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AI-Enhanced Bioactive 3D-Printed Scaffolds for Tissue Regeneration: Innovations in Healing and Functional Additives

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Abstract: Bioactive 3D-printed scaffolds have revolutionized tissue engineering and regenerative medicine by enabling precise fabrication of biomimetic structures that promote cell adhesion, proliferation, and differentiation. However, significant challenges remain, particularly in optimizing scaffold composition, bioactive additive integration, and long-term stability for clinical applications. This review provides a systematic analysis of recent advancements in AI-driven bioactive scaffolds and their role in personalized regenerative medicine. A comparative evaluation of major 3D printing techniques—Fused Deposition Modeling (FDM), Stereolithography (SLA), Selective Laser Sintering (SLS), and Direct Metal Laser Sintering (DMLS)—is presented, focusing on resolution, material compatibility, and bioactive additive incorporation. Additionally, we analyze key bioactive agents (growth factors, nanoparticles, peptides, and natural polymers) and their effects on biocompatibility, mechanical strength, and therapeutic efficacy. AI-powered optimization techniques, including machine learning-based scaffold design, computational modeling, and predictive analytics, are emerging as transformative solutions for improving scaffold architecture, drug delivery systems, and patient-specific applications. Despite significant progress, major challenges persist, including standardization in scaffold fabrication, long-term in vivo validation, and regulatory approval hurdles. Addressing these scientific and regulatory challenges is essential for the successful clinical translation of bioactive scaffolds. This review highlights the need for interdisciplinary collaboration to advance AI-assisted scaffold engineering and establish personalized treatment strategies for next-generation regenerative medicine.

Keywords: Bioactive Scaffolds; 3D Printing; Tissue Regeneration; Scaffold Fabrication; Bioactive Additives; Growth Factors; Nanoparticles; Biocompatibility.

1. Introduction

3D printing has been widely acknowledged as the leading technique for fabricating complex and specialized scaffolds for tissue regeneration. Usually, the scaffolds are designed to create interconnected porous structures that support cell growth, differentiation, adhesion, and migration. These traits are imperative to ensure tissue repair and regeneration [1]. Compared to the conventional methods of scaffold fabrication, including freeze-drying, micro/nano printing, electrospinning, and lithography, 3D printing has numerous benefits. These advantages include designing a complicated and personalized model regarding geometrical complexity, patient specificity, and the ability to build three-dimensional structures with similar geometries and bioactive properties. The effectiveness of these tailored scaffolds is supported by the capability to control the scaffold design, material, and pore size systematically [2]. Owing to such developments, 3D-printed scaffolds can replicate the native extracellular matrix (ECM) with high accuracy, which provides an appropriate setting for cell attachment and differentiation. A general depiction of the tissue engineering 3D printing is shown in Figure 1.

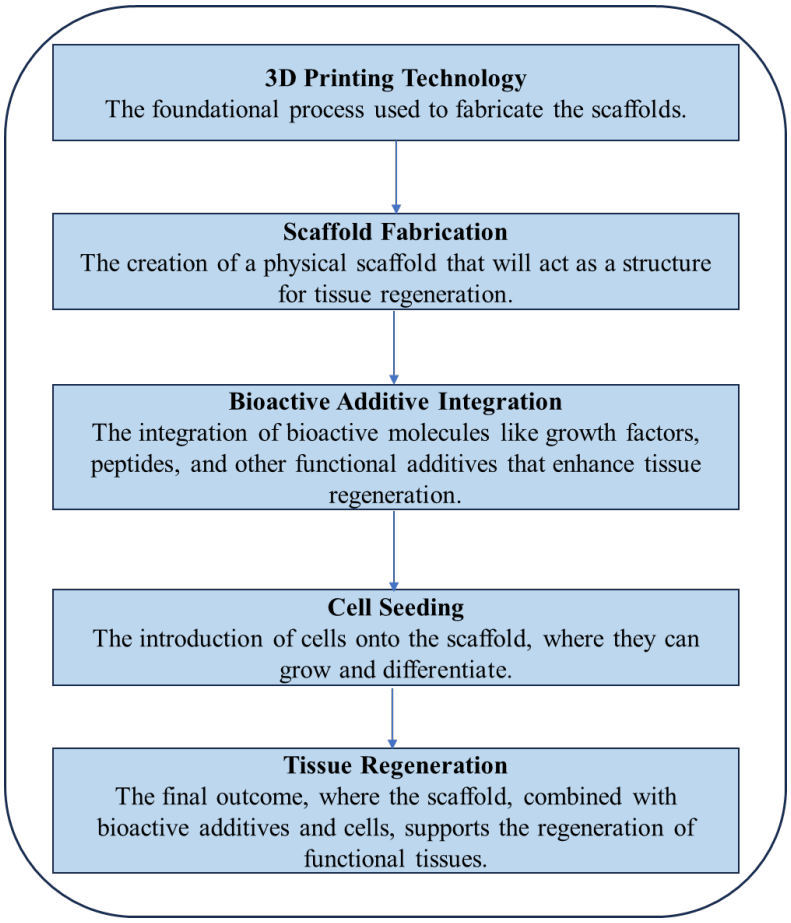

Figure 1. A general schematic diagram of the 3D printing process in tissue engineering.

Using bioactive chemicals in scaffold fabrication has garnered significant attention in improving their regeneration capacity. Some of the proteinaceous additives that have been reported to be of great importance in the enhancement of the performance of the scaffolds include enzymes, peptides, and growth factors. They are usually used to improve scaffold biocompatibility, control cell response, and replicate the ECM. In addition, these scaffold additions are widely recognized to have long-term biological effects, such as promoting vascularization, releasing bioactive molecules under control, and having antibacterial characteristics [3]. Several scientists are currently trying to design biomimetic scaffolds that will help regenerate and repair tissues, enhancing the general well-being of the patients [4] [5]. However, challenges persist in choosing the right scaffold materials, ensuring that the additive does not settle at the bottom during the printing process, and achieving uniformity during the release of the additive once the scaffold gets installed in a biological system [6].

Support structures in 3D printing can be made of many materials. Some of the commonly used materials include composites, polymers, and ceramics. Each used material has properties that qualify it for tissue engineering application, as pointed out by Mahmood et al. [4]. Biodegradable polymers include PLA and PCL since they are easy to work with and have good tissue biocompatibility. Elastomers are flexible and perfect for application in soft tissue models while polymer composites help in offering strength [7]. Calcium phosphate and bioactive glass are some of the ceramics that are mechanically sound and bio-compatible for load-bearing applications [6]. Therefore, it is crucial to choose scaffold material for 3D printing very wisely. This way, through the synergistic effect of several materials, one can create unique scaffolds to enhance tissue regeneration and repair.

While several reviews have discussed the role of 3D printing in tissue engineering, this paper provides a comprehensive and updated analysis of bioactive 3D-printed scaffolds, emphasizing AI-driven approaches for scaffold optimization and functional enhancement. This review focuses on the advancement in the incorporation of bioactive chemicals into 3D-printed scaffolds for tissue engineering applications. It also aims to elucidate the impact of different bioactive additives, including growth factors, peptides, nanoparticles, and natural extracts, on the properties of the scaffolds, biocompatibility, and tissue

repair. The paper also examines the issues of biodegradable scaffold stability and the controlled delivery of bioactive agents throughout the scaffold fabrication process. Last but not least, the review paper outlines the existing research gaps and the areas for further research with potential.

2. 3D Printing Techniques for Scaffold Fabrication

Most scaffolds used for tissue engineering have been fabricated through 3D printing, which offers control of structure composition and porosity. Bioactive substances can be added to a scaffold to enhance cell behaviors such as adhesion, proliferation, and tissue formation [8]. Table 1 outlines the main techniques of 3D printing and their features.

2.1. Fused Deposition Modeling (FDM)

Fused Deposition Modeling (FDM) is an additive manufacturing technology that builds an object through layer-by-layer deposition of thermoplastic filaments. This is suitable for creating functional prototypes, manufacturing scaffolds, and various other applications for end-product construction. This technique of 3D printing employs production-grade thermoplastics, thereby creating durable parts with moderate mechanical strength [9]. Certain significant advantages of this scaffold fabrication technique include the possibility of using a wide variety of materials in the fabrication of the parts, the possibility of manufacturing large parts without warping them, the ease of removing the support structure, and the relatively cheap nature of the process as compared to other manufacturing methods. The materials used in medical applications to build scaffold prototypes and finished parts include ABS, PLA, nylon, polycarbonate, and ULTEM [10]. The FDM is comparatively slower in fabricating scaffolds but is effective and inexpensive in creating functional plastic parts for various medical sectors [11].

2.2. Stereolithography (SLA)

Stereolithography (SLA) is one of the most used techniques for manufacturing scaffolds containing functional additives. It is an ideal method to fabricate scaffolds with smooth, high-resolution surfaces with fine details. The amount of control this printing technique provides makes it highly preferable to create scaffolds with tissue engineering specifications regarding size and surface finish [8, 12]. The most important aspect of the SLA fabrication method is that it is possible to introduce bioactive substances into the material and stimulate cells to adhere and regenerate tissues owing to biocompatible resins. The only complaint that has been made regarding this method of SLA scaffold 3D printing is on the post-processing and support removal. However, the use of a wide variety of materials and a high degree of accuracy makes it a preferred method for introducing bioactive substances and creating complex structures to improve biological properties [11].

2.3. Selective Laser Sintering (SLS)

Selective Laser Sintering (SLS) is a widely used process for manufacturing tissue engineering scaffolds. This is one of the prominent 3D printing techniques that aim at scaffold designs with open porous structures optimized for cell growth and tissue regeneration. The technique entails the development of structures with topological features without having to use templates. Scaffolds produced using the SLS technique usually have structures with interconnected porosities through which nutrients can easily pass, facilitating cell growth [13]. Different research studies have shown that SLS 3D-printed bioactive scaffolds can improve the formation of bones and tissue engineering. In general, nylon-based scaffolds are one of the most frequently used structures formed with the help of the SLS 3D printing method. These scaffolds have some growth factors and bioactive ceramics embedded in them, increasing the scaffolds' accuracy and adaptability [11]. SLS is, therefore, an appropriate technique for preparing bioactive and functional scaffolds for use in medicine.

2.4. Direct Metal Laser Sintering (DMLS)

Direct Metal Laser Sintering (DMLS) is one of the methods of additive manufacturing which utilizes a laser to melt metal powder for the purpose of developing complex parts with high precision. The approach fabricates items layer by layer, thereby reducing the need to build a scaffold and hence minimizing the time the time required to produce the scaffold [14]. One main advantage of this technique is that DMLS 3D printing can handle complex shapes by employing a range of metals for functional enhancements. Main elements used include titanium, stainless steel and aluminum. DMLS is widely applied in the aerospace industry for fabrication of aircraft parts, automotive industry for car parts, biomedical applications for implants and construction industry for scaffolds. However, DMLS has some

drawbacks, including: size constraints, unavailability of materials, and post-processing of the finished parts for surface finishing [15].

Table 1. Comparison of 3D printing techniques for scaffold fabrication and bioactive additive integration.

3D Printing Technique	Resolution	Materials Used	Speed	Cost	Suitability for Bioactive Additives	Sources
FDM	Low to Medium	Thermoplastics (ABS, PLA, Nylon, PC, ULTEM)	Moderate	Low	Limited	[11]
SLA	High	Photopolymer Resins (Standard, Engineering, Specialty Resins)	Slow	Moderate to High	High	[8, 11, 12]
SLS	Medium to High	Polymers (Nylon 12, Nylon 11, Glass-filled, Carbon-filled)	Moderate	High	Moderate	[8, 11, 13]
DMLS	Very High	Metals (Stainless Steel, Titanium, Aluminum)	Slow	Very High	Low	[14, 15]

3. Types of Bioactive Additives for Tissue Regeneration

Several bioactive agents can be incorporated into scaffold construction for tissue engineering applications. Some potent functional bioactive additives are growth factors, nanoparticles, natural extracts, enzymes, antibodies, nucleic acids, peptides, and vitamins [16]. These agents are reported to have a beneficial impact on cell growth, repair, and healing of tissues. They enhance the general properties of the scaffold and have the capability to mimic the natural tissue to enhance the process of regeneration [17]. Table 2 describes a list of some of the bioactive additives that are used in tissue engineering scaffolds regarding their sources, the intended effect, and the known limitations.

3.1. Growth Factors

Growth factors are essential in tissue engineering and regenerative medicine. It is used in the fabrication scaffold and is mainly employed as a bioactive additive. The main growth factor known to stimulate the formation of bone and cartilage is bone morphogenetic proteins (BMPs), while that of blood vessels by vascular endothelial growth factor (VEGF). GF-β is associated with cell growth and differentiation, while FGFs are involved in cell kel proliferation and angiogenesis. Further, the epidermal proliferation factor (EGF) is well known to play the role of proliferation and differentiation of epithelial cells [18]. Platelet-derived proliferation Factor (PDGF) is involved in the process of wound healing, while Nerve Growth Factor (NGF) is used in neuron growth and differentiation [19]. BMPs promote osteoblasts and chondrocytes differentiation, and TGF-β and FGFs are engaged in matrix synthesis and chondrogenesis. VEGF and FGFs take part in the process of angiogenesis since they supply nutrients to the regenerated tissue. In addition, PDGF and FGFs promote the chemotactic migration of cells to the site of injury, whereas IGF-1 promotes cell survival by reducing the apoptosis rate. In general, the aforementioned growth factors facilitate tissue regeneration by stimulating stem cell proliferation, differentiation, and synthesis of ECM. All of these reported traits of growth factors facilitate tissue repair and regeneration.

These growth factors are employed by tissue engineers in biomimetic scaffolds to replicate the body's healing process, though more research is required regarding the delivery systems [18].

3.2. Nanoparticles

Nanoparticles in tissue engineering scaffolds are highly adopted due to their distinct antimicrobial and osteogenic properties. Silver nanoparticles (AgNPs) are popular because of their high efficiency in combating various micro-organisms such as bacteria, fungi, and viruses. Such antimicrobial characteristics are advantageous in assisting to avoid infections in scaffolds [19]. In this regard, gold nanoparticles (AuNPs) are said to increase the efficiency of antibiotics, whereas zinc oxide and titanium dioxide are widely used nanoparticles that act by producing reactive oxygen species for the best results in combating microbes. Apart from this, copper nanoparticles also possess a very high antibacterial activity, especially against gram-negative bacteria, and therefore, these nanoparticles are very useful in preventing infection in tissue engineering applications [17].

Other than the antibacterial effects, nanoparticles are also known to enhance bone healing. Hydroxyapatite nanoparticles enhance the osteoblast attachment and growth, thus enhancing the scaffold's bone formation and mechanical properties. The bioactive glass nanoparticles play a role in osteogenesis and angiogenesis, while the silica nanoparticles are involved in collagen synthesis and bone mineralization. In addition, the nanoparticles may be used to deliver drugs and growth sub-sequentially. The popular choices for polymers used as nanoparticles for scaffold fabrication include liposomes, dendrimers, and mesoporous silica nanoparticles. The stated agents are some of the nanocarriers employed in drug delivery. According to Yılmaz et al. [21], the nanoparticles used in the scaffolds improve tissue regeneration because of their controlled release. Nanoparticles can be further explored to establish the efficiency of functional bioactive nanoparticles as supplements for scaffolds.

3.3. Natural Bioactive Agents

Scaffolds used in tissue engineering are improved with natural bioactive compounds about biocompatibility and functionality. The most common natural bioactive molecule is collagen, which can be added to synthetic polymers for mechanical strength and cell attachment [22]. Similarly, alginate is a bioactive natural polymer that prepares hydrogels for medicine delivery and wound healing. Chitosan is another natural bioactive compound with antibacterial activity well-recognized to enhance bone formation. Silk fibroin exhibits moderate mechanical strength and supports stem cell differentiation. Hyaluronic acid has a positive impact on cell migration and has anti-inflammatory properties. According to Joyce et al. [23], these organic compounds improve the biocompatibility of the scaffold and have a part to play in the repair process of tissues.

It has been revealed that the overall performance of scaffolds increases when natural materials are blended with synthetic polymers. These blends improve the mechanical properties, allow cell adhesion signals, and control the regulation of the degradation rate. They also enhance the printability of the materials, the release of growth factors, and the fabrication of the composite scaffold with antibacterial and wound-healing properties [23, 24]. In the future, scientists are believed to develop biomimetic scaffolds by embedding synthetic polymers and natural bioactive molecules to fabricate bioactive scaffolds.

3.4. Antibiotics and Antimicrobial Agents

Tissue engineering can be made free from infections using antibiotics and antibacterial chemicals to fabricate 3D-printed scaffolds [25]. Some of the polymers that can be blended with antibiotics during the polymerization process are polycaprolactone (PCL). The most often used one is based on creating PCL scaffolds filled with silver nanoparticles. These scaffolds are reported to have enhanced mechanical properties, including increased stiffness and antibacterial properties. PCL scaffolds with direct loading of antibiotics, such as ciprofloxacin or vancomycin microspheres, demonstrate that not only the drug release is efficient but also bioactive [26].

The two types of developed scaffolds with antimicrobial and anti-inflammatory properties are the graphene oxide-based scaffolds and the PCL/dexamethasone scaffolds. PCL has some benefits associated with its usage because it can provide a controlled release of antimicrobial agents. Silver nanoparticles are incorporated into scaffolds and possess the capacity to prevent the growth of different bacteria. They are also used to enhance the mechanical characteristics of the scaffold which is one of the properties of the scaffold. Additional antibacterial properties may be improved after production by employing antimicrobial treatments or drug-releasing microspheres. These approaches lower the probability of

bacterial colonization and biofilm development on scaffolds and have prolonged and particular antimicrobial effects [27]. The main advantage of these scaffolds is in the ability to release site-specific anti-infective agents; this will enhance the integration of the scaffold and tissue regeneration without necessarily needing systemic antibiotics [26, 28]).

3.5. Emerging Functional Additives

An exosome is a small vesicle released by cells that are well understood to be engaged in synthesizing tissue engineering scaffolds. MSCs-derived exosomes promote wound healing, immune regulation, and tissue regeneration. The main benefit of their usage is that they are less likely to cause immunological reactions or malignancies than stem cells [29]. In addition, exosomes can precisely deliver drugs to target tissues, which can be applied to treat diseases including bone fracture, cartilage damage, and nerve diseases [30].

Scaffolds containing peptides are widely used as they help in cell attachment and tissue-mimicking. Other stem cell components like secretomes are also under research. These help in tissue repair with the help of microRNAs, cytokines, and growth factors. Furthermore, exosomes are currently employed to generate 3D-printed scaffolds in the preliminary studies for delivering medications and enhancing tissue regeneration. More studies are required because the process of standardizing exosome extraction and utilization for therapeutic purposes is still a problem [30, 31].

Table 2. Overview of bioactive additives: sources, effects, and limitations in tissue engineering scaffolds [32, 33, 34].

Bioactive Additives	Sources	Intended Effects	Known Limitations
Growth Factors (BMPs, VEGF, TGF-β, FGFs, EGF, PDGF, NGF)	Stem cells, Synthetic production	Osteogenesis, Angiogenesis, Wound healing, Neuron growth	Difficult to control delivery, Complex interactions, Requires precise concentration
Nanoparticles (Silver, Gold, Hydroxyapatite, Bioactive Glass)	Silver, Gold, Hydroxyapatite, Silica, Copper, Zinc oxide	Antimicrobial activity, Bone regeneration, Drug delivery	Potential toxicity, Standardization issues, Need for controlled release
Natural Bioactive Agents (Collagen, Chitosan, Alginate, Hyaluronic Acid, Silk Fibroin)	Animal tissues (Collagen), Crustacean shells (Chitosan), Seaweed (Alginate), Plants (Cellulose)	Improves biocompatibility, Cell attachment, Bone growth, Reduces inflammation	Variability in natural sources, Risk of immune response, Limited mechanical strength
Antibiotics and Antimicrobial Agents (Ciprofloxacin, Silver Nanoparticles, Vancomycin)	Antibiotics, Metal nanoparticles, Coatings	Antibacterial activity, Preventing biofilm formation, Localized infection control	Possible antibiotic resistance, Difficult to balance antibacterial effect with bioactivity
Emerging Functional Additives (Exosomes, Peptides, Secretome)	Mesenchymal stem cells (MSCs), Synthetic peptides	Tissue repair, Drug delivery, Immune response, Enhances wound healing	Challenges in isolation, Standardization issues, Limited clinical applications

4. Mechanisms of Action for Bioactive Scaffolds

Bioactive scaffolds play a crucial role in tissue regeneration by influencing various biological pathways, including MAPK, PI3K/Akt, Wnt/β-catenin, and JAK/STAT. These pathways regulate cell

proliferation, differentiation, and survival, contributing to effective tissue healing and regeneration [23]. Figure 2 depicts a schematic diagram of specific biological pathways activated by bioactive scaffolds and their influence on cell behavior modulation.

4.1. Biological Pathways Activated by Growth Factors

Several important signaling pathways control Cell division and proliferation [35]. Zhang and Liu [36] identified that the MAPK pathway is involved in cell survival and proliferation, while p38 and JNK are involved in differentiation and cell death. Moreover, the PI3K/Akt signaling pathway regulates cell survival and significantly prevents apoptosis. Teo and Kahn [37] noted that Wnt/β-catenin signaling pathways are involved in stem cell division and differentiation, which is vital for tissue repair. In addition, the TGF-β/SMAD signaling is described to be involved in differentiation and proliferation in various cell types. Likewise, the JAK/STAT pathway supports cell division and longevity, thus supporting differentiation capacity in a wide range of cells.

Bioactive scaffolds impact several pathways in multiple ways. Various studies suggest that VEGF, FGF, or BMP can be incorporated into scaffolds and continuously provide signals to cells in essential signaling pathways. To activate integrin signaling that works with growth factor signaling, they can also offer cell adhesion molecules such as RGD peptides [26]. Mechanical properties, specifically the scaffold's stiffness, affect cell activity through the mechano-transduction pathways. This usually influences cell differentiation. Bioactive scaffolds are also said to release some chemicals, such as hydroxyapatite, that enhance osteogenic differentiation. Topographical features can alter cell shape, affecting cell differentiation [23].

4.2. Communication Between Bioactive Additives and the Scaffold Microenvironment

Scaffold bioactive additive highly depends on scaffold properties, such as porosity, stiffness and surface characteristics. Porosity and connected pores are integral properties analyzed while selecting bioactive additives, with the best pore width of 400 μm optimized for the breakdown of enzymes and the subsequent liberation of bioactive chemicals. Indeed, the stiffness of the scaffold influences the cellular response to bioactive compounds through different mechanotransduction pathways [38]. The surface properties, particularly wettability, affect the adsorption and desorption of bioactive molecules and, consequently, the rate of the scaffold biodegradation [24].

Bioactive scaffolds are biodegradable, and they disintegrate by hydrolysis and enzymatic action. Diffusion, degradation-controlled release, and desorption are some of the controlled release processes. Specific techniques like nanoparticle packing or covalent immobilization can monitor the release kinetics. For the scaffold to be effective in the regeneration of tissues, the degradation of the scaffold has to be in harmony with the healing rate of the tissue [39].

4.3. Manipulation of Cellular Response and Tissue Repair

Bioactive scaffolds are involved in the tissue regeneration process through changes in cell behavior, including migration, adhesion, and proliferation. The higher stiffness of the scaffold promotes cell growth, while the lower stiffness promotes neurogenesis. When growth factors are incorporated into scaffolds, they ultimately enhance tissue remodeling and stem cell development. Different works have described growth factors as bioactive agents in scaffold production. For example, it was established in a study that TGF-β is involved in cartilage synthesis, while hydroxyapatite and bone morphogenetic proteins (BMPs) are involved in bone repair. Similarly, it was discovered that VEGF in scaffolds promotes angiogenesis and skin repair. Several case studies demonstrate that bio ceramic scaffolds and MSC-CM could reconstruct bone tissue for long-term treatment. In addition, it has been reported that growth factor-releasing scaffolds and nanofibers enhance the stimulation of skin and cartilage regeneration [40, 41].

5. In Vitro and In Vivo Evaluations of Bioactive Scaffolds

5.1. In Vitro Studies

Several researches have been conducted on bioactive scaffolds using different types of cells to assess the effectiveness of scaffolds. The most often used cell types are osteoblasts, pre-osteoblasts, and mesenchymal stem cells (MSCs). Usually, cell selection for scaffolds containing either growth agents or bioactive glass is based on specific characteristics such as high cell viability and proliferation rate [23]. Multiple studies indicate the importance of these traits for appropriate cell choice. In a study, MC3T3-E1 cells attached and spread more on the composite scaffolds. When scaffolds were prepared by employing

growth factors like BMPs to construct bioactive glass to develop a bone-like matrix, there was a marked improvement in osteogenic differentiation. In another study, the authors reported that surface modification improved cell attachment. These investigations describe how the scaffold material and the incorporation of the right bioactive components affect cell response; this can be further studied before proceeding to in vivo models [42, 43].

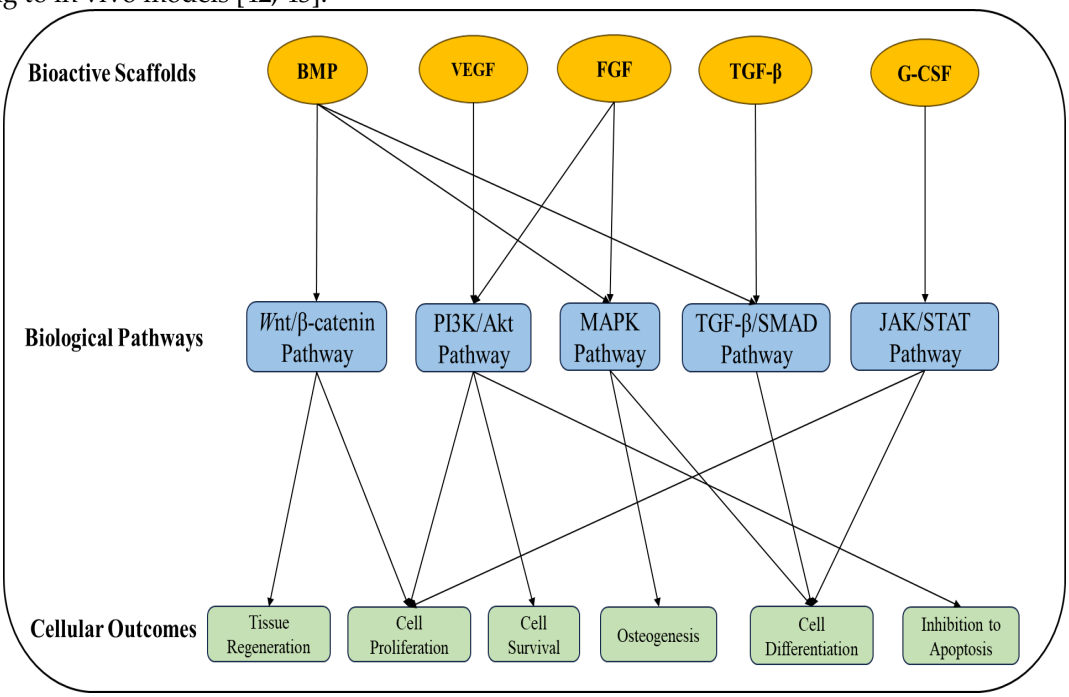

Figure 2. Biological pathways activated by bioactive scaffolds and their influence in cell behavior modulation [23, 24, 26, 36-41].

5.2. In Vivo Studies

Bioactive 3D printed scaffolds have been applied in vivo studies, and they are very efficient, particularly in tissue engineering. The animals reported commonly used in the in vivo analysis include rodents, rabbits, canines, and pigs. The animal model to be used in a given investigation depends on the extent of the probe required. For example, in one of the studies, rats' bone regeneration was performed using a nanohydroxyapatite/ collagen scaffold; in another study, chitosan-based scaffolds were used for mice cartilage regeneration [40]. However, skin repair and the formation of new blood vessels in the tissue have been reported in larger animals [42, 44]. This is even more evident in these studies where the focus has been placed on the development of scaffolds about the choice of animal models for the enhancement of tissue regeneration for future tissue engineering clinical applications.

5.3. Comparison of the Results Obtained In Vitro vs In Vivo

Due to the inherent nature of the living systems, the results obtained from in vitro and in vivo investigations of bioactive scaffolds often exhibit inconsistency. In general, research conducted in vitro under controlled conditions is likely to overemphasize the efficiency of scaffold material because conclusions made in such experiments are free from complex interactions of the environment in a living organism [45]. Due to the effects of such factors as the composition of the ECM and mechanical stimuli, the cell behavior, which is determined by the processes of proliferation and differentiation, may be different in vivo. Moreover, in vivo conditions include various types of cells, immune reactions, and systemic factors. Therefore, transitioning from the lab environment to the real world is somewhat unpredictable [46]. There are several reasons why results from in vivo studies may not correlate with those obtained from in vitro experiments. For instance, there is the likelihood that the host's immune response influences the integration of scaffolds and the healing process, and the complex biological systems may simultaneously affect the degradation rates of the scaffold. Besides, the cellular response of scaffold integration in vivo depends on the scaffold characteristics such as stiffness and porosity. Furthermore, it becomes hard to replicate the in vivo nutrient and oxygen availability conditions compared to tests performed in vitro. These factors reflect the need to cautiously approach in vitro results before moving to vivo studies [47, 48].

6. Clinical Applications and Challenges

6.1. Current Clinical Trials and Applications

The application of bioactive 3D-printed scaffolds is gradually becoming familiar in clinical trials to improve tissue repair. Several studies have been reported in the literature on fabricating bioactive 3-D scaffolds for tissue engineering in bone, cartilage, skin, and vascularized tissues. In bone tissue engineering, polycaprolactone (PCL) and hydroxyapatite (HA) have been used to repair the lesion, while PCL/β-TCP scaffold has been found to improve bone regeneration [49]. Some growth factors like TGF-β are incorporated in the scaffolds and used in cartilage repair to promote the differentiation of stem cells. Also, it has been observed that the bioactive synthetic and gelatin scaffolds enhance skin regeneration and wound healing. Further, scaffolds with complex vascular networks are developed to facilitate the regeneration of tissues by improving the supply of nutrients and oxygen [50]. These studies clearly show the enhanced use of bioactive 3D-printed scaffolds for wound healing and regeneration in the medical field.

Various clinical experiments have yielded excellent results, with bone scaffolds successfully mending and integrated; specifically, the early cartilage scaffold usage indicates excellent potential for future research. Besides this, skin regeneration scaffolds have also provided better healing with less scar formation. However, further work is needed to ensure that patients will remain successful in the long term and that scaffold design is as effective as possible [51, 52].

6.2. Regulatory Issues in the Approval of Bioactive Scaffolds

The primary issue remains in the approval of bioactive scaffolds by the regulatory bodies due to their composition and interactions [53]. In the U. S, the regulatory body FDA approves these scaffolds as medical devices, drugs, or other biological products depending on the application. In the case of employment of simple scaffolds, the FDA qualifies them for further expedited mechanisms. However, in most cases, the intricate bioactive scaffolds may need more elaborative Investigational Device Exemption (IDE) or Investigational New Drug (IND) applications. Likewise, in Europe, CE marking is followed by conformity with Medical Device Regulation (MDR) or In Vitro Diagnostic Regulation (IVDR), which mainly focuses on risk management and post-market monitoring. Therefore, the use of bioactive scaffolds with functional additives remains a challenge in countries with rigid regulatory authorities [54].

Also, the practical implementation of the results obtained in the laboratory is another issue because of the differences between the lab conditions and the organism. When the experiments are performed in vivo, the implanted bioactive scaffold perceives various challenges, including biological complexity, immune responses, and scaffold degradation. Further, the different regulatory bodies demand successive testing, which results in more costs and prolonged time to achieve desired results [52].

6.3. Commercialization and Manufacturing Issues of Bioactive Scaffolds

Many challenges have prevented the actualization of large-scale production and subsequent commercialization of bioactive scaffolds. One of the major problems is the stratified organization of the bioactive scaffold that should mimic the native ECM. The challenge is usually exacerbated by the variation in the natural and synthetic materials used to achieve the quality and performance of the material [40]. Also, the time and costs of producing the products are affected when working under the regulation of the set standard of protocols. The manufacturing process is further complicated by the need to control the scaffold's stability and bioactivity while incorporating bioactive agents such as growth factors. The drawback in clinical applications is the issue of cost since most of them are expensive to produce, particularly when they incorporate complicated technologies such as 3D printing [53, 54].

Small businesses face business investment costs in research, development, and equipment for bioactive scaffolds [45]. Due to the specificity of the product, it is still difficult to bring the costs down to the minimum, and the price must be set to be accessible to everyone. Thus, companies need to focus on long-term sustainability by improving the scaffold designs and working with clinical groups to demonstrate the effectiveness of the scaffolds. However, solving these issues is essential for the translation of bioactive scaffolds from the laboratory environment to practical clinical use [55, 56].

7. Current Research Gaps

7.1. Lack of Long-Term In Vivo Data

Several gaps are identified in the existing literature on bioactive scaffolds for tissue engineering, particularly in long-term analysis studies. Most of the research is based on short-term follow-up, ranging from 3 to 6 months, which does not reflect scaffold degradation or tissue integration [57]. Unfortunately, limited information is available on how scaffold degradation profiles relate to tissue regeneration over extended periods [58]. In addition, the effects of scaffold breakdown byproducts on the neighboring tissues are still unknown. Additional follow-up is also needed in clinical trials to assess the long-term impact and tissue regeneration outcomes since most current studies fail to provide sufficient follow-up time [59, 60]. Chronic in vivo studies face challenges because of the limitations in modeling human responses in animals, along with the costs and ethical issues associated with long-term investigations [45].

7.2. Limited Understanding of Mechanisms of Action

The knowledge of how bioactive scaffold engages with the host tissues in vivo is still limited. The relationship between the scaffold materials, the bioactive additives, and the host environment is complex and poorly elucidated [61]. Changes may influence such interactions in pH, degradation byproducts, and local tissue reactions. In addition, although it is known that several bioactive components can be incorporated into scaffolds, the nature of their interaction is not well understood. This is because there is no complex form of prototypes and approaches to work with for study-specific intervention forms [53, 62]. The existing in vitro models do not mimic the in vivo situation, and therefore, it becomes challenging to evaluate the effects of long-term administration and tissue reactions [45]. Thus, understanding these pathways is necessary to enhance the scaffold design and clinical result. Hence, further investigation is required to advance the translation of bioactive scaffold technology for use in clinical practices.

7.3. Variability in Additive Efficacy

The addition of bioactive compounds in scaffolds has been achieved with varying degrees of success based on tissue type [63]. BMPs are effective in bone tissue engineering, but not soft tissue engineering; VEGF is effective in angiogenesis, while its effect in cartilage is minimal [64]. The overall conclusions of the studies are somewhat inconclusive; some of the works have shown a positive impact on the process of bone formation, while others have pointed to moderate effects. Some variations include the type of materials used in the scaffold, the concentration of the additives used, the rate at which the additives are released, and the biochemical effects of the additives [62, 65]. To address these challenges, tissue-specific bioactive compounds in the scaffold and long-term in vivo studies must be incorporated in the scaffold design for different types of tissues and their effectiveness.

7.4. Standardization of 3D-Printing Techniques

Currently, there are no set procedures for 3D printing for bioactive scaffolds; however, because of the rapid advancement of the technology, it is challenging to set long-term procedures [53]. In many cases, it has been observed that scaffold designs are based on the software employed in additive manufacturing and not on tissue engineering. Some research groups even design their software, which explains why variations exist from one study to another [66]. Furthermore, no standard procedure exists for integrating bioactive chemicals into the scaffold material. Some of the methods include the use of chemicals in printing and applying coats at a later time. In addition, the structure of bioactive materials and their interactions with scaffolds are not easily defined, and the protocols and mechanisms involved are not standardized [23, 61, 62]. The lack of standard protocols for assessing the scaffold's performance and safety further complicates the inconsistency issue. Therefore, comparing data from different studies is difficult, which may hinder the clinical application process. Although 3D printing is helpful for bioactive scaffolds, the sector does not have well-established guidelines for material incorporation and scaffold construction, which poses challenges for researchers and physicians [67].

8. Future Prospects

The future of bioactive scaffolds incorporates complex structures such as bio-printed cells, gene editing components, and innovative drug delivery systems. These next-generation scaffolds may employ several technologies to enhance the functionality of the scaffolds [5, 68]. For instance, scaffolds can capture tissue regeneration and scaffold functionality over time. This would allow the changes to be made in the course of therapy and thus improve the outcome. Therapeutic substances can be delivered to the target site in a controlled manner by innovative drug delivery systems; this further enhances tissue regeneration in clinical applications [69].

The application of 3D printing in scaffolds means that there can be personalized treatment since the products can be tailored. This approach allows the scaffolds to be modified depending on the patient's requirements, thus increasing the chances of therapy outcomes [70]. It is also possible to design the scaffold to have a specific architecture that will complement the architecture of the patient's tissue, making the integration and functionality of the tissue better [71]. Furthermore, precision medicine ensures that the correct drug is administered in the proper dosage and formulation, hence enhancing the patients' adherence to treatment regimes as well as the effectiveness of the treatment. This is a significant boost in tissue engineering and personalized medicine, which can be implemented in subsequent studies [70, 72].

Therefore, scientists, biologists, and clinicians must collaborate to improve the scaffold's architecture and performance. Tissue engineering requires knowledge from other domains to solve issues associated with scaffold fabrication, incorporation of bioactive materials, and clinical application. These professionals can develop improved scaffold designs that address clinical practice objectives and enhance the quality of patients' lives [73-75].

Future developments of bioactive scaffolds will focus on the incorporation of new materials, the possibility of personalized medicine, the enhancement of the interactions between the scaffold and the additives, and collaboration between different fields. These developments will enhance tissue regeneration and drug delivery, hence enhancing healthcare outcomes.

9. Conclusion

This comprehensive reflects a detailed analysis of the possibility of employing bioactive 3D printed scaffolds in tissue engineering and regenerative medicine. An in-depth literature analysis suggests that bioactive scaffolds play a significant role in enhancing cell attachment, mobility, and differentiation, making tissue regeneration possible. Moreover, various techniques can be employed to integrate bioactive additives in scaffolds to improve regeneration and healing capacity. For instance, growth factors and nanoparticles can be added to the scaffold through FDM, SLA, SLS, and DMLS techniques, increasing the scaffold's effectiveness. However, challenges include identifying the long-term consequences of scaffold implantation, the degradation of scaffolds, and the relationship between scaffolds and host tissues. Furthermore, there is a problem of non-reproducibility and applicability to clinical practice due to the absence of clear guidelines. Future studies should focus on developing bioactive scaffolds for specific tissue types, optimizing the process of additives' release, and cooperating to optimize the scaffold design for better clinical performance.

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