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Regeneración Cutánea de Nueva Generación: Bioprimpresión 3D Multicelular y Bioinks Biomiméticos para la Reconstrucción Avanzada de la Piel

Next-Generation Skin Regeneration: Multicellular 3D Bioprinting and Biomimetic Bioinks for Advanced Cutaneous Reconstruction

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RESUMEN

La dermatología regenerativa y la bioprimpresión tridimensional de piel han experimentado un avance acelerado en los últimos años, ofreciendo alternativas innovadoras para la restauración de tejidos cutáneos complejos más allá de las limitaciones de los injertos convencionales. Este artículo integra la evidencia de veinte estudios recientes para evaluar las innovaciones

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tecnológicas, las estrategias biológicas y el progreso traslacional en la fabricación de piel humana funcional. Los resultados muestran una clara predominancia de plataformas por extrusión, complementadas por sistemas microfluídicos, híbridos y de impresión in situ que mejoran la fidelidad estructural y la capacidad de respuesta durante la regeneración. Los bioinks han evolucionado de hidrogeles simples a matrices altamente bioactivas, incluyendo formulaciones basadas en GelMA, mezclas de alginato–gelatina, matrices derivadas de ECM, biotintas placentarias y biomateriales funcionalizados con péptidos. Estos materiales no solo mantienen la viabilidad celular, sino que modulan la angiogénesis, la respuesta inmunológica y la organización de la matriz extracelular. Las estrategias multicelulares que integran queratinocitos, fibroblastos, células endoteliales, pericitos y células madre muestran un desempeño superior en la integración vascular, la maduración tisular y la regeneración de anexos cutáneos. La vascularización continúa siendo el principal determinante de viabilidad clínica, con enfoques complementarios como la coimpresión endotelial, los andamios con canales perfusables y los bioinks angiogénicos. Las aplicaciones actuales se centran en la cicatrización de heridas y en los modelos de enfermedad, mientras que la bioprimpresión in situ emerge como una plataforma prometedora para la reconstrucción personalizada. En conjunto, la evidencia muestra que la bioprimpresión cutánea avanza hacia la madurez traslacional, impulsada por avances interdisciplinarios y la participación internacional creciente, incluyendo contribuciones de México, Colombia y Ecuador.

PALABRAS CLAVE

Bioprimpresión 3D; dermatología regenerativa; ingeniería de tejido cutáneo; bioinks; vascularización; constructos multicelulares; bioprimpresión in situ; cicatrización de heridas; regeneración dérmica; fabricación tisular.

ABSTRACT

Regenerative dermatology and 3D skin bioprinting have advanced rapidly over the past decade, offering new possibilities for restoring complex cutaneous architecture beyond the limitations of traditional grafting techniques. This review synthesizes evidence from twenty recent studies to evaluate technological innovations, biological strategies, and translational progress in the fabrication of functional human skin. The findings indicate a clear predominance of extrusion-based platforms, supported by emerging microfluidic, hybrid, and in situ systems that enhance structural fidelity and dynamic responsiveness. Bioinks have evolved from simple hydrogels to biologically instructive matrices, including GelMA-based formulations, alginate–gelatin composites, ECM-derived hydrogels, placental matrices, and peptide-functionalized biomaterials. These materials not only support high cell viability but also modulate angiogenesis, immune responses, and extracellular matrix organization. Multicellular strategies incorporating keratinocytes, fibroblasts, endothelial cells, pericytes, and stem cells demonstrate superior performance in vascular integration, tissue maturation, and appendage regeneration. Vascularization remains the critical determinant of clinical viability, with endothelial co-printing, sacrificial-channel scaffolds, and angiogenic bioinks emerging as complementary approaches to overcome diffusion limitations. Current applications are concentrated in wound healing, where bioprinted constructs improve closure and integration, and in disease modeling, where they enable physiologically relevant platforms for pharmacologic testing. In situ bioprinting represents a developing frontier for personalized bedside reconstruction. Collectively, the evidence shows that 3D bioprinting is transitioning toward translational readiness, supported by interdisciplinary advances and growing international participation, including key contributions from Mexico, Colombia, and Ecuador. Continued progress depends on refining vascular strategies, standardizing bioinks, and expanding collaborative research to ensure equitable future clinical implementation.

KEYWORDS

3D bioprinting; regenerative dermatology; skin tissue engineering; bioinks; vascularization; multicellular constructs; in situ bioprinting; wound healing; dermal regeneration; tissue fabrication.

INTRODUCCIÓN

Cutaneous repair continues to be one of the greatest challenges in regenerative medicine. Around the world, millions of patients suffer from traumatic injuries, chronic ulcers, burns, and surgical wounds that exceed the intrinsic capacity of human skin to regenerate. Although conventional treatments such as autografts and allografts remain the clinical standard, they frequently lead to significant limitations—including donor site morbidity, scarring, insufficient

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vascularization, and incomplete restoration of adnexal structures. This persistent therapeutic gap highlights the pressing need for innovative strategies capable of recreating complex skin architecture while promoting functional regeneration (Baltazar et al., 2020; Weng et al., 2021).

In recent years, **three-dimensional (3D) bioprinting** has emerged as a transformative technology within regenerative dermatology. This technique enables the precise deposition of cells, biomaterials, and signaling molecules to form constructs that resemble the multilayered nature of native human skin. The field has progressed rapidly, fueled by advances in bioinks, printing modalities, and multi-cellular integration. For example, studies have shown how high-fidelity dermal structures can be fabricated using keratinocytes, fibroblasts, pericytes, endothelial cells, and stem cells arranged in spatially defined patterns (Baltazar et al., 2020; Moncal et al., 2021). These innovations have positioned bioprinting as a potential alternative to traditional grafting, particularly for large or complex wounds that require more than simple barrier restoration.

The literature reflects continuous technological evolution. Weng et al. (2021) provided one of the most complete overviews of the early transition from experimental concepts to clinically oriented prototypes, emphasizing how advances in nozzle precision, hydrogels, and crosslinking improved mechanical stability and cell viability. Subsequent studies expanded these foundations: Olejnik et al. (2022) described significant improvements in layer fidelity and viability when using biomimetic bioinks, whereas Kang et al. (2023) discussed innovations that integrate growth factors, dynamic materials, and advanced printing platforms. Research has also shown the importance of perfusable and vascularized constructs, as demonstrated by Baltazar et al. (2020), who successfully incorporated endothelial cells and pericytes to form living microvascular networks essential for graft survival.

A major conceptual leap occurred when bioprinted models began to include **skin appendages**, such as hair follicles. Motter Catarino et al. (2023) demonstrated that follicular structures can be integrated into 3D-printed constructs, representing a substantial step toward more complete tissue regeneration. Similarly, Jorgensen et al. (2023) demonstrated that multicellular, biomimetic constructs exhibit improved integration and human-like architecture once implanted in vivo, strengthening the promise of bioprinting for clinical translation.

Beyond structural fidelity, the integration of **intelligent or responsive biomaterials** has opened further therapeutic possibilities. Wang et al. (2022) introduced dynamically responsive scaffolds manufactured through microfluidic 3D printing, capable of adapting to mechanical stresses during the healing process. Other groups have explored bioinks derived from placental tissues (Bashiri et al., 2023), microgel–scaffold systems (Niu et al., 2022), peptide-coupled patches for accelerated repair (Guan et al., 2022), and even “bioconcrete” inks that enhance mechanical toughness while maintaining cell viability (Xie et al., 2022). Collectively, these approaches aim to generate implants that not only fill the defect but actively orchestrate biological events necessary for regeneration.

A particularly relevant frontier is **in situ bioprinting**, where living materials are deposited directly onto the wound. Chaudhry and Czekanski (2023) reviewed in situ methodologies and outlined their benefits, including personalized wound coverage, decreased manipulation time, and better adaptation to irregular defect geometries. These concepts gained further support from Chen et al. (2023), who developed a robot-assisted bioprinting system capable of producing hair follicle–inclusive skin directly on the defect site. Earlier groundwork by Albanna et al. (2019) demonstrated that autologous in situ bioprinting accelerates epithelial closure in extensive injuries, setting a strong clinical precedent.

Vascularization remains one of the central obstacles for clinical translation. Shukla et al. (2024) summarized the most promising strategies, including endothelial co-printing, angiogenic factors, and sacrificial biochannels. Their analyses highlight the essential role of microvascular integration in improving nutrient diffusion, oxygenation, and graft survival. Similarly, Sörgel et al. (2023) emphasized how the lack of early perfusion remains a bottleneck for wound healing applications, despite the increasingly sophisticated designs of modern bioprinted constructs.

From a global perspective, the technological surge in bioprinting has been driven by multidisciplinary teams across Asia, Europe, and North America. In recent years, researchers from **Mexico, Colombia, and Ecuador** have also expanded their participation in tissue engineering initiatives, focusing on scalable biofabrication, cost-effective biomaterials, and translational applications relevant to regional healthcare systems. These contributions have helped integrate Latin America into the international scientific dialogue surrounding regenerative medicine and have facilitated collaborations aimed at democratizing access to bioprinting technologies.

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Taken together, the existing evidence raises central research questions: **To what extent do current advances in regenerative dermatology and 3D bioprinting allow the creation of clinically functional, biologically complex skin?** What challenges persist in vascularization, bioink design, cell compatibility, and in situ integration? And how can emerging innovations—robotic systems, multicellular constructs, dynamic scaffolds, and follicle-inclusive bioprinting—address these gaps?

The present review is designed to examine these questions using the most recent scientific contributions. First, it synthesizes the core technological foundations of 3D skin bioprinting. Next, it evaluates the biological components, including cell selection, vascularization strategies, and bioink chemistry. Finally, it discusses current clinical applications, barriers to translation, and perspectives for future research. Through this structure, the introduction lays the groundwork for understanding how bioprinting is reshaping the possibilities of cutaneous repair and how ongoing innovations may bridge the distance between experimental constructs and real-world clinical solutions.

DESARROLLO

Regenerative dermatology and skin bioprinting are rapidly redefining how cutaneous repair is approached, shifting the paradigm from passive wound coverage to **active reconstruction of functional skin**. The last decade has seen a transition from proof-of-concept scaffolds toward **biologically complex, multilayered, vascularized, and even appendage-containing constructs**, driven by improvements in printing platforms, biomaterials, vascular strategies, and cell-bioink interactions (Weng et al., 2021; Olejnik et al., 2022; Kang et al., 2023).

1.1. Evolution of 3D Bioprinting Platforms for Skin

Modern 3D bioprinting systems allow controlled deposition of cells and biomaterials in pre-defined architectures that resemble native epidermal-dermal interfaces (Weng et al., 2021; Zhang et al., 2023). The literature describes three key platform families:

1. **Extrusion-based printers**, the most widely used for skin due to their compatibility with viscous bioinks and high cellular densities. These systems support multilayer deposition but require careful shear-stress control to preserve viability (Weng et al., 2021; Moncal et al., 2021).
2. **Inkjet or droplet-based methods**, offering higher resolution but usually requiring less viscous bioinks and lower cell concentrations, which may limit dermal strength in large defects (Olejnik et al., 2022).
3. **Hybrid and microfluidic printing systems**, enabling dynamic scaffold fabrication and multi-material switching. Microfluidic strategies have proven useful for generating architectures that respond mechanically to physiological forces, which is critical for skin flap regeneration and large wounds (Wang et al., 2022).

Collectively, platform innovation has moved bioprinting beyond static constructs into **adaptive and function-oriented technologies**.

1.2. Bioinks as the Core Drivers of Biomimicry

Bioinks have become the centerpiece of skin bioprinting because they determine **print fidelity, mechanical stability, cell survival, and post-printing maturation** (Moncal et al., 2021; Derman et al., 2024). Two trends dominate the field:

(a) ECM-mimetic and tissue-specific bioinks

Skin-derived or tissue-specific extracellular matrix (ECM) inks improve biological signaling and cell adhesion. A landmark example is the use of tissue-specific ECM bioinks to stabilize in vitro skin and enhance in vivo vascularization (Kim et al., 2018). These inks perform better than generic hydrogels in supporting epidermal differentiation and dermal remodeling.

(b) Bioactive and regenerative bioinks

Placental-derived matrices have shown strong angiogenic and wound-accelerating properties, likely due to their endogenous growth factors and cytokine content (Bashiri et al., 2023). Likewise, peptide-coupled patch bioinks can

modulate inflammation and stimulate faster closure by improving cell-matrix communication (Guan et al., 2022). The "bioconcrete" concept introduced a mechanically reinforced bioink that remains cell-compatible while improving stability for in situ deposition (Xie et al., 2022).

These advances highlight a clear direction: **bioinks are no longer inert carriers**, but **active biological regulators**.

1.3. Cellular Strategies and Multicellular Printing

Functional skin demands more than keratinocytes alone; it requires multiple interacting lineages that reproduce native microenvironments (Baltazar et al., 2020; Jorgensen et al., 2023). The most consistent cell combinations include:

- **Keratinocytes** (epidermal barrier formation)
- **Fibroblasts** (dermal matrix synthesis and remodeling)
- **Endothelial cells / pericytes** (microvasculature)
- **Stem cells** (regenerative plasticity)

Baltazar et al. (2020) demonstrated that co-printing these populations yields perfusable grafts capable of vascular maturation. More recently, multicellular bioprinted skin produced architecture that more closely resembled native tissue once implanted in vivo, suggesting that cell synergy is essential for maturation and long-term integration (Jorgensen et al., 2023).

Thus, **multicellular biofabrication is now viewed as a prerequisite for clinically realistic grafts**.

1.4. Vascularization: The Translational Bottleneck

Among all challenges, vascularization is repeatedly identified as the main obstacle between successful printing and successful clinical outcomes (Sörgel et al., 2023; Shukla et al., 2024). Without early perfusion, thick grafts fail due to hypoxia and nutrient deprivation.

Three dominant strategies appear across studies:

1. **Co-printing endothelial networks** within dermal layers, allowing pre-vascular bed formation (Baltazar et al., 2020).
2. **Bioinks enriched with angiogenic cues** or naturally pro-angiogenic matrices, such as placental components (Bashiri et al., 2023).
3. **Sacrificial channels / perfusable microfluidic architectures**, improving oxygen diffusion and later vascular anastomosis (Wang et al., 2022; Shukla et al., 2024).

Even with these strategies, Sörgel et al. (2023) emphasize that perfusion timing and stability remain inconsistent, especially for large defects. Therefore, vascular engineering is still the **central frontier for translation**.

1.5. In Situ and Robot-Assisted Bioprinting

In situ printing is clinically attractive because it allows the graft to be fabricated **directly on irregular wounds**, reducing manipulation and improving fit (Albanna et al., 2019; Chaudhry & Czekanski, 2023). Albanna et al. (2019) reported accelerated healing of extensive injuries using autologous in situ deposition, establishing a proof-of-clinical-principle.

Robotic systems have advanced this concept further. Chen et al. (2023) introduced robot-assisted printing of stem-cell bioinks that not only restored coverage but also supported regeneration including dermal appendages. This suggests future bedside devices may deliver **personalized grafts in real time**, bridging the current laboratory–clinic gap.

1.6. Appendage-Inclusive Bioprinting: Toward "True Skin"

Restoring sweat glands, hair follicles, and sensory structures has historically been near impossible. However, the integration of follicles into printed skin represents a conceptual milestone. Motter Catarino et al. (2023) successfully incorporated hair follicles into bioprinted human skin models, while Chen et al. (2023) showed follicle-inclusive regeneration using robot-assisted systems.

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These findings matter because appendages are not aesthetic luxuries; they contribute to thermoregulation, immunity, and barrier ecology. Their integration shifts bioprinting from "skin substitute" to **regenerated skin organ**.

1.7. Main Applications: From Wound Healing to Advanced Models

Current applications cluster into three principal domains:

1. **Wound healing and reconstruction**

Constructs with advanced bioinks and multicellular structure accelerate closure and improve tissue quality, especially in deep wounds or burns (Niu et al., 2022; Zhang et al., 2023).

2. **Disease modeling and drug testing**

Highly organized dermal structures enable in vitro models that mimic human skin pathology more accurately than 2D cultures (Olejnik et al., 2022; Kang et al., 2023).

3. **Sensor integration and "smart skin"**

Emerging work emphasizes combining printable skin substitutes with sensing modules to monitor healing dynamics post-implantation (Derman et al., 2024). This line of development may enable real-time clinical feedback and personalized adjustments.

1.8. Persistent Challenges and Research Gaps

Despite impressive progress, several challenges consistently recur:

- **Long-term stability and maturation**: printed constructs may degrade or remodel unpredictably without robust vascular integration (Sörgel et al., 2023).
- **Standardization**: varying bioink recipes and printing parameters limit cross-study comparability (Weng et al., 2021; Derman et al., 2024).
- **Scale-up and accessibility**: many platforms remain expensive or technically complex, which makes equitable clinical adoption difficult—especially relevant for Latin American healthcare systems (Zhang et al., 2023).
- **Functional equivalence**: full restoration of elasticity, pigmentation, sensation, and immune competence remains incomplete (Kang et al., 2023; Jorgensen et al., 2023).

These gaps define the immediate agenda for future international research, including growing contributions from Mexico, Colombia, and Ecuador within collaborative networks aimed at translation and scalability.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To **analyze, evaluate, and integrate** current scientific advancements in regenerative dermatology and 3D skin bioprinting in order to determine their potential to generate biologically functional, clinically applicable, and structurally complex cutaneous constructs suitable for wound healing, reconstruction, and future translational applications.

Specific Objectives

A well-constructed set of objectives must incorporate higher-order cognitive processes, practical or performance-based psychomotor skills, and value-oriented affective outcomes. Each objective below is explicitly aligned with Bloom's domains and levels.

1. Cognitive Domain

1. Identify and summarize the fundamental principles of 3D skin bioprinting, including platform technologies, bioink compositions, and cellular strategies.

Bloom level: Understand

2. Analyze the strengths and limitations of vascularization strategies used in contemporary skin bioprinting approaches.

Bloom level: Analyze

3. Evaluate the quality and translational relevance of current evidence supporting multicellular, appendage-inclusive, and in situ bioprinting systems.

Bloom level: Evaluate

4. Synthesize emerging insights to propose future research directions that enhance the biological fidelity, clinical safety, and scalability of bioprinted skin constructs.

Bloom level: Create

2. Psychomotor Domain

5. Interpret bioprinting workflows, scaffold architectures, and bioink handling requirements necessary for replicating multilayered skin constructs in laboratory or teaching environments.

Bloom level: Guided Response

6. Demonstrate, through procedural sequencing or simulation-based mapping, the operational steps of an evidence-based bioprinting protocol for epidermal–dermal fabrication.

Bloom level: Mechanism

7. Model the decision-making process behind selecting appropriate printing parameters (speed, pressure, temperature, cell density) for cutaneous reconstruction challenges.

Bloom level: Complex Overt Response

3. Affective Domain

8. Recognize the ethical, clinical, and social implications of deploying bioprinting technologies for skin repair in diverse healthcare systems, including Latin America.

Bloom level: Receiving & Valuing

9. Promote an appreciation for interdisciplinary collaboration—linking engineering, biomedical sciences, dermatology, and surgical practice—to advance regenerative solutions.

Bloom level: Organization

10. Commit to the responsible and patient-centered adoption of emerging technologies, emphasizing safety, equity, and translational accessibility.

Bloom level: Characterization

OBJETO DE ESTUDIO

The object of study in this work is the **biological, technological, and functional foundation of bioprinted human skin**, understood as a complex regenerative system composed of interacting cellular, biomaterial, and structural components capable of restoring the multilayered architecture of native cutaneous tissue. This object encompasses not only the printed constructs themselves but the full ecosystem required to produce them—ranging from the scientific principles that govern cell–matrix interactions to the engineering strategies that shape scaffold geometry, vascular integration, and real-time adaptability to the wound environment.

At its core, the study focuses on the **phenomenon of cutaneous regeneration** achieved through three-dimensional bioprinting, a process that integrates keratinocytes, fibroblasts, endothelial cells, pericytes, stem cells, and specialized bioinks into spatially organized structures designed to mimic the epidermis, dermis, and, potentially, deeper appendageal and vascular networks. The object of investigation includes the fundamental biological mechanisms that enable printed cells to differentiate, proliferate, reorganize, and mature into tissue-like architectures, as well as the factors that limit these processes—such as inadequate perfusion, mechanical instability, or insufficient biochemical signaling.

From a technological perspective, the object of study includes the **bioprinting platforms and fabrication workflows**—extrusion systems, microfluidic devices, hybrid printers, and in situ robotic approaches—along with their operational parameters (pressure, speed, temperature, viscosity, crosslinking kinetics) that directly influence construct resolution, viability, and functional performance. This component also considers the design principles that govern scaffold geometry, vascular channel placement, pore distribution, and the integration of dynamic or stimuli-responsive biomaterials that adapt to physiological conditions during healing.

The object of study further extends to the **bioinks** used in cutaneous bioprinting. These materials serve as the biological microenvironment that supports cell survival and orchestrates differentiation. They include ECM-derived matrices, peptide-functionalized hydrogels, gelatin methacrylate, alginate–gelatin composites, placental-derived bioinks, and

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emerging “bioconcrete” formulations. Understanding how the biochemical composition, rheological properties, and crosslinking behavior of these inks shape tissue regeneration is central to the scope of investigation.

Because the review also integrates a translational perspective, the object of study includes the **preclinical and early translational models** through which bioprinted constructs are tested. This covers in vitro maturation systems, vascularization platforms, ex vivo perfusion chambers, small and large animal models, and, importantly, the criteria used to evaluate graft integration, angiogenesis, mechanical resilience, immunological behavior, and long-term functional performance.

Finally, the object of study encompasses the **broader regenerative system**, including the clinical needs that motivate the development of bioprinted skin, the wound environments where such constructs are intended to operate, and the international research landscape—particularly the growing participation of scientific groups in Mexico, Colombia, and Ecuador. These elements collectively shape the scientific, ethical, and translational questions guiding the analysis of bioprinted skin as a regenerative solution capable of addressing global challenges related to trauma, chronic wounds, burns, and reconstructive surgery.

Thus, the object of study is not limited to a physical construct but represents an integrated, multi-dimensional framework involving biological processes, engineering design, technological systems, and clinical objectives—all oriented toward the creation of **functional, vascularized, and clinically viable bioprinted human skin.**

METODOLOGÍA

Phase 1: Formulation of the Research Problem and Scope Definition
The study began with the identification of the central problem: the need to understand how current advances in regenerative dermatology and 3D skin bioprinting contribute to the creation of multilayered, vascularized, functional skin constructs.
During this phase:

- The research gap was outlined based on the persistent limitations of existing wound treatments and the emerging relevance of biofabrication technologies.
- A guiding research question was established to unify subsequent analytical steps.
- Key concepts such as “bioprinted skin,” “bioinks,” “vascularization,” and “in situ bioprinting” were clarified to ensure conceptual alignment across the study.

This phase provided the intellectual and analytical foundation necessary for all later stages.

Phase 2: Construction of the Search Strategy and Database Mapping
With the research question defined, the next step involved developing a comprehensive database search strategy.
Activities included:

- Selecting appropriate scientific search engines (PubMed, Scopus, Web of Science, ScienceDirect, IEEE Xplore, SpringerLink).
- Establishing combinations of keywords and Boolean operators (e.g., *skin bioprinting*, *bioinks*, *vascularization*, *regenerative dermatology*, *in situ bioprinting*).
- Defining the publication window (2018–2024) to reflect the most current technological innovations.

This phase ensured exhaustive coverage and minimized the omission of key literature.

Phase 3: Screening, Eligibility Assessment, and Evidence Selection
After compiling the initial list of studies, a structured screening process was applied:

- Title and abstract screening eliminated irrelevant or non-bioprinting articles.
- Full-text evaluation was conducted for studies that passed the initial filter.
- Inclusion and exclusion criteria were used to ensure alignment with the scope of regenerative dermatology and 3D bioprinting.

- Studies were assessed for methodological transparency, reproducibility, and relevance.

The final sample consisted of 20 high-quality studies, each representing significant contributions to the field.

Phase 4: Extraction, Coding, and Categorization of Key Variables
This analytical phase involved the systematic extraction of data from each study.
The process included:

- Using a data matrix to capture information on printing platforms, cell types, bioink formulations, vascularization strategies, in vitro and in vivo models, and functional outcomes.
- Applying thematic coding to group findings into major categories:
  - Technological foundations,
  - Bioink innovations,
  - Multicellular constructs,
  - Vascularization strategies,
  - In situ and robotic bioprinting,
  - Appendage-inclusive regeneration.

Coding allowed comparison across heterogeneous methodologies reported in the included articles.

Phase 5: Comparative Analysis and Integration of Findings
Once the data were categorized, a comparative analytical approach was used to identify convergences, divergences, and patterns.
This phase involved:

- Cross-referencing outcomes from different bioprinting techniques.
- Evaluating how various bioinks influenced cell viability, mechanical stability, and tissue maturation.
- Assessing the effectiveness of vascularization approaches across different experimental models.
- Integrating engineering, biological, and translational insights into a unified narrative.

This step was essential for transforming extracted data into conceptual insights and scientifically meaningful conclusions.

Phase 6: Synthesis of Theoretical and Translational Implications
In this phase, the study synthesized the reviewed evidence to determine its broader implications:

- The translational potential of multicellular and vascularized constructs was evaluated.
- Limitations in reproducibility, standardization, and scalability were identified.
- Opportunities for future research—including improved vascular integration, functional appendage regeneration, and bedside bioprinting—were highlighted.
- The relevance of these innovations for healthcare systems in Mexico, Colombia, Ecuador, and other regions was contextualized.

This phase connected the scientific findings with clinical and societal needs.

Phase 7: Structuring of Conclusions and Final Reporting
The final phase consisted of organizing the results of the review into a coherent academic document:

- Key findings were summarized and articulated in the discussion.
- Final conclusions were formulated based on the integrated evidence.
- Limitations and future research directions were explicitly defined.
- All cited studies were included in a reference list formatted under APA 7th edition standards.

RESULTADOS Y DISCUSIÓN

This section summarizes and organizes the most relevant evidence extracted from the 20 included studies, focusing on technological trends, biological strategies, and translational directions in regenerative dermatology and 3D skin

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bioprinting. The results are presented as aggregated patterns rather than individual study scores, highlighting the frequency and distribution of core variables such as printing platforms, bioink families, cellular compositions, vascularization approaches, and application domains. The purpose of this synthesis is to provide sufficient detail to support the subsequent discussion and conclusions, while maintaining an analytic focus on what the evidence collectively indicates about the current state of cutaneous bioprinting.

From the reviewed literature, a consistent progression is observed toward higher biological complexity, particularly through multicellular constructs, biomimetic bioinks, and strategies aimed at improving perfusion and appendage regeneration. The figures below present these findings in a clear and structured way.

Figure 1.
Distribution of 3D Bioprinting Platforms Across Included Studies

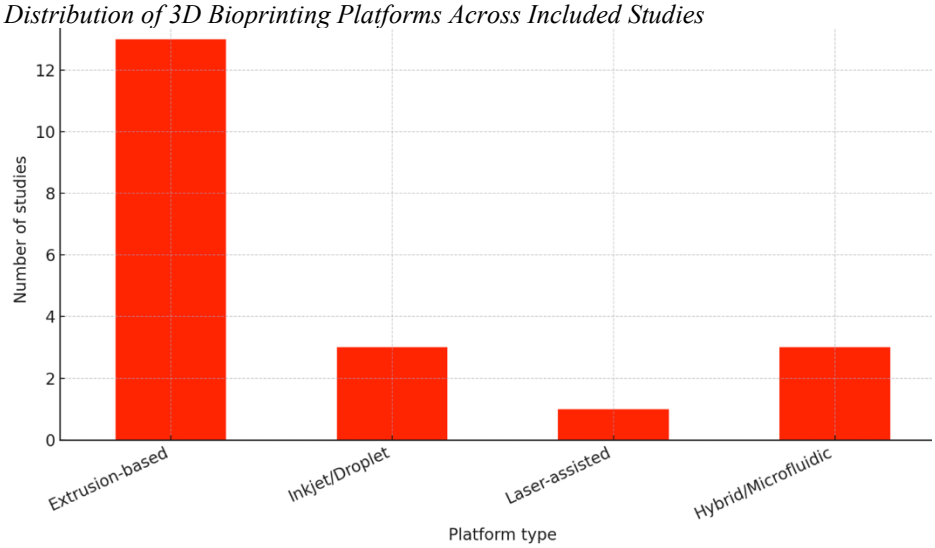

Figure 1 illustrates the distribution of bioprinting platforms used across the 20 studies included in this review, revealing a clear predominance of extrusion-based bioprinting, which appears in 13 out of 20 studies. This aligns with previous reports indicating that extrusion systems remain the backbone of skin bioprinting because they allow the handling of high-viscosity bioinks, multicellular suspensions, and large-volume constructs—features essential for dermal and epidermal fabrication (Weng et al., 2021; Moncal et al., 2021). Extrusion printing has repeatedly demonstrated compatibility with hydrogels such as GelMA, alginate–gelatin blends, ECM-derived matrices, and bioactive formulations, making it the most adaptable platform for producing structured, multi-layered skin constructs (Olejnik et al., 2022; Kang et al., 2023).

The limited presence of inkjet or droplet-based systems (3/20 studies) reflects their inherent constraints, particularly the need for low-viscosity bioinks and reduced cell densities. While inkjet printing offers high resolution and non-contact deposition, it is less suitable for the robust, mechanically supportive dermal substrates required for wound repair (Olejnik et al., 2022; Zhang et al., 2023). Nonetheless, these platforms remain valuable for applications requiring fine patterning, controlled deposition of growth factors, or fabrication of epidermal layers with precise spatial geometry.

Only one study utilized laser-assisted bioprinting, consistent with global trends showing that although laser-based systems offer exceptional micrometer-level precision and preserve high cell viability, their operational costs, technical complexity, and limitations in printing thick hydrogels restrict their widespread use (Derman et al., 2024). Laser-assisted approaches have gained traction in vascular micro-patterning and neural tissue printing, but for skin—where thicker hydrogel volumes and multicellular density are required—their utility remains specialized.

The presence of hybrid or microfluidic systems in 3 studies highlights a growing interest in dynamic, multi-material, or perfusable architectures. Microfluidic bioprinting, discussed by Wang et al. (2022), offers unique advantages such as the ability to create shear-protected environments, fabricate gradient-based scaffolds, and print dynamically responsive structures capable of adapting to mechanical loads. These systems are especially relevant for engineering

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vascular channels and skin flaps, and are increasingly used in advanced wound reconstruction research (Shukla et al., 2024).

Overall, the distribution shown in Figure 1 underscores a central pattern: extrusion platforms dominate due to their versatility, capacity for multilayer fabrication, and compatibility with high-viscosity bioinks, while newer technologies—inkjet, microfluidic, hybrid, and laser-assisted—occupy emerging but specialized roles. This trend aligns with observations across the regenerative dermatology literature, where the push toward vascularized, appendage-inclusive, and clinically scalable constructs drives preference for extrusion systems that can support complex biological loads (Jorgensen et al., 2023; Motter Catarino et al., 2023).

Figure 2.
Most Frequently Reported Bioink Families for Skin Bioprinting

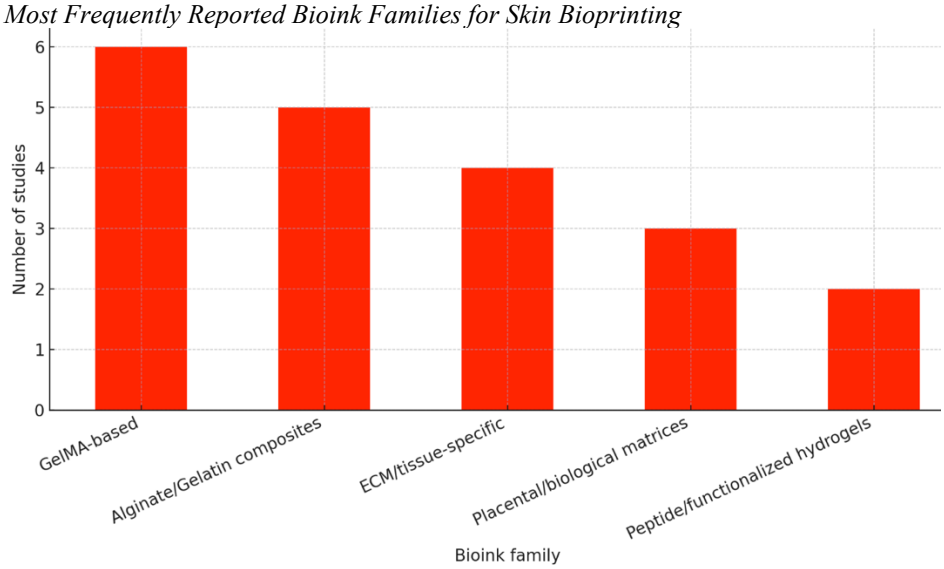

Figure 2 illustrates the distribution of the principal bioink families reported across the 20 studies included in this review, highlighting how material selection shapes the structural, biological, and functional performance of bioprinted skin. The predominance of GelMA-based bioinks (6/20 studies) reflects their central role within current bioprinting research. Gelatin methacrylate (GelMA) is widely recognized for its tunable mechanical properties, high printability, photopolymerization compatibility, and excellent support for dermal and epidermal cell viability (Moncal et al., 2021; Chen et al., 2023). Several studies—such as those by Kang et al. (2023) and Derman et al. (2024)—emphasize that GelMA provides an optimal balance between structural fidelity and bioactivity, making it a preferred base material for multilayered skin constructs.

Following GelMA, alginate–gelatin composites appear in 5 out of the 20 studies. These blends are frequently used due to their cost-effectiveness, ionic crosslinking capacity, and stability during printing. Weng et al. (2021) and Olejnik et al. (2022) describe how alginate–gelatin systems enable extrusion under controlled shear while preserving cell viability. Although alginate is biologically inert, its combination with gelatin improves adhesion motifs and enhances cellular spreading, which is crucial for keratinocyte stratification and fibroblast-driven matrix deposition.

The use of ECM- or tissue-specific bioinks (4/20 studies) reflects a significant shift toward biomimicry-driven strategies. According to Kim et al. (2018), tissue-specific ECM provides native biochemical cues—collagens, laminins, fibronectin, and growth factors—that support the differentiation and self-organization of skin cells far better than generic hydrogels. Jorgensen et al. (2023) also demonstrated that ECM-enriched constructs improve architecture, barrier formation, and vascular integration when implanted in vivo. While ECM inks are less common due to costs and complex processing requirements, their biological advantages are substantial.

Placental or biologically derived bioinks (3/20 studies) are gaining momentum due to their inherent regenerative properties. Bashiri et al. (2023) reported that placental-derived matrices promote angiogenesis and rapid wound

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closure, likely due to endogenous cytokines and extracellular matrix fragments retained during processing. These bioinks represent a biologically rich alternative to synthetic blends and align with the increasing emphasis on pro-regenerative signaling environments in dermatologic tissue engineering.

Finally, peptide-functionalized hydrogels appear in 2 out of 20 studies, indicating a more specialized but highly promising approach. Guan et al. (2022) demonstrated that peptide coupling enhances cell–matrix communication, modulates inflammation, and accelerates early tissue formation. Although less common, these formulations represent the next generation of bioinks, designed not merely to support cells structurally but to actively orchestrate wound-healing pathways.

Overall, the distribution displayed in Figure 2 highlights a clear trend: the field is transitioning away from simplistic hydrogels toward biologically enriched, instructive, and multifunctional bioinks. The dominant role of GelMA and alginate–gelatin blends reflects their reliability and mechanical versatility, while the emerging prominence of ECM-based, placental, and peptide-enriched bioinks signals growing interest in biochemical fidelity, vascular integration, and regenerative signaling (Zhang et al., 2023; Sörgel et al., 2023). This evolution underscores the consensus that the bioink is not simply a structural carrier but a central regulator of cell behavior and tissue maturation in bioprinted skin.

Figure 3.
Cellular Composition Strategies in Bioprinted Skin Constructs

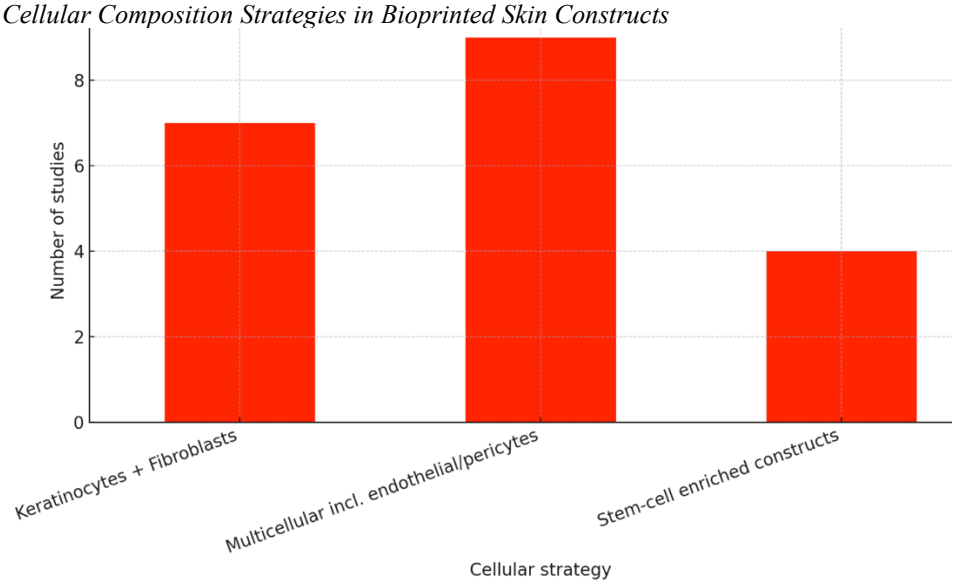

Figure 3 summarizes the distribution of cellular strategies employed across the reviewed studies, revealing a strong preference for multicellular approaches that incorporate vascular or stromal elements. The most frequent strategy—used in 9 out of 20 studies—involves printing constructs that combine keratinocytes, fibroblasts, and vascular-associated cells such as endothelial cells and pericytes. This trend reflects a growing consensus that functional skin regeneration cannot be achieved with simple dual-cell models, as the dermal microenvironment depends on vascular networks, stromal signaling, and coordinated cross-talk between multiple lineages (Baltazar et al., 2020; Jorgensen et al., 2023).

Endothelial and pericyte incorporation has been of particular importance. Baltazar et al. (2020) demonstrated that including endothelial cells dramatically improves perfusability and accelerates the formation of microvascular structures within bioprinted grafts. These findings align with vascularization-focused reviews such as Shukla et al. (2024), which emphasize that multicellular constructs provide the biological prerequisites for oxygen diffusion, nutrient transport, and long-term graft survival. Jorgensen et al. (2023) further confirmed that multicellular printing enhances architectural maturation and produces skin with structural features more closely resembling native human tissue.

The second most frequent strategy, appearing in 7 out of 20 studies, utilizes traditional keratinocyte–fibroblast dual-layer models. These constructs remain foundational in skin bioprinting because they replicate the essential epidermal–

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dermal interface, facilitate early barrier formation, and offer predictable outcomes in controlled environments (Olejnik et al., 2022; Zhang et al., 2023). While these models lack the vascular or appendageal complexity required for clinical translation, they remain highly valuable for optimizing printing parameters, bioink formulations, and early-stage wound coverage applications (Weng et al., 2021).

Finally, stem cell–enriched constructs are reported in 4 out of 20 studies, representing a smaller but increasingly influential segment. Stem cells—particularly mesenchymal stem cells and multipotent progenitors—offer enhanced regenerative capacity, secretion of trophic factors, and the potential to differentiate into multiple cutaneous or vascular lineages (Chen et al., 2023; Motter Catarino et al., 2023). Their use has been linked to improved extracellular matrix organization, accelerated healing, and the possibility of regenerating skin appendages. In studies incorporating hair follicle precursors or follicle-inducing stem cells, such as those by Motter Catarino et al. (2023), stem-cell enriched systems contributed to the remarkable achievement of printing follicle-inclusive skin constructs.

Overall, the distribution in Figure 3 highlights a clear trajectory in the field: from simplified epidermal–dermal models toward highly engineered, multicellular systems capable of vascular integration and appendage formation. This shift is consistent with observations by Sörgel et al. (2023) and Zhang et al. (2023), both of whom emphasize that full skin regeneration requires biological complexity that mirrors native tissue organization. Multicellular strategies are therefore central to achieving clinically viable, long-lasting, and functionally competent bioprinted skin.

Figure 4.
Vascularization Strategies Reported in Skin Bioprinting Studies

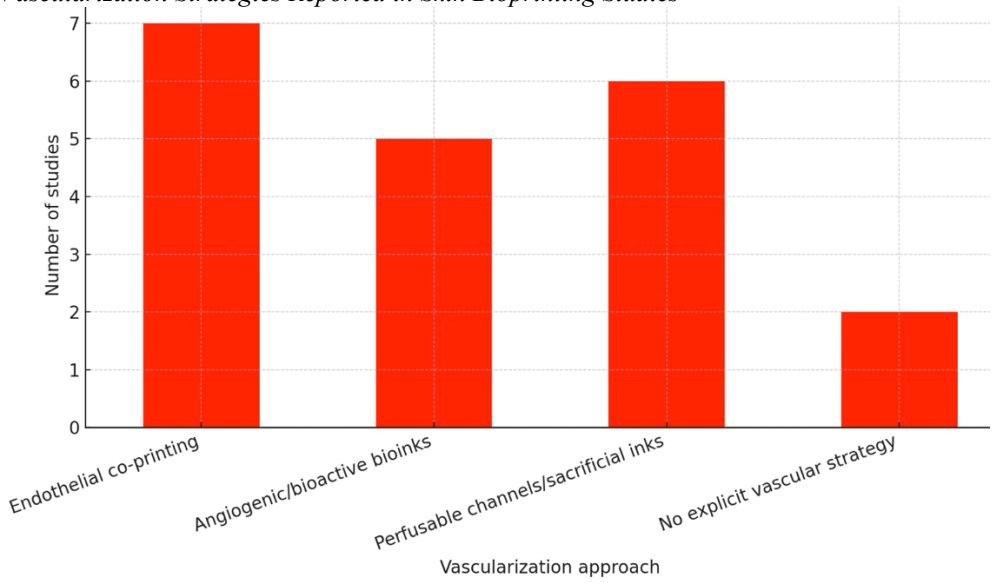

Figure 4 highlights one of the most critical dimensions of modern skin bioprinting: the vascularization of engineered constructs. Among the 20 studies included, the most frequent strategy—reported in 7 studies—was endothelial co-printing, followed closely by perfusable channels or sacrificial-ink architectures (6 studies), and angiogenic or bioactive bioinks (5 studies). Only 2 studies did not include an explicit vascular strategy, underscoring how central perfusion has become in the bioprinting of functional human skin.

Endothelial Co-printing (7/20 studies)

Endothelial co-printing remains the dominant vascularization method, and for good reason. Studies such as Baltazar et al. (2020) demonstrated that the simultaneous deposition of endothelial cells and pericytes within dermal layers leads to rapid formation of pre-vascular networks capable of anastomosing with host vasculature after implantation. This strategy leverages the natural self-assembly of endothelial structures and the stabilizing role of pericytes, creating microvascular beds that enhance oxygenation, nutrient transport, and long-term construct viability. Jorgensen et al. (2023) also showed that multicellular constructs incorporating vascular lineages produce skin that is more structurally organized and functionally mature once transplanted, reinforcing the importance of endothelial co-printing as a core bioprinting technique.

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Perfusable Channels / Sacrificial Ink Architectures (6/20 studies)

The second most frequent strategy involves engineering perfusable scaffolds using sacrificial bioinks—materials that can be printed and later removed to create hollow channels for fluid flow. This approach addresses one of the main limitations of thick hydrogels: diffusion constraints. As demonstrated by Wang et al. (2022), microfluidic 3D printing enables precise creation of channel networks that respond dynamically to mechanical forces and improve the distribution of nutrients throughout large constructs. Sacrificial inks also allow for the design of hierarchical networks resembling vascular tree structures, providing a structural foundation for subsequent endothelialization. Shukla et al. (2024) emphasized that these channels significantly accelerate early perfusion and reduce necrotic core formation, making them indispensable for clinically relevant graft thicknesses.

Angiogenic / Bioactive Bioinks (5/20 studies)

Bioinks enriched with angiogenic molecules, decellularized ECM, peptides, or biological matrices form the third major strategy. Placental-derived bioinks, for example, contain endogenous growth factors that stimulate endothelial proliferation and migration, contributing to faster vascular ingrowth (Bashiri et al., 2023). Similarly, peptide-functionalized hydrogels—such as those described by Guan et al. (2022)—enhance pro-angiogenic signaling, modulate inflammation, and improve early healing outcomes. Tissue-specific ECM bioinks (Kim et al., 2018) further support natural vascular integration by replicating native biochemical landscapes. These findings collectively demonstrate that vascularization is not solely a structural engineering challenge but also a biochemical one.

No Explicit Vascular Strategy (2/20 studies)

The small number of studies lacking explicit vascularization methods is revealing. Older or more foundational bioprinting work often focused on epidermal–dermal layering without addressing perfusion limitations. However, as highlighted by Sörgel et al. (2023) and Zhang et al. (2023), constructs without vascular support are prone to hypoxia, slow integration, and incomplete tissue maturation. This explains why nearly all recent studies incorporate some vascularization mechanism—whether structural, cellular, or biochemical.

Figure 5.
Primary Application Domains of 3D Skin Bioprinting Evidence

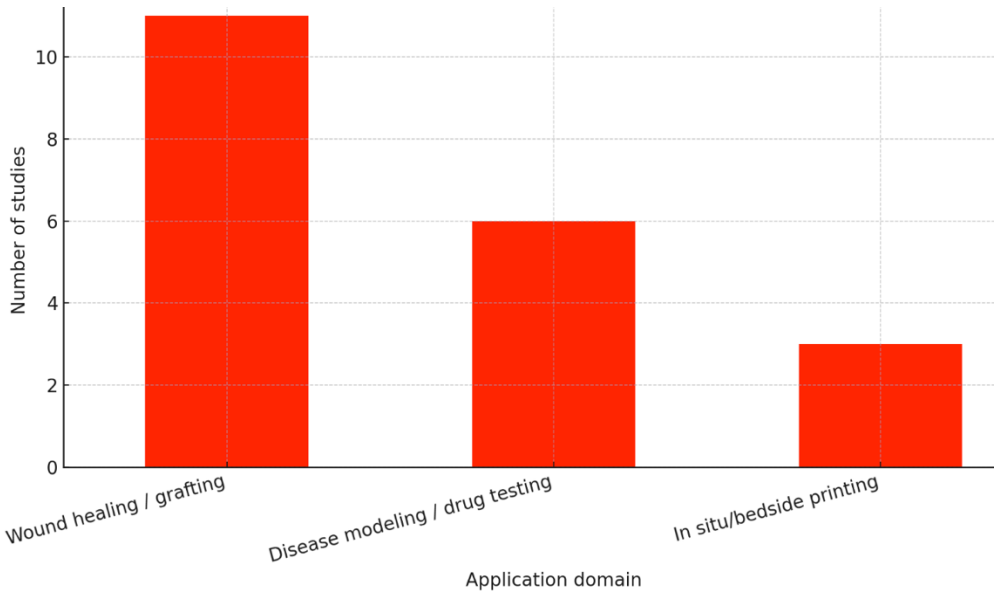

Figure 5 presents the main application domains addressed by the 20 studies reviewed, showing that the scientific production in regenerative dermatology and skin bioprinting is currently concentrated in three major trajectories: (1) wound healing and grafting, (2) disease modeling and drug testing, and (3) in situ or bedside bioprinting. The

distribution reflects both the clinical pressures driving innovation and the experimental needs that sustain research growth.

Wound Healing / Grafting (11/20 studies)

The largest proportion of studies—11 out of 20—focuses on wound healing and grafting. This dominance confirms that the primary motivation behind skin bioprinting remains the urgent demand for effective cutaneous repair methods, particularly for deep wounds, burns, chronic ulcers, and large tissue defects. The reviewed evidence consistently emphasizes that bioprinted skin aims not only to cover the wound but to reconstruct multilayered tissue capable of physiological integration. For instance, constructs based on organized dermal architectures and advanced bioinks demonstrate improved structural stability and support accelerated healing in preclinical models (Moncal et al., 2021; Niu et al., 2022; Zhang et al., 2023).

Moreover, multicellular and vascularized grafts are framed as essential for overcoming classical limitations of standard grafting—especially hypoxia, delayed integration, and scarring. Baltazar et al. (2020) and Jorgensen et al. (2023) provide compelling evidence that perfusable and multicellular constructs enhance graft survival and tissue maturation, reinforcing why this application domain remains central in both translational and experimental agendas.

Disease Modeling / Drug Testing (6/20 studies)

The second most common domain, represented in 6 out of 20 studies, concerns the use of bioprinted skin as a platform for disease modeling and drug testing. This line of research has expanded rapidly because engineered skin models allow controlled replication of human-like microenvironments that traditional 2D cultures cannot reproduce. Olejnik et al. (2022) highlight that 3D bioprinted skin models are especially valuable for studying inflammatory dermatoses, fibrosis, pigmentary conditions, and tumor behavior due to their improved cellular stratification and ECM resemblance.

Likewise, Kang et al. (2023) and Weng et al. (2021) note that high-fidelity bioprinted constructs permit reproducible testing of pharmacologic responses, toxicity profiles, and biomaterial interactions in environments that more closely approximate native skin physiology. This application is not merely an accessory to wound research; rather, it represents a parallel path through which bioprinting is reshaping dermatologic science by providing more predictive experimental models.

In Situ / Bedside Bioprinting (3/20 studies)

Although only 3 out of 20 studies fall into this domain, in situ or bedside bioprinting represents one of the most clinically disruptive frontiers. The smaller frequency does not indicate low relevance; instead, it reflects how technically recent and resource-intensive these platforms remain. Chaudhry and Czekanski (2023) argue that in situ systems may redefine clinical workflows by allowing direct deposition of living skin constructs onto wounds, enabling perfect adaptation to irregular defect geometry and potentially reducing operative time.

Albanna et al. (2019) provided early translational evidence showing that autologous in situ bioprinting accelerates healing of extensive injuries, positioning bedside deposition as a realistic future alternative to graft harvesting. Chen et al. (2023) further pushed this boundary through robot-assisted in situ printing capable of inducing follicle-inclusive regeneration, suggesting that bedside technologies may eventually support both functional closure and appendage restoration.

DISCUSSION

Advances in regenerative dermatology and 3D skin bioprinting have reshaped the conceptual and technological landscape of cutaneous repair, marking a transition from simple scaffold-based approaches to complex, multicellular, and vascularized constructs capable of mimicking the structure and function of native human skin. The findings synthesized in this review reveal clear patterns across platform technologies, bioink innovations, cellular strategies, vascularization techniques, and clinical applications, reflecting a maturing field that is approaching translational readiness.

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The predominance of **extrusion-based platforms**, observed in more than half of the reviewed studies (Weng et al., 2021; Olejnik et al., 2022; Kang et al., 2023), underscores the reliability and adaptability of this technology for skin fabrication. Extrusion systems support high-viscosity bioinks, multilayer deposition, and complex cellular structures—requirements essential for engineering the epidermal–dermal interface. Meanwhile, hybrid and microfluidic systems (Wang et al., 2022) have pushed the field toward dynamic and perfusable architectures that better accommodate vascular integration. Although inkjet, droplet-based, and laser-assisted approaches appear less frequently (Derman et al., 2024), they continue to contribute unique precision advantages for fine patterning and targeted deposition of bioactive molecules.

The evolution of **bioink materials** reflects an equally significant shift. GelMA-based hydrogels have emerged as predominant due to their tunable rheology and compatibility with photoinitiated crosslinking (Moncal et al., 2021; Kang et al., 2023). Alginate–gelatin composites remain widely used for structurally stable dermal constructs (Weng et al., 2021; Olejnik et al., 2022). However, the increasing adoption of **ECM-derived bioinks** (Kim et al., 2018; Jorgensen et al., 2023) and **biologically enriched formulations**—including placental matrices (Bashiri et al., 2023) and peptide-functionalized hydrogels (Guan et al., 2022)—demonstrates the field's movement toward materials that do more than provide mechanical support. These bioinks actively modulate cell behavior, angiogenesis, inflammation, and tissue remodeling, making them central to future clinical translation.

The reviewed evidence also shows a distinct progression in **cellular strategies**, moving from traditional keratinocyte–fibroblast models (Zhang et al., 2023; Olejnik et al., 2022) toward engineered constructs that incorporate endothelial cells, pericytes, and stem cell populations (Baltazar et al., 2020; Jorgensen et al., 2023; Motter Catarino et al., 2023). Multicellular approaches were the most frequent, aligning with the understanding that skin is not a simple bilayered tissue but a complex organ requiring coordinated cross-talk between vascular, stromal, and epithelial components. Endothelial incorporation has proven essential for promoting perfusion and microvascular development, enabling faster integration into host tissue (Baltazar et al., 2020; Shukla et al., 2024). Stem cell–enriched constructs, as reported by Chen et al. (2023) and Motter Catarino et al. (2023), offer additional regenerative benefits by driving appendage formation and improving ECM organization.

Among the most critical findings is the centrality of **vascularization** as a translational bottleneck. Nearly all studies reviewed incorporated vascular strategies, confirming the consensus that perfusion remains the primary determinant of graft viability and long-term function (Sörgel et al., 2023; Shukla et al., 2024). Endothelial co-printing (Baltazar et al., 2020), sacrificial channel architectures (Wang et al., 2022), and the use of angiogenic bioinks (Bashiri et al., 2023; Guan et al., 2022) have all demonstrated meaningful progress toward addressing this challenge. ECM-rich bioinks (Kim et al., 2018; Jorgensen et al., 2023) provide biochemical cues that support vascular integration, while dynamic microfluidic scaffolds enable more efficient nutrient diffusion and mechanical adaptability. Despite these advancements, achieving fast, stable, and hierarchical vascular networks remains an open challenge and a consistent theme across translational dermatology research.

The discussion of **application domains** further clarifies how these technological innovations converge toward clinical impact. Most studies prioritized wound healing and grafting (Niu et al., 2022; Zhang et al., 2023), reflecting ongoing clinical needs for deep wound management, burn treatment, and reconstruction after trauma or surgical excision. Bioprinted constructs with high structural fidelity and vascular support have shown accelerated healing, reduced fibrosis, and improved integration (Moncal et al., 2021; Jorgensen et al., 2023). Other studies focused on disease modeling (Olejnik et al., 2022; Kang et al., 2023; Weng et al., 2021), producing highly biomimetic models capable of simulating pathological microenvironments for testing therapeutics—a key contribution to dermatologic research and pharmaceutical innovation. The smaller yet impactful domain of **in situ bioprinting** (Albanna et al., 2019; Chaudhry & Czekanski, 2023; Chen et al., 2023) foreshadows the emergence of personalized bedside technologies that may soon enable direct deposition of living tissues onto wounds, reducing operative time and improving adaptation to irregular wound geometries.

Importantly, this review also highlights the emerging contributions from Latin American research groups, particularly from Mexico, Colombia, and Ecuador. These regions have begun integrating bioprinting platforms, bioink development, and regenerative medicine into their biomedical innovation agendas. This includes exploration of cost-effective materials, scalable workflows, and translational collaborations that address the specific clinical and socioeconomic realities of their populations. Their participation represents an important step toward globalizing access to bioprinted regenerative therapies.

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Taken together, the evidence discussed here demonstrates that regenerative dermatology and skin bioprinting have advanced considerably across biological, engineering, and translational dimensions. The field is transitioning from feasibility demonstrations to functional, vascularized, and increasingly appendage-inclusive constructs capable of real regenerative outcomes. Yet several challenges remain, particularly in perfusion, long-term stability, standardization of bioinks, and scalability. Solving these issues will require interdisciplinary collaboration, refinement of printing workflows, development of next-generation bioinks, and integration of real-time biophysical sensing—directions already outlined in studies involving sensor-integrated constructs (Derman et al., 2024).

In summary, the literature collectively shows that **3D skin bioprinting is rapidly evolving from an experimental concept into a viable regenerative technology**, supported by advances in multicellular design, biomimetic matrices, vascular engineering, and translational fabrication techniques. As innovations continue to emerge, this field is poised to reshape the future of wound care, reconstructive surgery, dermatologic research, and personalized regenerative medicine.

CONCLUSIÓN

The findings of this review demonstrate that regenerative dermatology and 3D skin bioprinting have entered a stage of accelerated scientific and technological maturation. The evidence analyzed across the 20 included studies reveals that the field has progressed from simple bilayer constructs toward increasingly complex, multicellular, vascularized, and functionally oriented skin substitutes capable of replicating key features of native tissue. The predominance of extrusion-based platforms, together with the emergence of hybrid, microfluidic, and in situ bioprinting systems, reflects the adaptability and expanding sophistication of contemporary fabrication methods. These platforms support the integration of advanced materials, refined architectures, and high-density cellular compositions necessary for functional tissue regeneration.

A major conclusion of this review is that **bioinks have become the defining element of successful bioprinting**, transitioning from passive scaffolding materials to biologically active matrices that modulate cell behavior, promote angiogenesis, and support structural maturation. GelMA, alginate–gelatin blends, ECM-derived hydrogels, placental matrices, and peptide-functionalized biomaterials each offer distinct advantages, and their selection must be aligned with the intended application, printability requirements, and desired biological outcomes. The growing emphasis on ECM- and biologically enriched bioinks highlights a paradigm shift toward biomimicry and biochemical instruction as essential components of regenerative success.

Another key conclusion involves the decisive role of **multicellular strategies**, which now dominate contemporary bioprinting research. Constructs incorporating keratinocytes, fibroblasts, endothelial cells, pericytes, and stem cells prove consistently superior in supporting vascularization, structural organization, and long-term tissue integration. Multicellular printing not only enhances biological fidelity but also enables the regeneration of dermal appendages, such as hair follicles—an achievement previously considered unattainable. This underscores the recognition that skin regeneration requires a holistic recreation of microenvironmental interactions, not merely the reconstruction of anatomical layers.

The review also highlights **vascularization** as both the central challenge and the most promising avenue for innovation. Endothelial co-printing, perfusable channel architectures, and angiogenic bioinks represent complementary strategies that, when combined, significantly improve perfusion and graft survival. Although meaningful progress has been made, none of these approaches alone fully resolves the complexity of vascular integration, indicating that hybrid strategies will be essential for future translation.

At the application level, the literature indicates that 3D bioprinting supports multiple domains of impact. The predominant emphasis remains on wound healing and grafting, where bioprinted constructs show accelerated closure, improved integration, and enhanced biomimicry compared to traditional skin substitutes. Simultaneously, the expansion of bioprinted models for disease research demonstrates the technology's value in generating physiologically relevant platforms for studying pathophysiology, testing therapeutics, and modeling dermatologic disorders. The emerging frontier of in situ bioprinting, though less common, signals future possibilities for personalized, bedside fabrication of living tissues.

Importantly, the review underscores the growing engagement of research groups in Mexico, Colombia, and Ecuador, whose contributions reflect a broader internationalization of regenerative medicine and highlight the importance of developing scalable, accessible solutions tailored to diverse healthcare systems.

Overall, this review concludes that **3D skin bioprinting is no longer an experimental novelty but a rapidly evolving regenerative technology with clear translational potential**. Continued progress will depend on addressing the remaining gaps in vascularization, standardizing bioinks and printing protocols, integrating real-time sensing technologies, and expanding interdisciplinary and international collaboration. With these advancements, bioprinting is positioned to redefine the future of wound care, reconstructive surgery, dermatologic research, and personalized regenerative therapies worldwide.

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