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BURNS

Systematic Review

CURRENT UPDATES OF BIOMATERIALS FOR SKIN REPLACEMENT: A SYSTEMATIC REVIEW

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ABSTRACT

Background: The human skin envelops the entire body surface and is highly susceptible to damage. Partial- and full-thickness skin loss often necessitates the use of skin substitutes. Autologous grafting remains the gold standard for skin replacement. Furthermore, the application is usually constrained by the limited availability of donor skin, the technical challenges of surgery, and the added difficulties encountered in severe cases. In this systematic review, we summarise the strengths and limitations of biological and synthetic biomaterials as skin substitutes, with evidence drawn from clinical practice, human trials, and preclinical animal studies. This systematic review evaluates the advantages and disadvantages of biological and synthetic biomaterials used as skin substitutes, drawing evidence from clinical practice, human studies, and animal studies."
Method: We performed a comprehensive literature review using the search engines OVID, ScienceDirect, Google Scholar, and PubMed databases. Search terms or keywords included "artificial skin," "biomaterials," "skin substitute," "full-thickness burn," "synthetic materials," "burn graft materials," and "wound care." From an initial pool of 97 articles, 65 met the inclusion criteria, which required peer-reviewed studies published in English after 2000, focusing on biomaterials for skin substitutes evaluated in clinical, human, or animal studies.
Result: Skin substitutes commercially available in the market were predominantly incorporated with human fibroblasts and keratinocytes within a three-dimensional matrix, with a preference for biological materials due to their biocompatibility. Nevertheless, biological substitutes face challenges such as limited availability, extended production time, high costs, and lack of immediate usability. In contrast, synthetic substitutes are more accessible and scalable but often do not integrate well with the recipient's tissue, which limits their clinical efficacy.
Conclusion: While both biological and synthetic artificial skin substitutes are available on the market, none of the current options fully meet the ideal criteria for skin replacement, such as affordability, availability, seamless integration with the surrounding tissue, and the ability to minimise scarring. More research is needed to address these limitations and advance the development of next-generation biomaterials that can effectively replace skin.

***Keywords**: Artificial skin, Biomaterials, 3-D scaffold, Skin substitute, Full-thickness burn*

Latar Belakang: Kulit manusia menyelubungi seluruh permukaan tubuh dan sangat rentan terhadap kerusakan. Kehilangan kulit parsial maupun total sering memerlukan penggunaan pengganti kulit. Cangkok autologus tetap menjadi standar emas untuk penggantian kulit. Namun, aplikasinya sering terkendala oleh keterbatasan ketersediaan donor kulit, tantangan teknis pembedahan, serta kesulitan tambahan pada kasus-kasus berat. Dalam tinjauan sistematis ini, kami merangkum kelebihan dan keterbatasan biomaterial biologis dan sintetis sebagai pengganti kulit, dengan bukti yang diambil dari praktik klinis, uji coba pada manusia, serta studi praklinis pada hewan.
Metodologi: Kami melakukan telaah pustaka komprehensif menggunakan mesin pencari OVID, ScienceDirect, Google Scholar, dan PubMed. Istilah pencarian meliputi: *artificial skin*, *biomaterials*, *skin substitute*, *full-thickness burn*, *synthetic materials*, *burn graft materials*, dan *wound care*. Dari 97 artikel awal, sebanyak 65 memenuhi kriteria inklusi, yaitu penelitian yang telah ditinjau sejawat, diterbitkan dalam bahasa Inggris setelah tahun 2000, dan berfokus pada biomaterial untuk pengganti kulit yang dievaluasi pada studi klinis, manusia, atau hewan.
Hasil: Pengganti kulit yang tersedia secara komersial umumnya dikombinasikan dengan fibroblas manusia dan keratinosit dalam matriks tiga dimensi, dengan preferensi pada material biologis karena sifat biokompatibilitasnya. Meski demikian, pengganti biologis menghadapi kendala berupa ketersediaan yang terbatas, waktu produksi yang lama, biaya tinggi, serta tidak dapat digunakan secara langsung. Sebaliknya, pengganti sintetis lebih mudah

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diakses dan dapat diproduksi dalam skala besar, namun sering kali tidak terintegrasi dengan baik pada jaringan penerima sehingga membatasi efektivitas klinisnya.
Kesimpulan: Meskipun baik pengganti kulit biologis maupun sintetis telah tersedia di pasaran, belum ada satu pun yang sepenuhnya memenuhi kriteria ideal pengganti kulit, seperti keterjangkauan, ketersediaan, integrasi sempurna dengan jaringan sekitarnya, serta kemampuan untuk meminimalkan jaringan parut. Penelitian lebih lanjut diperlukan untuk mengatasi keterbatasan ini dan mengembangkan **biomaterial generasi berikutnya** yang mampu secara efektif menggantikan kulit.

Kata Kunci: *Kulit buatan; Biomaterial; Rangka tiga dimensi; Pengganti kulit; Luka bakar total*

Conflicts of Interest Statement:
The authors listed in this manuscript declare the absence of any conflict of interest on the subject matter or materials discussed.

INTRODUCTION

The human skin, as the body's largest organ, envelops the entire surface area, rendering it highly susceptible to injury. Cutaneous lesions vary from minor abrasions to severe dermal damage. Minor abrasions, such as excoriations, typically resolve spontaneously within days. However, severe dermal damage necessitates the use of skin substitutes for effective treatment [1, 2]. Skin wounds or injuries might result from several factors, such as mechanical trauma (like cuts or diabetic ulcers), thermal injuries (such as burns from heat or chemicals), full and partial-thickness burns, and infections [3-7]. Burns are notably the fourth leading cause of injury worldwide, following traffic accidents, falls, and interpersonal violence [7]. Over 11 million cases of fire-related injuries occur annually, resulting in approximately 300,000 fatalities globally [8].

A meta-analysis of 19 economic studies in 13 countries with equal Human Development Index/ HDI scores indicated that total medical expenditures per patient with acute burn varied between US$10.58 to US$125,597.86, while the treatment cost of each 1% of body surface area ranged between US$2.65 to US$11,245.04, and hospitalisation cost was US$24.23 to US$4,125.50 per day[9]. The average budget per burn patient in countries with high GDP was $88,218, varying from $704 to $717,306 [10]. However, reliable information on Indonesian burn care expenditures is limited. According to published data, the allocation of burn treatment consumed around 5.6% of all medical expenses. This data excludes the significant spending in advanced surgical and comprehensive interventions for certain burn situations [11]. Hence, burn injuries impose a significant social and economic burden, particularly on individuals with disabilities, who face long-term challenges due to severe post-burn scarring. The high financial cost of managing burn patients underscores the urgent need for treatment strategies that are both clinically effective and economically sustainable.

Over the last 25 years, the tissue engineering field has made great progress in producing practical therapeutics for individual therapy. The initial clinical report, which used scaffolds in the treatment of large and fatal burns. O'Connor et al. in 1981 demonstrated the successful application of cultured epidermal autografts for treating extensive and life-threatening burns, marking a pivotal milestone in burn care [12, 13]. Biomaterials such as human placenta, hydrogel, collagen, cellulose, and chitosan offer advantageous properties, including biocompatibility, biodegradability, sustainability, and cost-effectiveness, thereby reducing the environmental impact associated with their production and disposal. Beyond their favourable material characteristics, these biopolymers enhance wound healing by promoting angiogenesis and reducing infection risk [14, 15].

This review extensively explores multifunctional biomaterials or natural sources with the potential to revolutionise burn management strategies by accelerating tissue regeneration, minimising scarring, and mitigating subsequent tissue damage [16, 17]. Compared to synthetic alternatives, biomaterial-based wound treatments have proven more effective in wound care management, primarily due to reduced frequency of dressing changes. Clinical studies have shown that microbial cellulose dressings for partial-thickness burns can reduce wound care costs by two to three times compared to polyurethane (PU) film dressings widely used synthetic materials [18]. The research indicates bio-cellulose dressings outperform

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conventional options (e.g., surgical pads, tulle grass, saline-soaked gauze) in terms of efficacy and cost. Key parameters evaluated include average dressing change interval, material costs, leakage, and complications. Conventional dressings typically require seven changes per week, whereas bio-cellulose dressings necessitate only 1.4 changes per week. Over three months, bio-cellulose dressings combined with foam reduced treatment costs by 61.9%, while bio-cellulose dressings with film achieved a cost reduction of 73.7%. These findings highlight the potential of biomaterials to significantly lower wound care management costs, which account for approximately 4% of total healthcare expenditures. With the global wound management industry projected to exceed $18.5 billion in 2021, the adoption of cost-effective and efficient biomaterial-based strategies promises substantial economic and clinical benefits [19].

The gold standard for treating severe wounds remains skin transplantation, utilising autografts from the patient's own healthy skin or, less commonly, allografts from a compatible donor [20]. However, this approach faces significant limitations due to the restricted availability of donor skin. The Healthcare Cost and Utilisation Project reported 160,000 skin transplantations annually in the US, performed in 1 out of 3 of all burn patients [21]. Autologous grafts are constrained by the need for multiple surgical procedures, limited availability of healthy skin, and challenges in elderly or critically ill patients. Allogeneic grafts, requiring human leukocyte antigen (HLA) matching, are similarly limited by availability and compatibility issues.

Consequently, there is an urgent demand for materials which available, accessible and effective as skin substitutes. An ideal skin substitute should be cost-effective, shelf-stable, non-immunogenic, biomechanically robust, flexible, resistant to evaporative water loss and microbial contamination, adherent to the wound bed, adaptable to the recipient's size and age, applicable in a single procedure, and capable of minimising scar formation [22]. This review evaluates a range of biological and synthetic biomaterials which currently available or under investigation as skin substitutes, drawing on evidence from human clinical studies and animal models.

METHOD

Inclusion criteria

This systematic review included studies evaluating biomaterials for skin substitutes, encompassing both synthetic and biological materials, commercially available products, and those under investigation. Only peer-reviewed articles published in English after 2000 were considered. Studies published before 2000 or in languages other than English were excluded.

Data collection

A literature review was selected using OVID, ScienceDirect, Google Scholar, and PubMed databases. Search terms included "skin substitute," "human and animal study," "biomaterial," and "synthetic artificial skin." The initial pool of 97 articles was then reduced to 65 were selected for review, focusing on biomaterials (biological and synthetic) used in clinical settings or evaluated in human or animal studies. The review adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

RESULTS

This systematic review focuses on both biomaterials and synthetic materials that are commercially available and frequently used in clinical settings, as well as those that remain under investigation in human studies and animal models.

Skin artificial used currently in the market Biological Source

Several scaffolds made from biological sources contain emollient, demulcent, epithelialisation, astringent, antibacterial (topical antibiotics and antifungal medicines), and antioxidant characteristics beneficial for wound recovery [23]. The scaffolds are impregnated with collagen, enzyme debriding agents and antimicrobials (topical antibiotics and antifungal medicines). Silver sulfadiazine, methylene blue, violet crystals, honey, polyhexamethylene biguanide (PHMB), and cadexomer iodine, to prevent localised infections, particularly in chronic wounds [24]. Commercially available biological scaffolds discussed in this review: Epifix® (Epidermal substitutes) (MiMedx, USA), ReCell CellSpray (Epidermal substitutes) (Avita Medical Europe Ltd, Melbourne, UK), Grafix

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(Dermal substitutes) (Osiris Therapeutics Inc. in Columbia, MD, USA), Dermagraft (Smith and Nephew, USA), Apligraf (Organogenesis Inc., USA), OrCel (Ortec International, Inc., USA).

RECELL® CellSpray (Avita Medical Europe Ltd, Melbourne, UK)

An epidermal substitute utilising autologous keratinocytes and fibroblasts, isolated from a small split-thickness biopsy and diluted in a lactate solution for application at a 1:80 donor-to-recipient ratio. FDA-approved in September 2018 for acute partial-thickness burns in patients aged ≥18 years and for use with meshed autografts in pediatric and adult patients, RECELL® demonstrated outcomes comparable to autologous skin grafts in a study of 82 burn patients [25]. However, its use in full-thickness burns requires a meshed split-thickness autograft, and direct application as an epidermal autograft yields suboptimal scarring outcomes. The latest version of the product requires primarily manual procedures or hands-on steps involved in cell preparation. After cutting a small piece of skin (no more than 6 cm^2) with enzymes inside the instrument, the clinician must physically separate the skin layers, scrape the tissue to release the cells, draw them up, filter them, and ultimately combine them into a solution to be sprayed back onto the patient. Further development is needed [26].

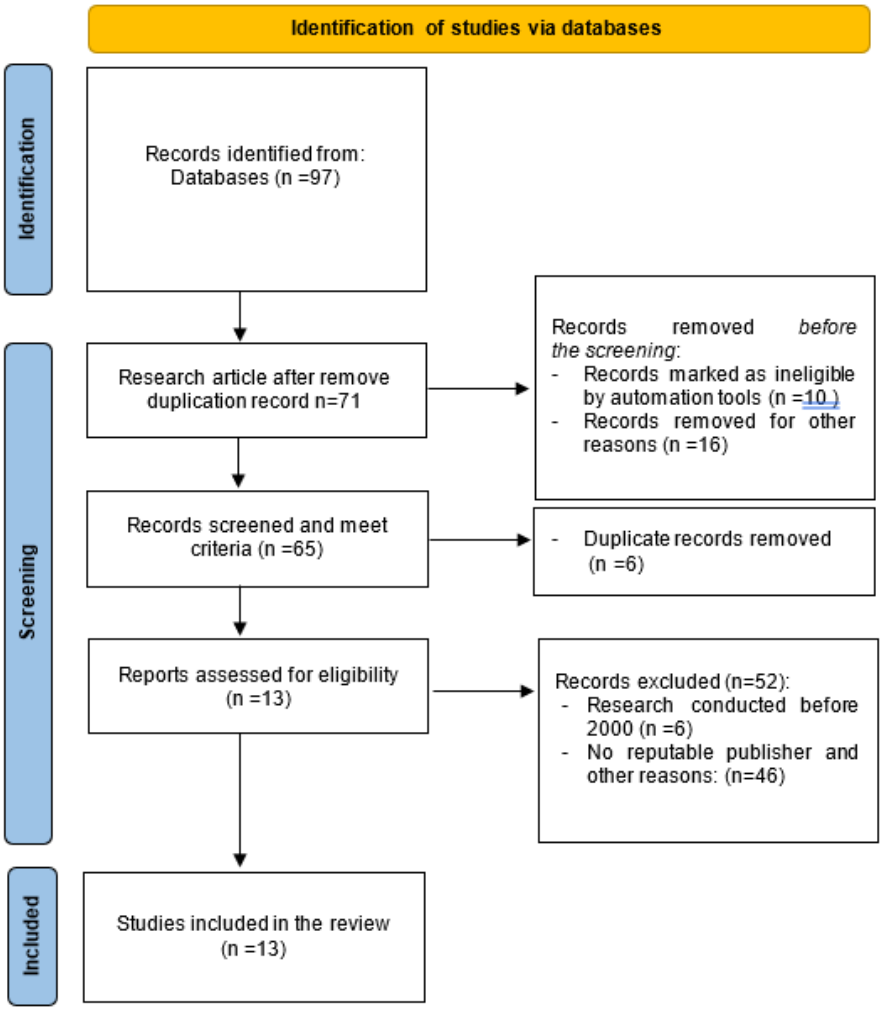

Figure 1. *PRISMA flowchart illustrating the selection and identification process for systematic review.*

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EPIFIX® (MiMedx, USA)

Epifix is a skin substitute consisting of dehydrated allograft, amniotic, and chorionic membranes used to treat acute or long-term wounds caused by dehydrated allograft, amniotic, and chorionic membranes [27, 28]. A total of 52 patients getting Epifix® weekly are more likely to undergo complete wound repair compared to those obtaining routine wound treatment and compression (60% versus 35% at 12 weeks) [29].

Study of 100 diabetic foot ulcer patients treated using EpiFix and Apligraf (Organogenesis Inc., Canton, MA, USA) compared to SOC (Standart of Care) within 12 weeks, by week 12, 97% of Epifix® patients had completely closed their wounds; in contrast to 73% of Apligraf patients and 51% of those who received SOC alone (adjusted P=0.00019) [30]. A total of 52 venous ulcer patients getting Epifix® weekly are more likely to undergo complete wound repair compared to those obtaining routine wound treatment and compression (60% versus 35% at 12 weeks) [29]. Epifix® is the most commonly used and effective treatment for ulcers [30].

Dermagraft® (Smith and Nephew, USA)

A three-dimensional allogeneic human neonatal foreskin fibroblast matrix in a bioabsorbable polyglactin scaffold, degrading via hydrolysis within 20–30 days. In a study of 18 patients with venous ulcers, Dermagraft® with compression therapy achieved wound closure four times faster than compression alone [31], also in the leg, various ulcers. Studied in 18 patients; the Dermagraft® (n=10) with compression treatment, versus the standard treatment as the control, indicated that the Dermagraft group recovered four times faster than the control. However, its usage is limited by allogeneic mismatch, complex or advance preparation, high costs and fresh handling requirements [1, 32].

Apligraf® (Organogenesis Inc., USA)

A bilayered bioengineered skin substitute comprising a bovine type I collagen lattice with human fibroblasts and a keratinocyte layer, containing growth factors, cytokines, and extracellular matrix (ECM) components [33]. FDA-approved for diabetic foot ulcers and partial- or full-thickness burns (excluding grade-4 ulcers) [4, 34]. Apligraf® demonstrated a 73% healing rate within one week in 107 patients with partial- or full-thickness wounds, with 53.6% showing further improvement by four weeks and no rejection signs after one year [33, 35]. The study showed Apligraf is safe, beneficial, although it lacks of bioactive wound covering [35].

OrCel™ (Ortec International, Inc., USA)

An FDA-approved dermal-epidermal substitute composed of allogeneic human fibroblasts and neonatal keratinocytes in a non-porous bovine type I collagen sponge. OrCel™ releases vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor-1 (FGF-1), and keratinocyte growth factor-1 (KGF-1) to promote cell proliferation and wound healing [36]. OrCel™ was beneficial in providing early wound closure and shrinking the wound size of split-thickness skin donor areas with less fibrosis than Biobrane-L (UDL Laboratories, Inc., Rockford, IL, USA), which has been used as the standard dressing. In a study of 82 burn patients across 12 centres, OrCel™ achieved faster wound closure (median 95% closure by day 10, 100% by day 32) compared to Biobrane-L® ($p < 0.001$) [36]. A combination of collagen sponge, cytokines, and growth factors made OrCel™ a potential therapy for stimulating and speeding up wound healing while reducing scarring [4].

Grafix® (Osiris Therapeutics Inc. in Columbia, MD, USA)

A placental-based cryopreserved allograft containing viable mesenchymal stem cells, fibroblasts, and epithelial cells within a three-dimensional ECM. Used for burns, diabetic ulcers, epidermolysis bullosa, and surgical wounds, Grafix® supports epidermal formation and wound contraction through fibroblast growth factors [37]. Grafix® provides a 3D-extracellular matrix (ECM) containing viable mesenchymal stem cells, fibroblasts, and epithelial cells, which are native populations in the placenta [37]. Fibroblast growth factors/FGFs in the placenta enhance the environment for epidermal formation, wound regeneration and contraction [38]. According to multiple clinical

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studies, Grafix® can be used to treat severe chronic wounds [37-40].

Synthetics biomaterials

Synthetic wound matrices are engineered for chronic wound management, offering scalability, flexibility, and control over microstructure, degradation, and mechanical properties [41, 42]. Common materials found in studies included in this systematic review are polycaprolactone (PCL), poly L-lactic acid (PLLA), poly lactic-co-glycolic acid (PLGA), polytetrahydrofuran (PTHF), polyvinyl alcohol (PVA), and polyurethane (PU), polyethene glycol diacrylate (PEGDA) [43]. While synthetic materials reduce disease transmission risks, they lack native ECM components and cellular adhesion molecules, limiting biocompatibility compared to biological scaffolds [43].

Synthetic matrices provide favourable composition and biomechanical properties, without risk of disease transmission. Nonetheless, it lacks cellular adhesion molecules/ CAM or the native tissue ECM and structure that enhance graft biocompatibility to the recipient site. Examples of synthetic dressings include Tegaderm™ (3M, Maplewood, MN, USA) and Opsite® (Smith & Nephew, Andover, MA, USA), which provide temporary barriers against mechanical stress, bacteria, and dehydration [44].

RESTRATA® Wound Matrix/ RWM (Acera Surgical, St. Louis, Missouri)

A porous synthetic nanofabricated scaffold (<2000 nm) composed of polyglactin 910, PLGA, and polydioxanone (10:90 ratio), FDA-approved for resorbable sutures. In a porcine full-thickness burn model, RESTRATA® reduced wound area by 98% after 30 days, compared to 64% with Integra® [44].

RWM study in the porcine with a full-thickness burn showed a decrease in wound area by 98% after 30 days, while Integra had a wound area reduced by 64% [44]. A clinical study of second-degree burns (6% total body surface area) showed 90% wound recovery with fresh skin after 10 days [45]. In a trial of 46 diabetic ulcer patients (<30 cm²), 74% of RESTRATA®-treated wounds achieved complete re-epithelialization by 12 weeks, compared to 33% with standard care. Patients with diabetic ulcers less than 30 cm² showed 100% re-epithelialization after 12 weeks of application, compared to the standard care/ SOC. A total of 46 participants were enrolled and randomly assigned to two groups. In the per-protocol (PP) population, 14/19 lesions (74%) in the group treated with RESTRATA showed complete re-epithelialization, compared to 6/18 wounds (33%) in the SOC [46]. Matrix appears to be a potential substitute for current treatment techniques for chronic wounds.

Skin artificial used currently in human studies

A. Biological source

Dermo-epidermal skin substitutes (DESSs), such as DenovoSkin developed by the Tissue Biology Research Unit at the University of Zurich, closely mimic native human skin. Evaluated in porcine models [47]. The scaffold was evaluated in a porcine [48]. DenovoSkin was successfully applied in a phase I clinical trial involving 10 pediatric patients at the University Children's Hospital Zurich, followed by a phase II study in Switzerland and Europe[49].

B. Synthetic source

Electrospun nanofiber scaffolds

These scaffolds maintain a moist wound microenvironment, promoting healing through high porosity. A case series at Astria Sunnyside Hospital involving five patients (venous leg ulcer, diabetic foot ulcer, Charcot foot deformity, and pressure ulcers) reported wound closure over exposed structures, reduced exudate, and infection control in most cases, with granulation tissue formation observed. The case report study was conducted at Astria Sunnyside Hospital, with patients suffering from a venous leg ulcer (n=1), a diabetic foot ulcer (n=1), a Charcot foot deformity (n=1) and pressure ulcers (n=2). Wound closure over exposed structure in three cases, reduction of wound exudate in two instances, and elimination of a recurring infection with and without antibiotics in four cases. The wound still exhibited the formation of granulation tissue. Hence, future research needs to be conducted to enhance the scaffold for clinical used [50].

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The Biodegradable Temporising Matrix (BTM)

A synthetic matrix designed to form a neodermis in complex wounds. In a pilot study of 18 diabetic foot ulcer patients with exposed structures or ascending aortic aneurysm or high shear stress areas, 13 patients completed BTM treatment, achieving full wound closure in a median of 13 weeks. Infection and re-ulceration rates were low (15.4% each), suggesting BTM's potential as an alternative to free flap reconstruction. The BTM was used in cases of high shear stress (66.6%), exposed bone (16.6%), exposed fascia (5.6%), exposed tendon (5.6%), and chronic non-healing lesion (5.6%). The duration to complete healing, infection rate, and the incidence of future wound breakdown were also investigated. All BTM patients (n=13) achieved full wound closure within a Median = 13 weeks. One person had only partial BTM treatment, while four withdrew from the trial after receiving BTM. Infection and re-ulceration occurred in 15.4% of cases for each result. This pilot cohort study represents the initial evaluation of BTM in the treatment of complicated diabetic foot ulcers. The data suggest that BTM might assist in healing non-infected, non-ischemic diabetic foot wounds with exposed deeper structures, as well as chronic wounds exposed to severe shear stress. Within this high-risk sample, the chances of re-ulceration and infection were relatively low [51].

Artificial skin is currently used in animal studies.

A medical implant is ideally observed in a comparable animal model to identify problems, application methods, and efficacy before being applied in humans. Several skin artificial candidates biological and synthetic materials, were studied in animals, such as:

A. Biological source

3-D printed chitosan (CH)

Recently, a 3D bi-layered or amnion bilayer scaffold can delay the grafting of full-thickness burns in rat models [52]. Further, studies on the 3D-printed versions of cell-laden hydrogels have appeared as an innovative matrix approach. The design of the hydrogel contains cells layer-by-layer to create a complicated bio-scaffold [53]. Tissue engineering studies developed a hydrogel bio-ink using an alginate/gelatine mixture for 3D printing, seeded with amniotic stem cells and Wharton's jelly-derived mesenchymal stem cells [54]. A 3D-printed chitosan scaffold, biocompatible with human fibroblasts and keratinocytes, promoted cell proliferation and outperformed commercial patches in diabetic rat wound healing after 20–35 days [55].

Amnion bilayer (AB)

An acellular amniotic-fibrin matrix tested in full-thickness rat burns showed 100% epithelialization by days 10–14, compared to day 21 for controls. AB reduced pro-inflammatory gene expression (TNF-α, IL-6, MMP-1) and scar formation, achieving complete wound closure by day 28. It showed that the epithelialisation was significantly faster in the AB group (100%), found on Days 10 and 14, compared to the control group (Sofra-Tulle®, National Hospital of Indonesia protocol) on Day 21. The pro-inflammatory genes such as TNF-α, IL-6, and MMP-1 were significantly higher in the control group compared to the AB group. The higher expression of inflammatory genes increases the prevalence of scar formation. The epidermis was also found to be significantly thicker in the control group, with less expression of collagen and WF. The wound was completely closed after Day 28 in the AB group, while the control still had an actively inflamed area in the centre [52].

B. Synthetic source

3D-printed elastic scaffolds

A 3D-printed chitosan scaffold has three layers of polylactide-co-caprolactone (PLCL) scaffold and collagen gel/ rat tail skin (PLCL + Col + MFUS). Biocompatible with human fibroblasts and keratinocytes, promoted cell proliferation and outperformed commercial patches in diabetic rat wound healing after 20–35 days. This 3D synthetic matrix was used. This configuration aimed to enable cellular penetration and migration, matrix deposition and distribution. The average thickness was 0.49 ± 0.0583 mm, length 1.21 ± 0.0898 mm, and width 1.17 ± 0.0527 mm. This matrix had 100 pores, each 1.2 mm in length. The mechanical properties of the 3D-printed PLCL elastic scaffold are similar to those of rat skin [56].

A study in full-thickness burns in rats comparing PLCL + Col + MFUS, PLCL + Col or

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with micro skin (Micro skin), or no treatment (natural healing). The PLCL + Col + MFUS was healed at day 21, with skin appendages such as functional hair follicles and sebaceous glands, while at day 60, the wound in the group PLCL + Col + MFUS was closed completely. Meanwhile, the PLCL + Col had rapid healing, but no skin appendages were formed [56].

DISCUSSION

Autologous skin transplantation, the gold standard for wound closure, is limited by donor site availability, surgical risks, and challenges in severe cases like full-thickness burns or large ulcers [20]. A sufficient vascular supply for tissue survival and a decent donor match are also important for a satisfactory cosmetic outcome [57]. Still, the availability of adequate healthy skin donors, as well as the added health concerns involved with the surgery, can be problematic. It is tough to apply for severe cases, such as full-thickness burns or leg ulcers with massive wounds [57, 58]. Surgeons should select the effective closure that yields the best cosmetic outcome.

The latest research in biomaterials and tissue engineering showed artificial skin substitutes are prominent as a new standard protocol [1, 59]. Skin substitutes offer an appealing alternative to the constraints of conventional therapy. It sticks to the tissue regeneration principle, requiring three components: scaffold, tissue-inducing substances, and isolated cells that will integrate collectively to generate a skin substitute [60]. The selection of adequate biomaterial tissue engineering is critical for guiding cell behaviour and preventing scar development [61].

A full-thickness skin artificial is a full skin repair to cover the wound, reconstruct both skin layers (epidermis and dermis), and promote skin cell renewal and wound repair[62]. According to the material origin, artificial skin is categorised into natural-derived and synthetic-polymer biomaterials [63]. Natural-derived skin usually has distinct features due to production processes, such as cellular removals, sterilisation, freeze-drying, and cross-linking protocols [61]. Scaffolds also have different features and functions depending on the depth and complexity of the wound. There are several commercial scaffolds used in clinical properties.

Burke et al. invented the Integra ® Dermal Regeneration Template, which is currently regarded as the "benchmark" for repairing full-thickness burn trauma [1, 64]. However, the first burn scaffold clinically used and certified by the FDA was TransCyte in 1997, a nylon mesh cultured with foreskin-fibroblast cells, but it still needs immunosuppressive drugs to prevent rejection [65]. Nowadays, commercial skin substitutes commonly used in clinics are more specific, such as Celladerm used for burn injuries and venous ulcers (Celladermceldon science LLC., Brooklins, Mass, 2008) [27]; Grafix is used for epidermolysis bullosa and burn therapy (Osiris Therapeutics Inc. in Columbia, MD, USA) [37-39]; Dermagraft (Smith and Nephew, Largo, FL, USA) for diabetic foot ulcer [66]; and Apligraf (Organogenesis Inc., Canton, Massachusetts, CA, USA) for partial- and full-thickness wounds and ulcers [33].

Nevertheless, the availability of commercial artificial skin substitutes until recently is far more than ideal; biological matrices are time-consuming waiting in production; meanwhile, an open wound in the patient leads to diminished vascularisation, scarring at graft borders, and practical, physical, and aesthetic issues. Further research is needed to address different difficulties and unanswered questions, and to provide viable options towards an artificial skin substitute with great engraftment and long-term survivability [27].

Recent studies using laboratory-grown skin offered a novel alternative therapy for patients struggling with severe, full-thickness burns [47, 67], such as Dermo-epidermal skin substitutes (DESSs/DenovoSkin), which mimic native human skin underdeveloped in the laboratory of the University of Zurich, Switzerland [49]. Another potential skin substitute is Chitosan-marine peptide hydrogels, currently still tested in the animal trial stage. Hydrogels can regenerate the epithelium on the 14th day and upregulate the expression of FGF2 and VEGF. Further research used a material, polycaprolactone/chitosan nanofibrous scaffold, tested in rats enhanced wound closure and regeneration [68, 69]. Skin substitutes offer a promising alternative, adhering to tissue regeneration principles requiring scaffolds, tissue-inducing substances, and cells [60]. Biomaterial selection is critical for guiding cell behaviour and minimising scarring [61]. Natural-derived scaffolds undergo complex processing (e.g., decellularisation, sterilisation,

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freeze-drying, cross-linking). In contrast, synthetic scaffolds offer scalability but lack native ECM components. Therefore, biomaterials and tissue engineering research are quickly expanding. However, not every substitute has been quality-verified, confirmed in clinical research, and authorised by the FDA, despite the fact that certification is crucial for the safety of patients [62].

CONCLUSION

Chronic wound management remains a significant clinical challenge. Ideal skin substitutes protect wounds, promote tissue regeneration, and enhance aesthetic and functional outcomes. Advances in tissue engineering have produced synthetic and biological scaffolds that address acute and chronic wounds. While some technologies are still in preclinical stages, they demonstrate significant potential for improving burn and wound care.

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