cell viability (Table 2).

6.5 Applications of 3D bioprinted skin

3D bioprinted skin can be utilized in various sectors and industries, including healthcare, beauty, *etc.*:

- ***Wound healing and burns treatment:*** In major wounds and burns, the available substitute tissue immediately covers the torn skin and promotes the regeneration of the affected area [69].
- ***Cosmetic testing:*** There is a significant shift away from animal use. For example, a cosmetic skin bioprinter now has a skin bioprinter that tests cosmetics marketed to women.
- ***Disease modelling:*** It enables research on the pathologies of skin diseases such as melanoma or psoriasis, which would be hard to do *in vivo*.
- ***Personalized medicine:*** This would be preferable in situations where bioengineered somatic cells are strong enough to withstand immune rejection.

6.6 Challenges in 3D skin bioprinting

Despite its advantages, the bioprinting of skin in 3D is faced with the following issues:

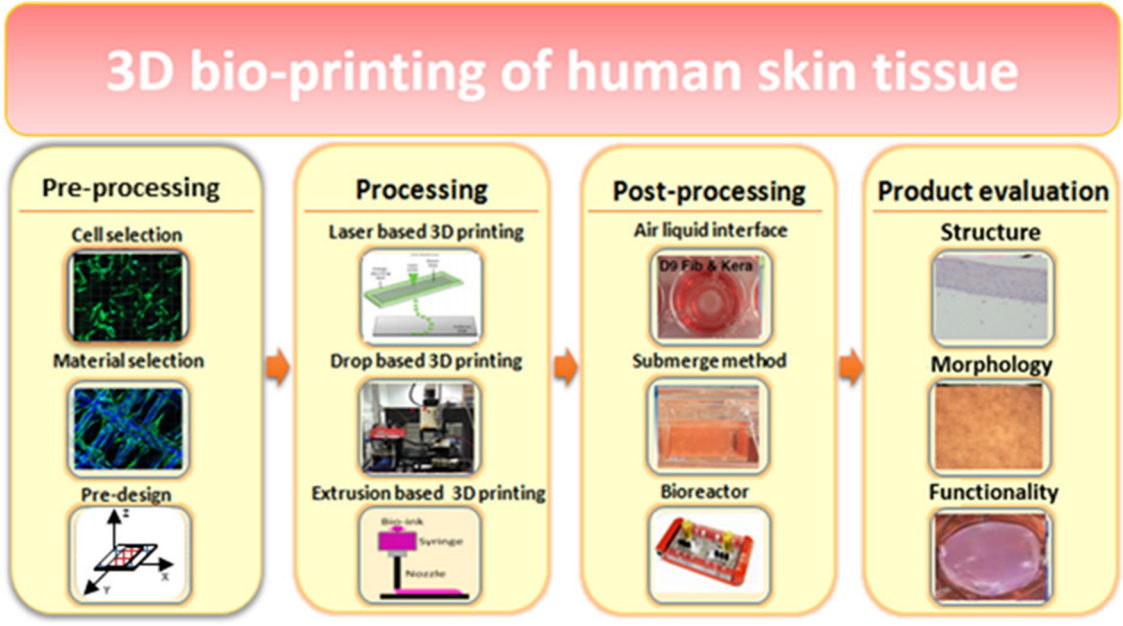

Figure 8: Process of 3D bioprinting [60].

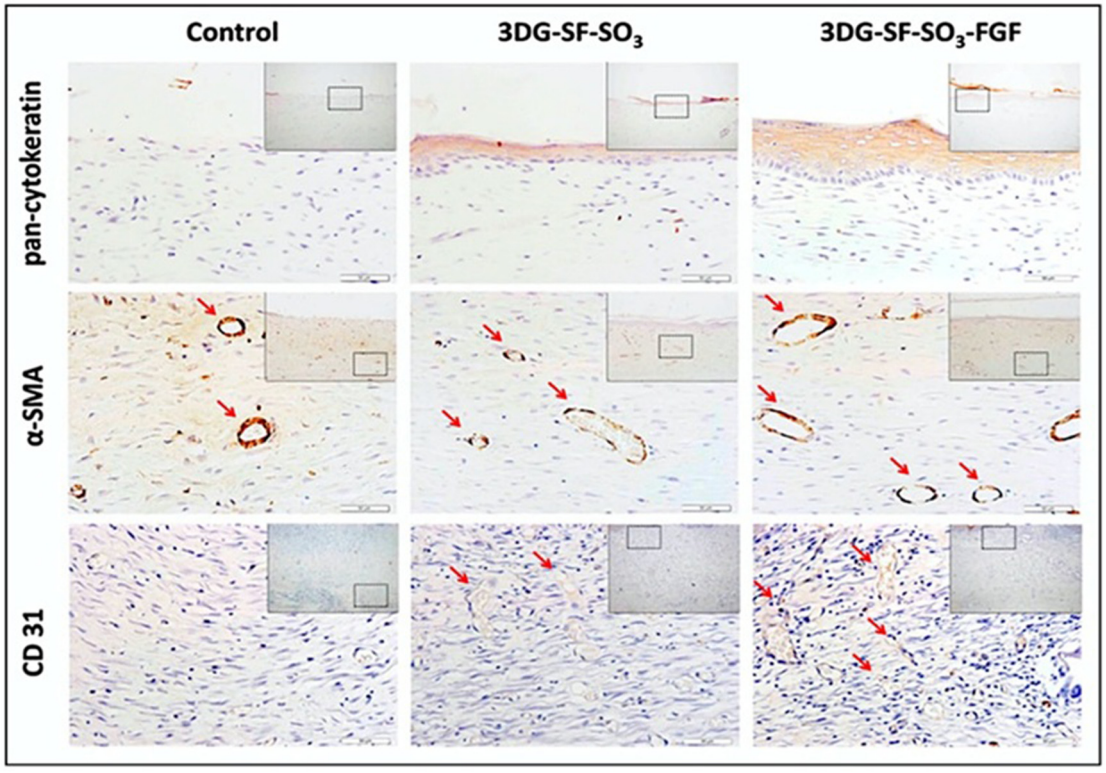

Figure 9: Epidermis and blood vessel formation in skin defects [61].

Table 1: Degradation, integration, and impact of bioink

Bioink	Degradation and integration	Impact on long-term efficacy
Natural polymers	Enzymatically degraded, integrates well with host tissue	Enhances cell adhesion
Synthetic polymers	Slower degradation may cause inflammation if not biocompatible	Provides structural stability
Cell-loaded bioinks	Gradual breakdown promotes tissue regeneration	Supports long-term functionality
dECM-based bioinks	Mimics native ECM enhances vascularization	Improves host compatibility
Nanocomposite bioinks	Controlled degradation, improved mechanical strength	Ensures durability

- ***Vascularization:*** Reinforcing the supply of blood to thick constructs of skin from within is a problem. Without vascular networks, larger grafts risk necrosis.
- ***Mechanical properties:*** Skin substitutes possessing mechanical and elastic properties found in natural skin are complex mostly when the substitutes are designed for parts subject to a lot of action, for example, joints.
- ***Cost and scalability:*** The production and availability of bioprinters, bioinks, and cell culturing are regulated by their high demand in the market, making their production more costly.

Table 2: Comparison of techniques

Techniques	Resolution	Speed	Cost-effectiveness	Cell viability	Key advantages
Inkjet bioprinting	Moderate	High	Cost-effective	Moderate	Rapid, scalable, low cost
Extrusion bioprinting	Low	Moderate	Affordable	High	Prints dense bioinks
Laser-assisted bioprinting	High	Low	Expensive	High	Precise, enhances vascularization

- ***Regulatory and ethical issues:*** To be able to use bioprinting of skin for clinical approaches, it has to pass through several regulations to be verified as safe and effective.

6.7 Future directions

There are developments that are designed to target the current gaps in bioprinted skin and increase the scope of bioprinted skin:

- ***Advanced biomaterials:*** Functionality is designed to be improved through the emergence of shapes whose focus is on enhancing their bioinks so that they can react to stimuli such as temperature or pH.
- ***Incorporating appendages:*** Additional aims include genetically printing skin with hair follicles, sebaceous glands, and sweat glands to improve the appearance of the skin and to provide functionality [70].
- ***Automation and scalability:*** Automation of the print bioprocess and improved scalability will reduce the cost and availability of the technology.
- ***Artificial intelligence (AI):*** AI allows for optimization of the parameters for the printing of inks, and this directly influences the composition of a bioink with a bioprinter, improving bioprinting and increasing efficiency [71].

Some good ideas for nanotechnology-modified bioinks are worth investigating, especially those with good mechanical strength and activity. Furthermore, the use of microfluidic systems that may aid in vascularization could be successful, such as bioprinting with immune-modulatory biomaterials, which might improve graft integration

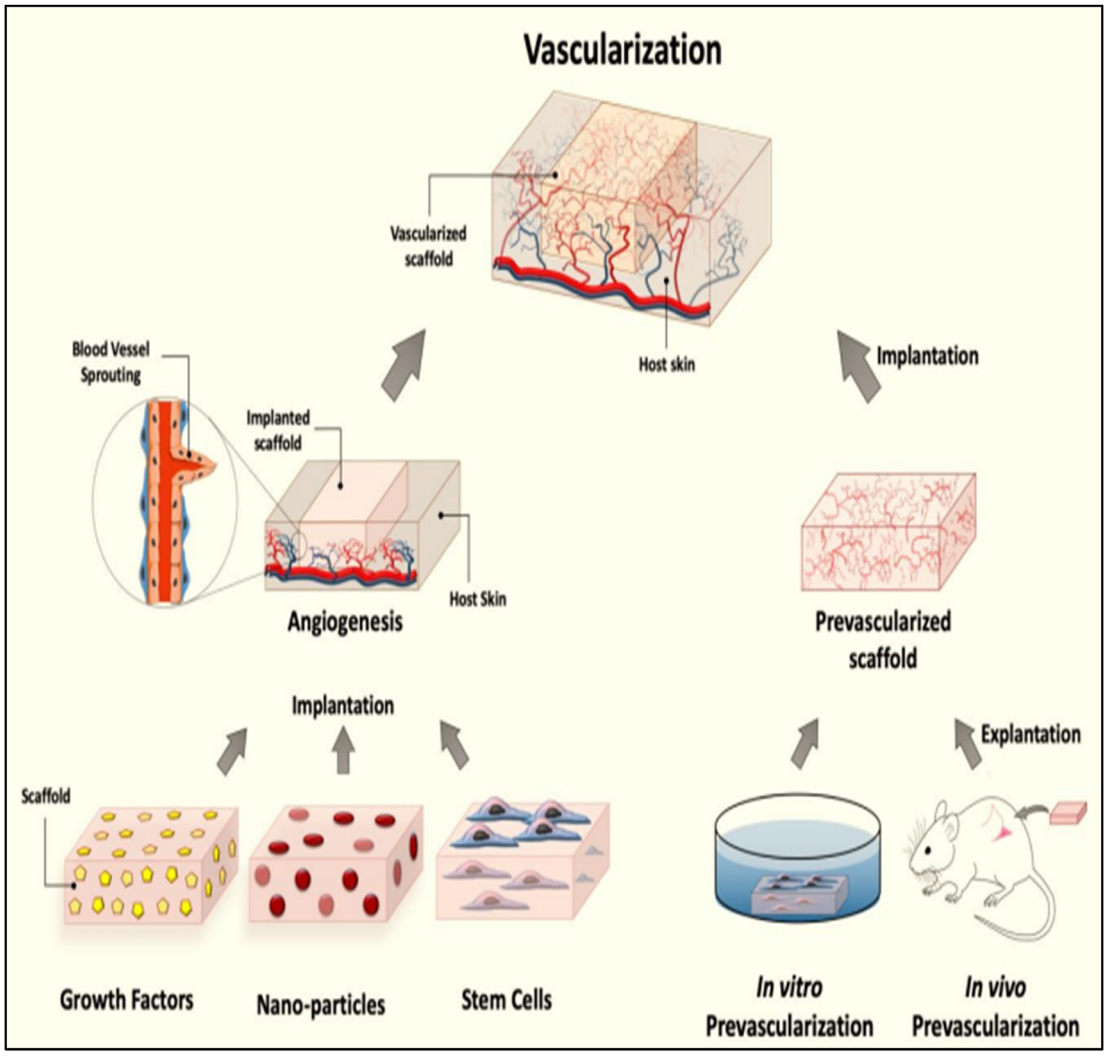

Figure 10: Vascularization [72].

and lower the risk of rejection as well as the expansion of the clinical applications of bio-printed skin [73].

7 Challenges and future direction

In a very intriguing fashion, the use of 3D bioprinting to create skin is still in its adolescent stage, and many hurdles need to be overcome to extract maximum benefit from it. Bioprinting has a multitude of restrictions that include the incorporation of biology, technology, and policy, which influence both its commercialization and usage in treatments.

7.1 Challenges

- ***Vascularization:*** A major downside is that it is not yet possible to integrate working vascular systems into our bioprinted skin, which is a need in order for it to work with efficacy. As shown in Figure 10, the skin tissue is printed without blood vessels and is able to provide an inadequate supply of nutrients, which may lead to skin decomposition [72]. On the other hand, the skin will decompose if it is too thick without the blood vessels to ensure growth. Co-printing of endothelial cells could be a good alternative; however, it is not a long-term solution.
- ***Mechanical properties and durability:*** Artificially constructed skin, on some occasions, is unable to mirror the strength, flexibility, and endurance that natural skin possesses. This is a huge concern, especially for the skin placed on joints or hands, because there is excessive movement in these places, and devices find it hard to maintain a good level of physical integrity [8]. This is an age-old problem of striking a balance between biology and physical integrity; this is something that has yet to develop.
- ***Biocompatibility and immune response:*** As effective as biomaterials are in lowering immunogenicity, some substitutes always lead to an inflamed or rejected body [74]. However, this issue can be handled through personalized bioprinting, but it is expensive and time consuming.
- ***Cost and scalability:*** 3D bioprinters, bioinks, and the entire process of cell culturing are still too costly for general use in the clinic [75]. The increase in volume of production without compromising quality and functionality is one of the greatest obstacles to commercialization.
- ***Regulatory hurdles:*** For bioprinter skin to be used in clinics, the implementation of different legislative policies should be addressed. The task of assuring safety, efficacy, and uniformity while addressing the ethical controversies surrounding bioengineered tissues is quite time-consuming.

7.2 Future directions

- ***Advancements in vascularization:*** A detailed research work is underway in order to combine angiogenic factors with state-of-the-art printing methods such as microfluidics so that vascular networks are formed. With improved vascularization, the survival rate of the thicker constructs will be better.
- ***Smart biomaterials:*** Improved smart bioinks are in the research stage that requires biological inks, which would respond actively to the environment, such as healing themselves or degrading themselves in a controlled manner [76].
- ***Incorporating appendages:*** Strategies to add hair follicles, sweat glands, and sebaceous glands would improve transplant outcomes by restoring the functional and cosmetic properties of the skin.
- ***Automation and AI integration:*** Through automation and AI, we aim to improve bioprinting approaches, such as the formulation of bioinks and printing parameters, making the technology more efficient and economical [77].
- ***Collaboration and regulation:*** Greater engagement between researchers, industry actors, and regulators can facilitate the translation of research into clinical use. Efforts to ease the processes of gaining approvals and develop specific guidelines will promote uptake.
- ***Integration of nanotechnology:*** The mechanical strength and tissue integration of artificial skin is one of the foremost challenges for researchers. The integration of nanotechnology may resolve this issue. The incorporation of silica, nanocellulose (based nanoparticles), and hydrogel-based nanocomposites may improve the mechanical strength and tissue integration.

Getting regulatory clearance for 3D bioprinted skin is tough because the FDA and EMA are unyielding when it comes to safety, effectiveness, and moral concerns [77]. The significant challenges are in vessel development, immune effect, and technology in large quantities. Enterprises like Organovo and experts are doing an excellent job of refining the process of developing bioengineered supports

and overseeing the quality of production by using intelligent artificial channels [78].

8 Conclusions

The 3D bioprinting technology for skin development is a significant innovation in tissue engineering and regenerative medicine. This technology helps to meet vital requirements for wound healing, burn treatment, cosmetic purposes, and even tailored medicine, as it strives to replicate closely the complex architecture and functionality of human skin [58]. The issues, however, with vascularization, mechanical strength, costs, and regulations are still considerable obstacles to applying this technology in practice. However, there are emerging trends in biocompatible materials, printing methods, as well as, the use of AI, which promise to resolve these problems.

A further headway is expected to be the production of fully functional skin substitutes, with appendages, that can be produced in a wide variety of formats and are more compatible with body tissues. Joint efforts among the researchers, the industry, and the regulators will be crucial for enabling faster clinical translation. In summary, while the 3D bioprinting of skin has not fully matured yet, it is bound to change the way the future operates, and it is already easy to see a time when the desired replacement of skin would be easier, quicker and more efficient. In the future, AI-assisted bioprinting will be capable of printing with high precision and efficiency or the utilization of custom skin grafts derived from a patient's cells to ensure they are compatible and their integration is successful.

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