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*Review Article*

# Review on Advances in Growth Factor Loaded Bioinks for 3D Bioprinting

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3D bioprinting is an advanced technique that involves depositing bioink in layers to create three-dimensional structures of cells, tissues, and organs. Bioink, which contains living cells and biomaterials, is a crucial component in this process. Bioinks are generally classified as either natural or synthetic. The properties of bioink—such as physicochemical, rheological, and biocompatibility characteristics—play a vital role in successful bioprinting. The development of optimized bioink formulations supports cell differentiation and tissue formation. Growth factors are proteins that promote cell differentiation, regeneration, and tissue repair. Incorporating site-specific growth factors into bioinks can enhance their effectiveness. Growth factors improve cell viability, direct differentiation, promote tissue formation, and enhance the structural and functional properties of bioprinted tissues. Different types of growth factors have distinct roles in the regeneration process. This review analyzes the use of growth factors in 3D bioprinting for various regenerative applications, the formulation of bioinks, and the resulting outcomes. Additionally, it discusses the limitations of incorporating growth factors into bioinks and explores future directions in 3D bioprinting.



## Introduction

Bioinks are defined as a formulation of cells suitable for processing by an automated biofabrication technology that may also contain biologically active components and biomaterials [1]. For the development of structures, two approaches for bioink materials are used which includes scaffold-free cell-based & cell-scaffold based approaches. The scaffold based method, biomaterials and live cells are combined as bioink for 3D bioprinting of structures. When scaffold biodegrades, the set tissue structures arise and the live cells expand, filling the space. In a scaffold-free cell-based approach, the live cells are printed directly which resembles normal embryonic cell growth [2]. The physicochemical properties of an ideal bioink must result in (i) the tissue constructs have mechanical strength and robustness, while retaining the tissue-matching mechanics, preferably in a tunable manner; (ii) gelation and stabilization should be adjustable to aid the bioprinting of structures with high shape fidelity; (iii) biocompatibility and, also mimics the biodegradability of the natural microenvironment of the tissues; (iv) tissue-specific for chemical modifications and (v) potential for large-scale production with minimum variations [3]. Bioinks are classified into two types depending on the biomaterials, natural polymer and synthetic polymer. Bioinks formulations are from natural materials that have biocompatibility for use in the printing process. Natural environment of cells able to be replicated and support cell functions.But synthetically derived bioink lacks biocompatibility, while exhibiting enhanced mechanical characteristics [4].

Natural bioinks are derived from natural sources, most common bioinks are agarose, alginate, gellan gum, dextran, hyaluronic acid (HA), silk, fibrin, collagen, dECM, Matrigel, cellulose, gelatin, and chitosan [5]. Natural bioinks are crucial because it enables cells to organize structurally and functionally through their scaffolding system which offers a supportive framework in 3D bioprinting. It also has unique properties including biocompatibility, non - toxicity and biodegradability [6]. The primary components of various 'bioinks' are these natural polymers, which are crucial for 3D bioprinting bioartificial organs, enabling the creation of cell-specific, tissue-specific, and organ-specific structures with their functionalities. Natural polymer bioinks poor mechanical properties limit the application in the intricate 3D printing of organs including the complex networks of neural, vascular, and lymphatic systems. Utilizing methods such as physical blending, chemical crosslinking, or a combination of both natural and synthetic polymers can effectively address the geometrical,

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mechanical, structural, physiological, and clinical challenges [7].

Polymers artificially created through chemical reactions involving monomers, are synthetic polymers often sourced from petroleum. Their hydrogels are typically generated through bulk, solution, and reverse dispersion methods [8]. Synthetic polymers can have adjustable mechanical properties, with molecular weights tailored from low to ultra-high based on the specific needs. Because of their bio inertness, organic solvent used and structures synthetic polymer solutions, hydrogels, and scaffolds, including - PLGA, poly(glycolic acid) (PGA), poly(hydroxypropyl methacrylamide) (PHPMA), PU, PCL, PLA, and poly(methyl methacrylate) (PMMA), have poor cytocompatibilities [9].

3D bioprinting is an additive manufacturing technique used for the construction of complex 3D functional living tissues or artificial organs [10] by placement of living cells and biomaterials in a layer-by-layer fashion [11]. The goal of bioprinting is to replace animal testing for disease research and therapy development, as well as to offer an alternative to autologous and allogeneic tissue implants [12]. There are four primary techniques in 3D bioprinting which includes, extrusion, inkjet, stereolithography, and laser-assisted bioprinting.

In extrusion based, bioink is extruded through a nozzle by a microfluidic, or pneumatic system. Through layer by layer deposition of the extruded bioink filament, three-dimensional structures are created. Bioprinting resolution depends on the diameter of the nozzle tip [13]. The inkjet printing is classified into two different types. They are thermal and piezoelectric inkjet printing. When using thermal inkjet printing, a small amount of ink close to the nozzle is heated quickly creating a vapor bubble that pushes the ink out of the nozzle. In piezoelectric inkjet printing, droplet formation is formed by using piezoelectric materials at the printing nozzle. On applying suitable voltage on the ends of the piezoelectric element, it changes shape by bending and it causes the droplet to be squeezed out through the nozzle. Upon releasing voltage, the piezoelectric element is restored to its original shape [14]. Laser assisted bioprinting (LAB) uses laser induced forward transfer technology to precisely deposit cells and biomaterials. The biomaterials are mainly treated by photo polymerization methods. A high-pressure bubble that ejects the bioink droplets onto the receiving substrate is created when the metal layer on top of the hydrogel is vaporized by the laser beam pulses that focus on the ribbon for a predetermined amount of time [15]. Stereolithography is a bottom up approach in the 3D bioprinting process. In stereolithography, UV lights are used to selectively solidify photosensitive polymers in a layered manner and a complex structure is formed. The UV light solidifies the lower layer and layers are overlapped to generate the structure [16].

Growth factors are also proteins which are naturally released by the cells and are anchored by the extracellular matrix for presenting to cell surface receptors. They are endogenous signaling molecules which regulate cellular responses and are secreted by epithelial cells, fibroblasts, leukocytes, and platelets, which is upregulated during tissue damage. When growth factors are released, they bind to cytoplasmic or membrane receptors to produce their effects through autocrine, paracrine, or endocrine mechanisms [17]. Cell migration, adhesion, proliferation, growth, and differentiation are all triggered by specific growth factor receptor binding, which also activates cellular signal transduction pathways [18]. Growth factors are grouped into several families depending on their structural and functional characteristics. They are transforming growth factor (TGF-β), platelets derived growth factors (PDGFs), hepatocyte growth factors (HGFs), granulocyte macrophage colony stimulating

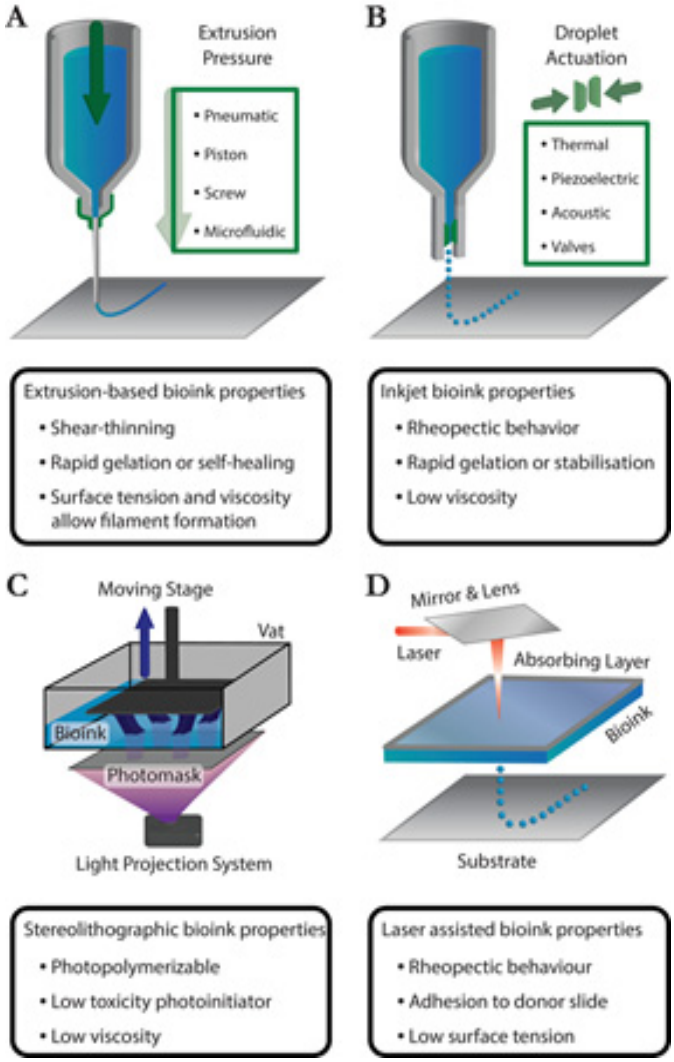


**Figure 1: Types of 3D bioprinters; A) Extrusion based B) Inkjet bioprinting C) Stereolithography bioprinting D) Laser-assisted bioprinting [13]**

factor (GM-CSF), neurotrophic factors (NFs), insulin-like growth factors (IGF), fibroblast growth factors (FGFs), connective tissue growth factor (CTGF). GFs stimulate cell proliferation and differentiation of progenitor cells, motility, morphogenesis, and angiogenesis [19]. Degradation and protection of enveloped molecules can be controlled by growth factors by regulation growth factor release by hydrogels. The structure of hydrogels has crosslinked hydrophilic polymers with water. These hydrophilic molecules encapsulate the growth factors without denaturation and aggregation [20].

The figure explains the phases of wound healing with the help of growth factors, (a) Haemostasis phase: platelets produce platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and transforming growth factor-β1 (TGF-β1 which act as chemoattractants for inflammatory immune cells; (b) Inflammation phase: Cytokines, reactive oxygen species (ROS), and growth factors are secreted by inflammatory immune cells such as neutrophils, mast cells, and macrophages; (c) Proliferation phase: bFGF, VEGF,

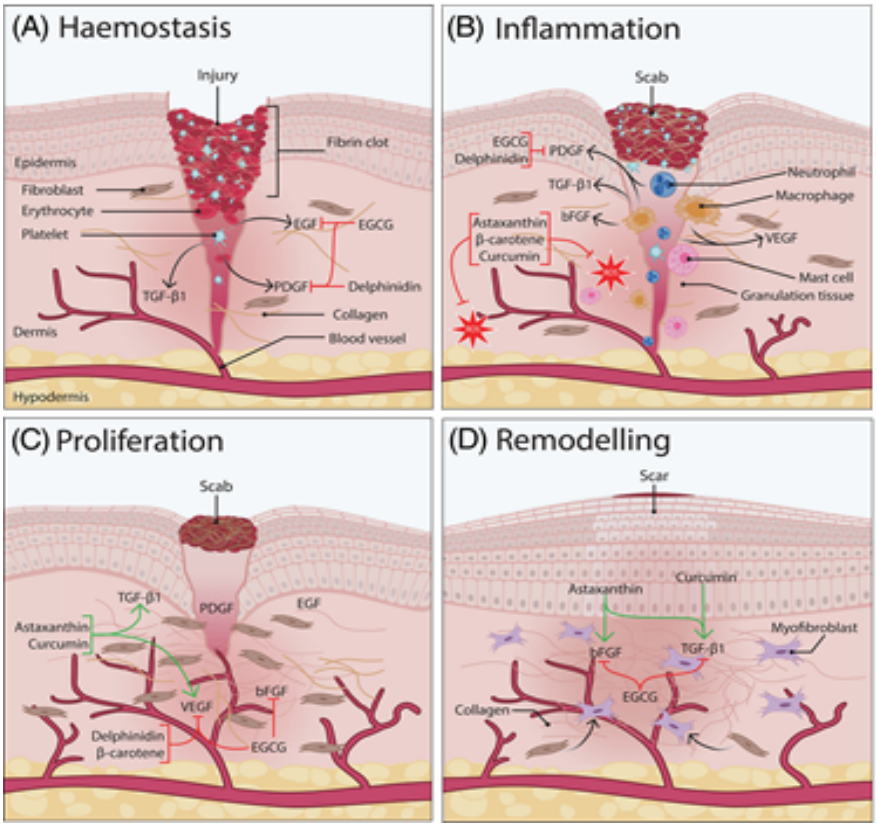


**Figure 2: Four phases in wound healing process [21]**

PDGF, and TGF-β growth factors activate cellular responses which promote angiogenesis, keratinocyte migration and proliferation, fibroblasts migration and differentiation, and collagen synthesis; d) Remodelling phase: scar maturation and remodelling of extracellular matrix (ECM) occurs [21].

This article seeks to provide a concise summary on bioink loaded with growth factors and its role in 3D bioprinting. The bioink with growth factors formulation and applications of those bioink in bioprinting and their results have been analysed. The limitations of using bioink loaded growth factors in 3D bioprinting are

**Table 1: Types of growth factors and their functions**

| Growth Factors | | Functions |
|---|---|---|
| FGF | Fibroblast growth factor | Development & regeneration of tissues, enhance osteogenesis, bone regeneration (Charoenlarp et al. 2017) |
| VEGF | Vascular endothelial growth factor | Promotes bone repair and regeneration (Hu & Olsen, 2016). Plays role in the endothelial cells survival, migration, and proliferation |
| HGF | Hepatocyte growth factor | Muscle regeneration (Choi et al. 2019), Liver regeneration (Michalopoulos 2020) |
| EGF | Epidermal growth factor | regulates growth of epithelial cell, proliferation and differentiation of epithelial cells. |
| PDGF | Platelet-derived growth factor | proliferation, growth and migration of endothelial cells and bone regeneration (Shah et al. 2014) |
| HGF | Hepatocyte growth factor | Proliferation, differentiation & stimulate migration of mesenchymal stem cells |
| FGF - 2 | Fibroblast growth factor - 2 | differentiation of embryonic stem cells, migration, proliferation and survival of endothelial cells |
| TGF-β1 | Transforming growth factor type beta 1 | promote fibrosis formation, improve ability of skeletal muscle to repair, improve muscle regeneration (Delaney et al. 2017) |
| BMP 2 | Bone morphogenetic protein 2 | promotes regeneration of bone (Zhang et al. 2014) |

explored. This review outlines the future advancement in future using 3D bioprinting and development of related methods and techniques.

## Methods for Loading Growth Factors in Bioink

### Thermo-responsive NanoComposite bioink loaded with (BMP-2) & (TGF-β1)

Thermo responsive (TR) bioink is prepared as a solution at low temperatures such as 4-20 °C and at 37°C it forms the gel state. To formulate TNC bioink, thermo responsive bioink is added to laponite at 4°C. BMP-2, TGF-β1, and both growth factors were loaded to TNC bioink, creating TNC-B, TNC-T, and TNC-BT bioinks. TNC-B, TNC-T, andTNC-BT bioinks were prepared by mixing the TNC bioink with BMP-2 (100 $\mu gmL^{-1}$), TGFβ1 (5 $\mu gmL^{-1}$), and BMP-2 (100 $\mu gmL^{-1}$) + TGF-β1 (5 $\mu gmL^{-1}$), respectively, at 4°C where incorporated into the TNC bioink through physical interaction [22].

### TGF-β3 within sulfated - IPN bioink

The bioinks were made in DMEM and they were combined with human TGF-β3. Utilizing a dual-syringe technique with 240 ng/ construct of TGF-β3 equal which is typically added to chondrogenic media during a six-week culture. Following a thorough mixing of the TGF-β3, they were cast in 3 % agarose molds and subjected to the dual crosslinking process. Each construct was incubated at 37°C in 2 millilitres nutrient growth media in hypoxia (5% O2) to ascertain its release kinetics. ELISA was used to measure the amount of TGF-β3 in the supernatant [23].

### VEGF-mimicking peptide incorporated hydrogel

In DMEM at a 15% w/v concentration the lyophilized GelMA was mixed with gelatin and hyaluronic acid (HA) and incubated at 37°C for 2 hours. Following sterilization with 0.2 µm filter, the resultant hydrogel mixture was combined with 1% photo-initiator and vascular endothelial growth factor peptide (0. 02 % w/v). The ink was stored at - 4°C until further use [24].

### VEGF IN GelMA

Lyophilized GelMA was dissolved in warmed DPBS for preparing bioink. To the dissolved GelMA, a 50X LAP solution (3.35 percent weight by volume in DPBS) of 50:1 ratio was added. Then VEGF (400 ng/ml) within the hydrogel precursor is added and thoroughly pipetted up and down for even LAP and VEGF distribution. This was prepared under the biosafety cabinet hood, for sterility bioink was preheated and filtered using syringe filters (0.22 µm pore size) into a 50 mL centrifuge tube and kept in a warm bath (37°C) before the experiments [25].

### Silk Fibroin with TGF-β1

Approximately 4 µg/mL of TGF-β1, 10% of Silk Fibroin and 5% DCM were mixed with Phosphate Buffered Saline for preparing Silk Fibroin/DCM mixtures. To achieve gelation of DCM/SF bioinks, these mixtures were dissolved with the same amounts of 80% PEG. Therefore, final concentration becomes 5% w/v Silk Fibroin, 2 µg/mL TGF-β1 and 2.5% w/v DCM. For preparing BMP-2-loaded DBM/SF bioink, BMP2 4 µg/mL is added instead of TGF-β1 [26].

### Bioactive composite scaffold with BMP-2 and PDGF

To obtain a homogenous ink, dissolve lyophilized 15% GelMA, 5% Bioactive glass microsphere (BGM) and 0.5% PI 2959 in deionized water. 10% Sodium alginate solution was added to improve bioink printability. The bioink was loaded into a 3D printer's printing barrel, equipped with a 400 µm nozzle. The temperature of the printing platform was maintained at 5°C, where bioink temperature was at 20°C. The extruded strands are able to solidify and gain initial stability due the temperature difference. After scaffold printing, the scaffold was cross-linked in 4% $CaCl_2$ for 5 minutes, then exposed in UV light at 365 nm for 30s, then rinsed three times using deionized water. And it was frozen at -80° C overnight, and finally freeze-dried for 48 h. In order to improve the biological activity of the scaffold, BMP-2 and PDGF were added into the bio-inks with a final concentration of 5 ug/mL and 100 ng/mL, respectively [27].

### PCL based microencapsulation using BMP-2 and VEGF

PCL was solubilized in methylene chloride at different concentrations. Then using sonication, aqueous BMP-2 and VEGF solutions were dissolved in mixture at 50 Hz for 15 seconds, forming an emulsion. The emulsion was mixed to a 4% poly(vinyl alcohol) and subjected to additional sonication following similar parameters. A 0.3% PVA solution was added to homogenize the double emulsion and the solvent was removed by evaporating under through constant stirring overnight.. After that the microcapsules were rinsed with Tris-HCl (10 mM pH:7. 4) & lyophilized for 24 hours [28].

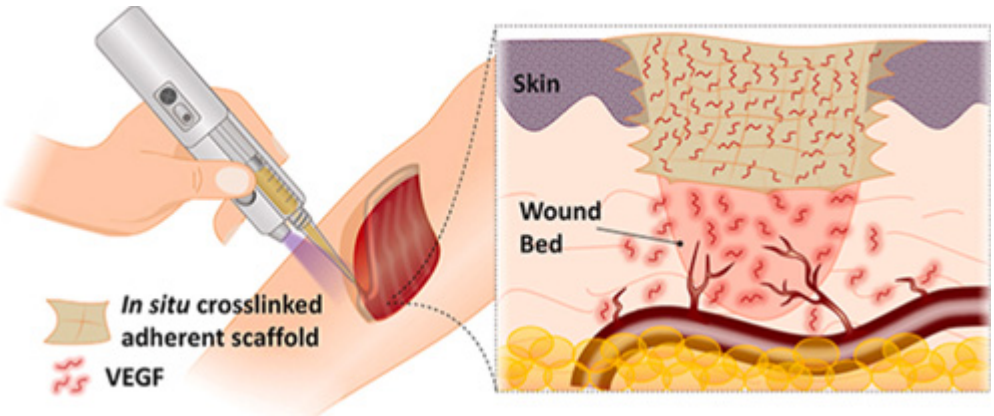


**Figure 3: Hand-held 3D bioprinter [25]**

## Applications of Growth Factors Loaded Bioink

### Wound Healing

A hand-held 3D bioprinter is used to deliver GelMA hydrogel loaded with VEGF into porcine wounds. As a result, wound contraction was minimized , decreased scar formation and promoted neoepidermal regeneration (the growth of new skin tissue known as neoepidermis). Sustained release of VEGF from an in vivo printed scaffold whereas handheld printer enhanced the wound bed angiogenesis and resulted in more advanced healing [25].

A Bioink formulation synthesized by free radical copolymerization by incorporating nicotinamide as growth - factor for subcutaneous tissue reconstruct for 3-D Bioprinting. It showed an enhanced survival rate of 92 % when compared with pure chitosan was 67 % reported survival rate with maximum stability. It showed a clear healing clue for the infected subcutaneous tissue [29]. VEGF was loaded on a GelMA hydrogel 3D printed patch and was used for wound dressing in a pig model. It enhanced wound healing by increasing collagen deposition & angiogenesis at the site of wound [24].

### Bone Regeneration

The thermoresponsive Nanocomposite bioink network was incorporated with growth factors BMP-2 & TGF-β1 by hydrophobic and ionic interactions. Thereby, the resulting bioink loaded with growth factors were transplanted into a calvarial bone injury model. It resulted in new bone formation and implanted TNC bioink scaffold degraded over 6 weeks [22].

3D printed bilayered scaffolds are used to reconstruct osteochondral tissue by controlled release system, each layer of scaffold having mechanical strength & degradation rate. Growth factors such as BMP-2 & TGF-β1 encapsulated into the scaffolds to enhance differentiation of BMSC. Then it was implanted in a rabbit knee joint model, which resulted in osteochondral regeneration [26].

### Cartilage Regeneration

Hyaluronic acid based bioink with dual stage crosslinking enabled covalent bonding with transforming growth factor - β1. The TGF-β1 tethered bioink structures inducing chondrogenic differentiation of MSCs was much higher than that of constructions with non-covalently included TGF-β1, resulted after three weeks of in vitro culture of bone marrow derived MSCs. Also this enhanced TGF-β1 signaling, ECM deposition, chondrogenic gene expression, and the stiffness of the resultant construct. Additionally, the covalently bonded TGF-β1 retained its functions during 3D printing is shown. All things considered, the ink composition that was given made it possible to produce high-quality cartilaginous tissues without requiring an ongoing supply of external growth factors [30].

### Tissue Regeneration

The PLGA microparticles were encapsulated with growth factors to ensure the stability of protein. PLGA microparticles incorporated with GelMA bioinks with or without IGF - 1 (control group) are suspended in myoblast cells. The release of IGF-1 from GelMA bioink enhances tissue maturation & cell differentiation after 3D bioprinting. Fusion of multiple myoblasts into myotubes promoted the spontaneous contraction of the formed tissue when IGF-1 releasing microparticles were incorporated in the 3D bioprint construct [31]

GelMA, SA and BGM, a multicomponent hydrogel, was fabricated in the scaffold using the extrusion method of 3D printing. The ability of the hydrogel remains unchanged despite adding cells or growth factors during printing, also the incorporated growth factors could replicate the biological effects on these scaffolds. Scaffolds are loaded with PDGF and BMP 2 improved mouseBMSCs osteoblastic differentiation and enhanced healing capacity of soft tissue, respectively. This dual functional scaffold showed effective periodontal tissue regeneration by restoration of the alveolar bone and the healing of gingival tissue in the periodontal defect model of beagle dogs [27].

A collagen-based tympanic membrane scaffold was 3D bioprinted with hASCs, bFGF and hUCS. In vitro studies showed growth factors loaded in collagen TM scaffolds improved proliferation of cells and by enhancing cell signaling, improved keratinocyte proliferation. Through the rat TMP model, a combinational mixture of the growth factors, hUCS and FGF, laden in the hASCs-laden collagen structure clearly promotes the TMP regeneration [32]. By precisely localizing growth factors in both space and time it is possible to tightly control the formation of new tissue and angiogenesis which reduces off-target effects [33].

## Limitations

Growth factors are proteins that encourage tissue development and differentiation handling them in vitro can quickly deactivate them. To maintain their efficacy it is essential to choose an appropriate carrier. Also hydrogels, polymer particles and other materials are used, to maintain the stability is very difficult. The safety and efficacy of growth factor-containing 3D-printed scaffolds in humans remain largely unknown despite their promising performance in lab and animal models [34]. The current work doesn't cover any methods for incorporating growth factors on scaffolds through 3D bioprinting. Except, the common methods include immersion of scaffold in growth factor containing solution and injecting growth factor solution into scaffold pore channels [35].

## Future Direction

Machine learning has advanced in situ 3D bioprinting significantly. By directly applying bioinks onto intended surfaces, it guarantees exact geometrical precision, even on intricate or dynamic surfaces such as wound areas or cardiac tissues. Utilizing robotic arms or portable handheld printers, this self-sufficient method is particularly suited for surgical applications where dimensions and weight are crucial [36]. In tissue engineering and regenerative medicine (TERM), 4D bioprinting is a crucial development that makes it possible to create structures that gradually respond to changing environmental stimuli [37]. The formulation and processing parameters of bioinks, particularly their biocompatibility and printability must be optimized in order to create the ideal bioink. Eventually dynamic tissues and organs that react to stimuli at the human scale could be created by emerging 4D bioprinting technologies like in situ bioprinting [38]. Integrating 3D bioprinting with microfluidics accurately mimics the human tissues architecture and microenvironment, resulting in predictive models for testing of drugs and in disease research. Microfluidic systems regulate chemical gradients & fluid flow to preserve the cell functions and viability in bioprinted tissues. This facilitates the creation of multi-organ systems that can simulate complex inter-organ interactions, providing an understanding of systemic responses to drugs and disease processes [39].

## Conclusion

The bioink loaded with growth factors led to the tissue formation and enhanced regeneration. This review summarizes the

applications of growth factor laden bioink in regeneration and development of bioink by loading growth factors. It also explores various formulations of bioink in 3D bioprinting. Different types of growth factors aimed for regeneration of tissue, cartilage , bone and wound healing outcomes. This paper highlights the effects of growth factor loaded bioink for 3D Bioprinting.

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