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3D bioprinting bioinks: An up-to-date overview

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ABSTRACT

3D bioprinting has emerged as a transformative technology in the fields of regenerative medicine and tissue engineering, empowering the precise fabrication of complex biological structures. At the core of this innovation is the creation of bioinks that merge living cells with biomaterials to produce scaffolds that replicate the natural extracellular matrix. This review explores the various types of bioinks, including natural, synthetic, and hybrid formulations, also their unique properties such as rheological behavior, biocompatibility, degradability, and printability. Recent advancements in bioink development, particularly the rise of smart bioinks that react to environmental stimuli and bioinks customized for specific tissues, are discussed in detail. Additionally, the applications of 3D bioprinting with bioinks are examined, including their roles in tissue engineering, drug delivery systems, organ printing, and regenerative medicine. This study aims to guide researchers and practitioners in selecting optimal bioinks for specific bioprinting applications, ultimately contributing to the translation of 3D bioprinted tissues into clinical practice.

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Table of Contents

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1. Introduction

3D printing is a technique of additive manufacturing (AM) used to produce a variety of structures and intricate geometries from three-dimensional (3D) model data [1]. 3D bioprinting, denotes 3D printing and biology, is a state-of-the-art in AM and deposition of biomaterials in a layer-by-layer fashion on stratums when inserted in compatible biomaterials [2]. Bioprinting can generally be categorized into four main levels.

Level one is to manufacture structures without biocompatibility requirements, such as 3D printed products used in surgical path planning; level two is to create non-degradable products that are required to be biocompatible, such as titanium alloy joints and silicone prostheses for defect repair; level three is to fabricate biocompatible a degradable product, such as active ceramic bone and biodegradable vascular stent; level four which is the same concept of bioprinting in the narrow sense, is to manipulate living cells to build biomimetic 3D tissues, such as cell models used for drug screening and mechanism research, liver units, skin, blood vessels [3]. Alongside with the variety in the technology of 3D bioprinting, the selection of biomaterials is related to the application of end product. As an example, those consumed in the dental applications should entail prolonged biodegradation rates and high mechanical strength. It was first developed in the 1990s by the means of laser-based bioprinting in fabrication of cells. 3D bioprinting encompasses the potential of solving numerous requirements in medical research such as drug delivery, regenerative medicine, and functional organ replacement [2]. 3D bioprinting technologies enable the digital creation of living structures that encapsulate cells, biomolecules, and biological components in spatially arranged patterns. There are three primary methods for 3D bioprinting: inkjet, laser-assisted, and extrusion bioprinting [4]. Additionally, multiple materials can be printed simultaneously or sequentially using multi-head deposition systems (MHDSs). A custom-made bioprinting system is also available. The bio printed construct is designed using a computer-aided design/computer-aided manufacturing (CAD/CAM) system [5]. The ability to digitally direct and deliver cells has opened up applications in the fabrication of tissue models for studying disease pathophysiology, as complex multicellular constructs to perform drug screening and as constructs to model cancer growth. Compared to traditional techniques, the single biggest advantage of 3D bioprinting is the ability to digitally define the tissue construct of interest and reproduce the physical 3D structure through automated techniques and at resolutions not possible through any conventional photolithography techniques.

In all of these different bioprinting strategies, however, the bioinks are an essential component. The adoption of bioinks for mimicking tissue and organ systems was a pressing need in order to manage organ transplantation-related requirements. The combination of fabrication and clinical practice has been the fundamental basis for the present-day 3D-BP and tissue engineering [6]. In any case, biomaterials can be divided in two main classifications: based on their source, they can be synthetic or natural. According to the characteristics of the materials they are composed of, the bioinks can be classified as structural, fugitive, support and functional [7].

A bioink is defined as a bio printable formulation, which is composed of live cells alone (cell-based bioinks) or combined with a hydrogel formulation (hydrogel-based bioinks). Cell-based bioinks comprise cell suspensions or aggregates, and cell spheroids, whereas hydrogel-based bioinks include cell-laden natural, synthetic, and decellularized tissue hydrogels. Bioinks usually lead to mechanically weak constructs that could hardly self-support themselves, which expressively hinders the complex bioprinting of human-scale constructs [8]. the bioinks are an crucial component, and are cross-linked or stabilized during or immediately after the bioprinting to create the final shapes of the intended tissue constructs [9].

Bioinks can be categorized into two main types: scaffold-free bioinks and scaffold-based bioinks. In scaffold-free bioinks, embryonic development mimics the formation of a neo-tissue. Tissue spheroids, cell pellets, and tissue strands are used in this approach for the fabrication of large-scale functional tissue. Scaffold-based bioinks contain cells loaded in hydrogels, microcarriers or decellularized matrix compounds [10]. By allowing precise fabrication of complex biological structures, 3D bioprinting has revolutionized tissue engineering and bio medicine. The aims of this review are to present a detailed overview of the developments in 3D bioink materials that are utilized to preserve cell viability and function. This discussion focuses on the different types of bioinks, which include natural, synthetic, and hybrid formulations. Also, we discuss their properties, including printability, biocompatibility, degradability, and rheological behavior. Additionally, the review covers the uses of 3D bioprinting with bioinks and recent developments in the field.

2. Types of bioinks

In the realm of 3D bioprinting, bioinks are crucial as they provide the structural and functional foundation for tissue engineering. Among the various types of bioinks, natural bioinks are mainly substantial due to their biocompatibility and ability to mimic the natural extracellular matrix (ECM). In addition, various synthetic bioinks and hybrid bioinks have appeared as important alternatives in 3D bioprinting.

2.1. Natural bioinks

Natural bioinks are derived from biomaterials that closely mimic the properties of the natural ECM, providing an ideal environment for cell growth and tissue development [11].

Composed of polysaccharides, proteins, and other natural polymers, these bioinks exhibit excellent biocompatibility and biodegradability while supporting cell adhesion and proliferation. Their use in 3D bioprinting facilitates the creation of complex tissue constructs that can replicate the structure and function of native tissues, making them suitable for applications in tissue engineering and regenerative medicine [12].

2.1.1. Alginate

Alginate is a polysaccharide derived from brown seaweed, widely recognized for its excellent biocompatibility and ability to form hydrogels through ionic cross-linking [9]. When exposed to divalent cations such as calcium ions, alginate undergoes gelation, allowing for the encapsulation of cells within its matrix. This property makes alginate an ideal candidate for 3D bioprinting applications aimed at tissue engineering. Its hydrophilic nature promotes cell viability and proliferation, while its biodegradability allows for gradual replacement by natural tissue as it degrades [13].

2.1.2. Gelatin

Gelatin is a natural polymer derived from collagen via hydrolysis. It has high biocompatibility and non-immunogenic characteristics. Gelatin dissolves in water, forming hydrogels that increase cell adhesion and proliferation [14].

Gelatin's molecular structure closely resembles that of collagen, which is vital for promoting cellular activities necessary for tissue regeneration. In 3D bioprinting, gelatin can be modified with methacryloyl groups (GelMA) to improve its mechanical properties and cross-linking capabilities when exposed to light. This modification improves printability and enables the formation of stable structures capable of withstanding the challenges of biological environments. However, gelatin is favored as a bioink in tissue engineering due to its beneficial biological properties, but its mechanical strength and degradation rate limit its use in load-bearing applications [15].

Fig. 1 illustrates the improved mechanical properties and high-fidelity fabrication achieved by combining GelMA with HAMA in DLP-based 3D bioprinting. The process includes enzymatic digestion to modify matrix stiffness and promote cell functions, enabling tissue-mimicking constructs with tailored mechanical properties [16].

2.1.3. Collagen

Collagen is the most abundant protein in the human body and serves as a fundamental component of the extracellular matrix. As a bioink, collagen provides an ideal microenvironment for cell attachment, growth, and differentiation due to its inherent biological activity [9]. Collagen-based bioinks can be formulated into hydrogels that replicate the structure and function of the natural extracellular matrix, promoting cellular behaviors essential for tissue development [17]. However, while collagen promotes excellent cell interactions, it also presents challenges such as rapid biodegradation and poor mechanical properties compared to synthetic alternatives. However, collagen's unique properties make it invaluable in regenerative medicine and tissue engineering, where cell functionality is essential [15].

Natural bioinks such as alginate, gelatin, and collagen each offer distinct advantages and challenges in 3D bioprinting Biocompatibility, mechanical properties, and desired cellular interactions determine their selection.

2.2. Synthetic bioinks

Engineered bioinks provide greater control over mechanical and functional properties needed for effective 3D bioprinting. With these bioinks, specific requirements such as viscosity, gelation kinetics, and degradation rates can be met, making them suitable for a variety of tissue engineering applications [18]. Two prominent examples of synthetic bioinks are Polyethylene Glycol (PEG) and Polylactic Acid (PLA).

2.2.1. Polyethylene glycol

Polyethylene Glycol (PEG) is a popular synthetic polymer in 3D bioprinting due to its biocompatibility and adjustable properties. Researchers can change its molecular weight and functional groups to raise viscosity and gelation for numerous printing processes [18]. A key advantage of PEG is its ability to form hydrogels that can encapsulate cells while fostering their growth and differentiation.

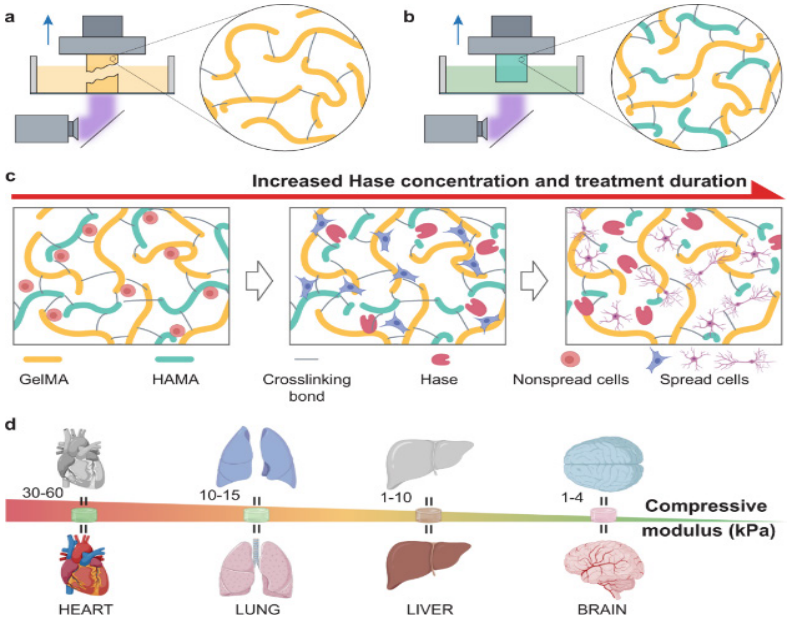

Fig. 1. High-fidelity DLP bioprinting with GelMA/HAMA bioinks offers improved printability and highly adjustable mechanical properties [16].

During the printing process, several cross-linking methods can be used to control hydrogel formation, including photopolymerization. Furthermore, PEG's hydrophilic nature improves cell viability and endorses nutrient diffusion within the printed constructs. However, while PEG offers superior printability and mechanical strength compared to several natural bioinks, it often lacks the biological cues essential for promoting cell adhesion and functionality. In order to overcome this limitation, scientists are exploring approaches to incorporate bioactive molecules into PEG-based bioinks, which would increase their ability to mimic the natural ECM and boost cellular responses [19].

2.2.2. Polylactic acid

Another popular synthetic bioink is PLA, which is known for its biodegradability and mechanical strength, making it suitable for long-term structural applications. PLA can be derived from renewable sources such as corn starch or sugarcane for biomedical applications [20].

Its ability to be processed into various forms such as filaments or powders, empowers versatility in fabrication techniques beyond just bioprinting. In 3D bioprinting, PLA can be used to create scaffolds that provide mechanical support while gradually degrading in vivo, allowing for tissue regeneration as the scaffold is replaced by natural tissue.

However, PLA's hydrophobic nature can pose challenges for cell adhesion, necessitating surface modifications or blending with other materials to augment biocompatibility [21]. Recent progress has concentrated on creating PLA-based composites that integrate natural polymers or bioactive substances to improve cellular interactions and facilitate tissue integration.

2.3. Hybrid bioinks

Hybrid bioinks integrate both natural and synthetic materials to create bioinks that capitalize on the advantages of each component while addressing their individual limitations [22]. This combination allows for superior mechanical properties, biocompatibility, and biological functionality, making hybrid bioinks specifically suitable for a variety of tissue engineering applications.

Two notable subcategories of hybrid bioinks are Gellan Gum and Sodium Alginate Combinations and Methacrylated Silk Fibroin-Based Bioinks [23].

2.3.1. Gellan gum and sodium alginate combinations

One innovative approach in hybrid bioink development involves the combination of gellan gum (GG) and sodium alginate (SA) with a thixotropic magnesium phosphate-based gel (TMP-BG). This specific formulation has been shown to exhibit excellent printability due to its shear-thinning properties, which facilitate smooth extrusion during the 3D printing process [24].

GG-SA/TMP-BG hybrid bioinks can be cross-linked with calcium and magnesium ions to mimic different extracellular matrix structures found in tissues.

This adaptability is crucial for creating constructs that can provide adequate support for cell proliferation and tissue integration. In vitro studies have demonstrated that cells encapsulated within this hybrid bioink maintain high viability, with important cell proliferation observed over time [25].

Moreover, when immersed in simulated body fluids, the bioink promotes apatite deposition, suggesting that it could be used for bone tissue engineering. Overall, this hybrid formulation showcases promising characteristics for regenerative medicine, combining mechanical support with biological activity to increase tissue repair processes [26].

2.3.2. Methacrylated silk fibroin-based bioinks

Another major advancement in hybrid bioinks is the development of methacrylated silk fibroin-based bioinks, which combine methacrylate gelatin (GelMA) with methacrylated silk fibroin (SFMA). This hybrid formulation leverages the excellent rheological properties of both components to create a bioink suitable for extrusion bioprinting [27].

The GelMA/SFMA bioink can undergo dual cross-linking processes both thermal and photopolymerization allowing it to retain its shape after printing while providing a stable environment for cell encapsulation. This versatility facilitates the creation of complex 3D structures that mimic the cellular microenvironment at a microscale level. Cells encapsulated within these constructs are highly viable and proliferate over extended periods of time, including human umbilical vein endothelial cells (HUVECs) and rat pheochromocytoma (PC12) cells [28]. Additionally, the GelMA/SFMA hydrogels have been evaluated for their biocompatibility and degradability in living organisms, showcasing their promise for a range of biomedical uses, such as tissue engineering and soft robotics [27].

The development of hybrid bioinks represents an expressive step forward in the field of 3D bioprinting, offering researchers the ability to create tailored materials that meet specific requirements for diverse tissue engineering applications. By combining the strengths of natural and synthetic materials, hybrid bioinks pave the way for more effective strategies in regenerative medicine. Diagram 1 summarizes various natural bioinks and their properties based on the provided search results. It can be helpful for readers looking to understand the different types of natural bioinks and their specific attributes.

3. Properties of bioinks

The characteristics of bioinks are essential for the effectiveness of 3D bioprinting, affecting aspects such as cell survival and the structural strength of the printed structures. Key properties include rheological properties, biocompatibility, degradability, and printability. Each of these characteristics plays a vital role in ensuring that bioinks can effectively support tissue engineering applications.

3.1. Rheological properties

Fow behavior and deformation characteristics of bioinks are determined by their rheological properties. These properties are essential for achieving optimal printability during the bioprinting process[31]. A bioink must exhibit appropriate viscosity to allow for smooth extrusion through the printing nozzle while maintaining shape fidelity after deposition. A bioink's viscosity should decrease under shear stress, enabling easier printing and enabling it to regain its viscosity afterward [32].

This property is essential for maintaining structural integrity in the printed construct. Also, the viscoelastic properties of bioinks characterized by their ability to display both viscous and elastic behavior are important for ensuring that the printed structures can withstand mechanical forces without collapsing or deforming. The stability between these rheological properties must be sensibly optimized to confirm successful bioprinting outcomes, as they exactly impact cell survival and functionality within the printed tissue constructs Table 1.

Table 1
Summarizing various natural bioinks and their properties.

Natural bioink	Composition	Viscosity (Pa·s)	Biocompatibility	Degradability	Applications	Refs.
Alginate	Polysaccharide from seaweed	0.1 - 1.0	High	Moderate (ionic cross-linking)	Cartilage, bone tissue engineering	[11, 17]
Gelatin	Denatured collagen	0.05 - 0.5	Very high	Rapid (enzymatic degradation)	Skin, cartilage, vascular tissues	[11, 17]
Collagen	Major structural protein	0.1 - 2.0	Very high	Moderate (enzymatic degradation)	Soft tissue repair, wound healing	[11, 29]
Fibrin	Blood protein	Varies (depends on concentration)	High	Rapid (fibrinolysis)	Wound healing, vascular grafts	[17, 30]
Hyaluronic acid	Glycosaminoglycan	Varies	Very high	Moderate (hydrolytic degradation)	Cartilage, skin regeneration	[17]
Decellularized ECM (dECM)	Derived from natural tissues	Varies (tissue-specific)	High	Slow (depends on tissue type)	Organ printing, complex tissue engineering	[11, 17]

3.2. Biocompatibility

Biocompatibility is a fundamental property of bioinks, as it determines how well the material interacts with living cells and tissues without eliciting an adverse immune response. A biocompatible bioink should support cell adhesion, proliferation, and differentiation while providing a suitable microenvironment that mimics natural extracellular matrices (ECMs) [33]. This characteristic is essential for ensuring that cells remain viable throughout the printing process and can function effectively once printed into tissue constructs. Natural polymers such as gelatin, alginate, and collagen are often favored for their inherent biocompatibility, but synthetic polymers like polyethylene glycol (PEG) can also be revised to improve their compatibility with biological systems.

The insertion of bioactive components such as growth factors or peptides within the bioink formulation can further promote cellular activities necessary for tissue regeneration. Ultimately, achieving high biocompatibility is crucial for the success of 3D bio printed tissues in clinical applications [34].

3.3. Degradability

Degradability refers to the ability of a bioink to break down over time within a biological environment, which is essential for tissue engineering applications where scaffolds need to be gradually replaced by natural tissue. Ideally, a bioink should degrade at a rate that matches the rate of tissue regeneration, allowing for seamless integration of new tissue while preventing excessive accumulation of material that could hinder healing processes [35]. Natural polymers like gelatin and alginate typically exhibit favorable degradability due to their biological origins, while synthetic materials like PLA can be engineered to possess specific degradation rates through modifications in their molecular structure or copolymerization with other materials. The breakdown products must also be non-toxic and readily metabolized by the body to guarantee safety throughout tissue repair processes [9]. Optimizing bioink performance in regenerative medicine requires understanding and controlling degradation kinetics.

3.4. Printability

Printability encompasses several factors that influence how well a bioink can be processed through a 3D printer to create precise and accurate structures. Key considerations include viscosity, shear-thinning behavior, and thermal stability during printing[33]. A bioink must maintain its shape after deposition while allowing for sufficient flow during extrusion; thus, achieving an optimal balance between these characteristics is crucial for successful printing outcomes [9]. Additionally, printability is affected by the temperature at which printing occurs; bioinks should ideally have print temperatures that do not exceed physiological levels to prevent damaging cells within the ink. The ability to form stable structures with high shape fidelity is essential for creating complex geometries that closely resemble native tissues. Furthermore, post-printing cross-linking methods may be employed to enrich structural integrity and stability of printed constructs after they have been deposited [36]. Fig. 2 outlines the key properties of bioinks, broken down into the main categories along with their specific sub-features.

4. Bioink formulation strategies

The formulation of bioinks is a critical aspect of 3D bioprinting, as it directly influences the performance, biocompatibility, and functionality of the printed constructs [37].

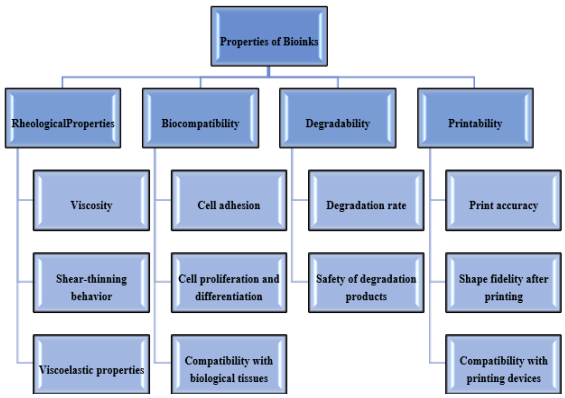

Fig. 2. Properties of bioinks.

Various strategies have been developed for bioink formulation, which can be broadly categorized into single-component systems, multi-component systems, and the incorporation of additives and modifiers. Bioinks can be tailored for specific tissue engineering applications using each strategy's unique advantages and challenges.

4.1. Single-component systems

Single-component bioinks utilize a single type of biomaterial to create the printing medium. These systems are often simpler to formulate and can provide consistent properties throughout the printed construct [38]. Common examples include natural polymers like alginate, gelatin, and collagen, which are favored for their biocompatibility and ability to support cell growth. For instance, alginate-based bioinks can be easily cross-linked using divalent cations such as calcium ions, resulting in hydrogels that maintain shape fidelity during printing. However, single-component systems may lack the mechanical strength or specific

biological functionalities required for certain applications. Therefore, while they are beneficial for basic tissue engineering tasks, they may not be sufficient for more complex structures that require enriched mechanical properties or specific cellular interactions [39].

4.2. Multi-component systems

Multi-component bioinks combine two or more biomaterials to create a composite bioink that leverages the strengths of each component. This approach allows for greater customization of mechanical properties, degradation rates, and biological functionality. For example, a hybrid formulation of gelatin and PEG can improve both printability and cell viability while providing a supportive environment for tissue regeneration [40]. Multi component systems can also include combinations of natural and synthetic materials to achieve desired characteristics that single-component systems cannot provide alone [41]. The formulation process can be optimized to adjust the ratio of components based on specific application needs, assisting the creation of complex tissue architectures with heterogeneous material properties. However, the complexity of these formulations may introduce challenges in achieving consistent printability and ensuring compatibility between different materials [39].

4.3. Additives and modifiers

In addition to selecting appropriate base materials, the incorporation of additives and modifiers into bioink formulations can meaningfully enrich their properties. Common additives include growth factors, peptides, or nanoparticles that promote cell adhesion, proliferation, or differentiation within the printed construct [42].

For instance, incorporating bioactive molecules into a gelatin-based bioink can stimulate specific cellular responses necessary for tissue regeneration. Modifiers such as cross-linking agents or rheological modifiers can also be used to regulate the viscosity and mechanical properties of the bioink, improving its printability and structural integrity after printing [43]. Furthermore, recent advancements in machine learning have been useful to optimize bioink formulations by calculating how different additives will affect printability and cellular behavior in real time. While these strategies offer exciting opportunities for improving bioink performance, careful consideration must be given to ensure that additives do not compromise biocompatibility or introduce toxic effects [44].

The development of effective bioink formulation strategies is essential for progressing 3D bioprinting technologies and enriching their applicability in regenerative medicine and tissue engineering. By leveraging single-component systems, multi-component systems, and strategic use of additives and modifiers, researchers can create tailored bioinks that meet the specific needs of various biomedical applications [45].

5. Applications of 3D bioprinting with bioinks

Using 3D bioprinting technology, complex biological structures can be precisely fabricated to improve tissue engineering and regenerative medicine. Among the applications of bioinks in this domain are tissue engineering, drug delivery systems, organ printing, and regenerative medicine. Each application leverages the unique properties of bioinks to create functional constructs that can mimic natural tissues and organs [46]. Fig. 3 illustrates the projected growth of the bioink market over time, based on an annual compound growth rate (CAGR) of 12.5%. The data points include market values for key years.

5.1. Tissue engineering

Tissue engineering is one of the primary applications of 3D bioprinting, where bioinks are used to create scaffolds that support the growth and development of new tissues. By combining various biomaterials with living cells, bioprinted constructs can closely mimic the architecture and functionality of native tissues [9]. Bioinks made from natural polymers like alginate, gelatin, and collagen provide a conducive environment for cell adhesion and proliferation, essential for successful tissue regeneration. The ability to precisely control the spatial arrangement of cells and biomaterials during the printing process allows for the creation of complex tissue architectures that can improve nutrient diffusion and waste removal, critical factors for cell survival [47]. Hydrogel-based bioinks have demonstrated their potential to produce functional tissues such as cartilage, skin, and vascular structures, thereby improving patient outcomes in regenerative medicine. Byoung Soo Kim et al. [48] aimed to develop and evaluate a skin-derived extracellular matrix (S-dECM) bioink for 3D cell printing in skin tissue engineering. Their study demonstrated that S-dECM bioink supports better tissue stabilization, improves epidermal organization and dermal ECM secretion, and develops in vivo wound healing through the use of pre-vascularized skin patches. This research highlights S-dECM bioink as a promising next-generation material for advanced skin tissue engineering and regenerative medicine.

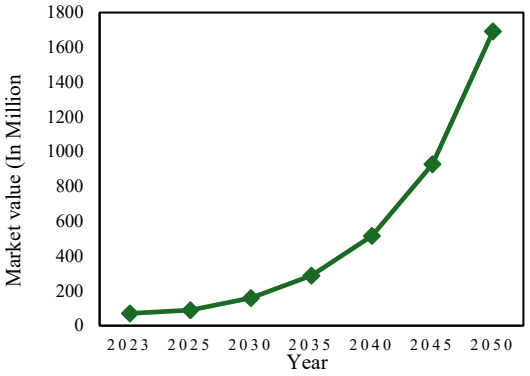

Fig. 3. Bioink market growth forecast (2023-2023).

5.2. Drug delivery systems

Another promising application of 3D bioprinting with bioinks is in the development of advanced drug delivery systems. Bioinks can be engineered to encapsulate therapeutic agents within 3D-printed structures that release drugs in a controlled manner over time [32]. This approach allows for localized delivery of medications right to targeted tissues, increasing therapeutic efficacy while reducing systemic side effects. For instance, hydrogels used as bioinks can be designed to respond to environmental stimuli such as pH or temperature changes, authorizing on-demand drug release tailored to specific patient needs. Furthermore, incorporating bioactive molecules within these bioinks can improve cellular responses and promote healing processes, making them valuable tools in personalized medicine [50]. The ability to fabricate complex geometries also facilitates the creation of microenvironments that mimic natural tissue conditions, further enhancing drug delivery effectiveness. Jun Yin et al.[51] developed a strategy for 3D bioprinting 5% (w/v) cell-laden methacrylated gelatin (GelMA) bioinks with high cell

viability by incorporating gelatin for a two-step cross-linking process. This approach improved the rheological properties and shape fidelity of printed structures, allowing for the successful printing of 5% GelMA with 8% gelatin, achieving similar resolution to higher concentration GelMA bioinks. The resulting scaffolds demonstrated above 90% cell viability for bone marrow stem cells, emphasizing the potential of GelMA/gelatin bioinks in drug delivery.

5.3. Organ printing

Organ printing represents a groundbreaking advancement in 3D bioprinting technology, where bioinks are utilized to fabricate functional organ-like structures for transplantation or research purposes. Given the global shortage of donor organs, bioprinting offers a potential solution by creating patient-specific organs that reduce the risk of rejection and improve compatibility [47]. By using a combination of living cells and biomaterials as bioinks, researchers have successfully printed simplified organ models such as liver, kidney, and heart tissues that exhibit functional characteristics similar to their natural counterparts. These constructs not only serve as valuable tools for studying disease mechanisms but also hold promise for future applications in organ transplantation [32]. The ongoing development of vascularized structures within printed organs is crucial for ensuring nutrient and oxygen supply, which is essential for long-term viability post-transplantation.

5.4. Regenerative medicine

In regenerative medicine, 3D bioprinting with bioinks is importamt in developing therapies aimed at repairing or replacing damaged tissues or organs. The ability to create custom scaffolds that integrate with existing biological systems allows for tailored treatments based on individual patient needs. Inks can include growth factors or signaling molecules to promote tissue regeneration along with specific cell types. This approach has shown promise in treating conditions such as bone defects, cartilage injuries, and soft tissue damage by running a supportive environment that inspires natural healing processes [52]. Furthermore, advancements in bioprinting technologies succeed the fabrication of complex tissue constructs that can be implanted straight into patients, facilitating faster recovery times and improved outcomes compared to traditional surgical procedures [53].

The applications of 3D bioprinting with bioinks continue to expand rapidly across various fields of medicine and biotechnology. As research progresses and technologies advance, the potential for creating functional tissues and organs through bioprinting holds great promise for transforming healthcare practices and addressing critical medical challenges worldwide [54].

A recent study by Jo et al. [55] revealed that mesenchymal stem cells positively impact skin regeneration by enhancing cell proliferation, reducing skin inflammation, and boosting collagen and elastic fibers. Another study developed a thermoresponsive composite bioink using carboxymethyl cellulose (CMC) and agarose in a 5:5 ratio, which demonstrated superior gel formation at 37 °C. The CMC-agarose bioink exhibited excellent cytocompatibility, maintaining over 80% cell viability in vitro with skin fibroblasts and successfully fabricated complex 3D structures through extrusion bioprinting. In vivo studies on rat full-thickness wounds indicated its potential in promoting skin regeneration. Overall, CMC-agarose bioinks show promise for applications in tissue engineering and regenerative medicine [56].

6. Recent advances and challenging in bioink development

Recent progresses in bioink development have expressively heightened the capabilities of 3D bioprinting, leading to more complex and functional tissue constructs. Two notable areas of progress include the emergence of smart bioinks and the development of bioinks for definite tissues [57]. These innovations are paving the way for more useful applications in regenerative medicine and tissue engineering.

6.1. Smart bioinks

Smart bioinks are designed to respond dynamically to environmental stimuli, such as temperature, pH, or light, allowing for controlled release of therapeutic agents or changes in their physical properties. This adaptability is crucial for creating bioinks that can mimic the complex behavior of biological tissues [58]. For instance, researchers have developed bioinks that incorporate thermoresponsive materials, which can transition from a liquid state to a gel state at physiological temperatures. This property not only facilitates easier handling during the printing process but also increases the stability of printed constructs once they are placed in the body [59].

Another exciting development in smart bioinks is the incorporation of self-healing hydrogels that can recover from damage after being subjected to mechanical stress. These hydrogels utilize supramolecular interactions, allowing them to flow under shear stress and self-repair immediately after printing [60]. This capability is remarkably beneficial for applications where mechanical integrity is critical, such as in load-bearing tissues. Additionally, stimuli-responsive materials have been explored for use in 4D bioprinting, where structures can change shape or function over time in response to specific triggers [61]. The integration of smart bioinks into bioprinting workflows represents a substantial leap toward creating more functional and responsive tissue constructs that can adapt to their biological environment.

6.2. Bioinks for specific tissues

The development of bioinks tailored for specific tissues has become a focal point in advancing 3D bioprinting technologies. Researchers are increasingly focusing on creating bioinks that replicate the unique mechanical and biochemical properties of various tissues, such as cartilage, bone, skin, and vascular structures [62]. For example, bioinks designed for cartilage tissue often incorporate components like gelatin and hyaluronic acid to increase cell proliferation and mimic the extracellular matrix found in natural cartilage [63].

Additionally, decellularized extracellular matrix (dECM)-based bioinks have gained attention due to their ability to provide native biochemical cues essential for cell behavior [64]. These bioinks are derived from specific tissues by removing cellular components while preserving the ECM structure, allowing for the creation of scaffolds that closely resemble natural tissue environments. The use of dECM-based formulations has shown promise in engineering complex tissues like cardiac patches or vascularized structures [64].

Moreover, advances in marine-derived biomaterials are expanding the repertoire of available bioinks. Materials such as alginate and chitosan offer unique properties that make them suitable for various biomedical applications while being environmentally sustainable [65]. By focusing on tissue-specific

characteristics and integrating innovative materials into bioink formulations, researchers are making major strides in developing functional constructs that can more effectively support tissue regeneration and repair [66].

Advanced bioinks and formulations tailored for specific tissues are advancing 3D bioprinting technology, improving its potential uses in regenerative medicine [67]. As these advancements unfold, they promise to improve patient outcomes by assisting in the creation of customized solutions tailored to individual medical needs [68].

6.3. Integration of different types of cells within bioinks

The integration of different types of cells within bioinks presents a promising strategy for improving the functional outcomes of bioprinted tissues and organs. Optimization of this integration involves careful consideration of various factors, including cell compatibility, mechanical properties of bioinks, and the establishment of an appropriate microenvironment that fosters cell differentiation and functionality.

The choice of bioink composition can meaningly influence the integration of various cell types. For instance, gelatin-based bioinks have been shown to enable high-density cell loading while maintaining acceptable rheological properties for bioprinting. This enables the development of structures that accommodate various cell types, including organoids and vascularized tissues, by establishing a supportive microenvironment, as shown in research using prevascularized spheroids to improve tissue constructs [69]. The compatibility of cell types within the bioink formulation can dictate not only the printability but also the functional outcomes of the printed structures.

Additionally, the rheological properties of bioinks, influenced by cell density and type, must be optimized to ensure successful bioprinting. Diamantides et al. [70] indicates that higher cell densities can lead to altered rheological behaviors, requiring adjustments in print parameters to ensure the bioink's performance during the printing process.Furthermore, the mechanical and biochemical signals delivered by the bioink matrix can expressively impact cell fate and functionality. Previous studies emphasize the importance of extracellular matrix (ECM) mimics within bioinks, which play a role in regulating cellular responses [71, 72].

6.4. Specific challenges faced in the mass production of bioinks

The development and mass production of smart bioinks face several major challenges that directly impact their clinical and industrial application. These challenges encompass formulation consistency, large-scale production while ensuring cell viability, managing degradation rates, mechanical properties, and the integration of advanced materials. One of the primary challenges is ensuring consistency in bioink formulations. Variations in viscosity and rheological properties are critical to maintaining the printability of bioinks during the 3D printing process. Reports indicate that bioinks must exhibit high viscosity to support cell suspension and initial structural integrity while maintaining shear-thinning properties to avoid damage to cells during extrusion [73]. A.A. Golebiowska et al. demonstrated that bioinks modified with viscosity savories like xanthan gum (XG) or Laponite® not only develop viscosity but also maintain essential shear-thinning behavior, emphasizing the delicate balance needed for effective bioink formulations. [74].

Controlling the degradation rates and mechanical properties of bioinks across large batches also poses a substantial hurdle. The mechanical properties, which are crucial for the intended biomedical applications, need to remain consistent for effective tissue regeneration. Variability in the mechanical characteristics of printed constructs has been highlighted, where differing hydrogel formulations resulted in varied performance metrics even within the same processing conditions [69].Integrating self-healing hydrogels or other advanced materials can further complicate these properties, which must be tailored to support bioactivity and printability without hindering the bioinks' intended functionality [75]. This balance is critical as the bioinks must not only provide structural integrity but also accommodate cellular interactions that promote tissue regeneration.

The integration of advanced materials, such as self-healing hydrogels or nanomaterials, into bioinks while maintaining their printability and biological activity presents yet another substantial challenge. While nanomaterials boost the mechanical strength of bioinks and facilitate bioactivity, they can also disrupt the cellular microenvironment if not properly balanced [76].The conflicting needs for high printability often associated with more viscous formulations and the need for low viscosity during cell infusion highlight the intricate design requirements that challenge the mass production of bioinks.

7. Conclusion

Developing scalable bioprinting techniques that can produce large quantities of bioinks and bioprinted tissues efficiently and cost-effectively is essential for widespread clinical adoption; Optimizing the integration of different cell types within bioinks to create more complex and functional tissue constructs. This includes understanding cell-cell interactions and developing strategies to maintain cell viability and functionality; Enhancing the vascularization of bioprinted tissues to ensure adequate nutrient and oxygen supply, which is critical for the long-term viability of larger tissue constructs and organs.

These advancements have profound implications. A 3D bioprinting technology is poised to revolutionize not only tissue repair and organ transplantation, but also drug testing and disease modeling as it matures. The ability to create patient-specific tissues could expressively reduce the risk of transplant rejection and improve recovery outcomes, addressing critical shortages in donor organs. Furthermore, using innovative materials derived from natural sources or specifically designed for certain applications boosts the sustainability of biomedical practices. Methods should be investigated to identify new materials that can further improve biocompatibility and functionality. It will be crucial for researchers, clinicians, and industry professionals to work together to translate these advances into clinical applications that heighten patient care.

The advancement of advanced bioinks is leading the way in turning 3D bioprinting into a substantial instrument for regenerative medicine. With recent advances in intelligent technologies and designs tailored to specific tissues, the goal of fabricating fully functional tissues and organs is becoming closer. This progress will enable us to gain a deeper understanding of biological processes and address some of today's most pressing healthcare needs. As we continue to explore this exciting frontier, the potential for 3D bioprinting to reshape medicine is both inspiring and transformative, paving the way for a future where personalized medicine becomes a reality.

Author contributions

Aramis Moradi: Writing—Original Draft Preparation, Resources, Conceptualization. **Negin Khosravi:** Writing—Original Draft

Preparation, Resources. **Bhekumuzi Sfundo Khanyiled:** Investigation, Writing—Review and Editing. **Fariborz Sharifianjazi:** Writing—Original Draft Preparation, Writing—Review and Editing, Supervision. **Matin Sorkhabi:** Writing—Original Draft Preparation, Writing—Review and Editing.

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Data availability

No data is available.

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