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Review Article

# A Comprehensive Review on Nano-Scaffolds in Regenerative Medicine: Types, Preparation Methods and Applications

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Abstract

Nano-scaffolds are a major advancement in biomedical engineering, providing essential support for tissue repair, drug delivery, and regenerative medicine. These tiny structures have a high surface area, making them suitable for promoting cell growth and interaction with biological systems. They are created using methods like electrospinning, 3D printing, solvent casting, and biomimetic techniques, which allow for controlled strength, porosity, and biodegradability. Nano-scaffolds are extensively utilized in medicine to improve drug delivery by providing accurate and sustained release of therapeutic substances. In wound healing, they help tissue repair while reducing infections and inflammation. Bone regeneration benefits from scaffolds containing bioactive materials like hydroxyapatite, which support new bone formation. Additionally, conductive Nano-Scaffolds assist in nerve repair by guiding nerve growth and maintaining synaptic connections. Their potential in gene therapy is also significant, as they allow for controlled genetic modifications. Despite their many benefits, challenges such as large-scale production, immune response, and long-term stability still exist. Ongoing research aims to improve scaffold durability, incorporate smart biomaterials, and refine manufacturing techniques. With continuous advancements, Nano-Scaffolds hold great potential in revolutionizing regenerative medicine and personalized healthcare. This review covers the history of nano-scaffolds, types, preparation methods, and their uses in drug delivery, wound healing, bone regeneration, nerve repair, and gene therapy. It also highlights recent research and innovations, showing their future potential in medicine.

**Keywords:** Nano-scaffolds, Nanofibers, Hydrogels, Nanoparticles, Electrospinning

## Introduction

**A nano-scaffold** is a nanoscale material designed to provide structural support, commonly utilized in biomedical applications. Its high surface area, adjustable physical properties, and interaction capacity with biological molecules make it highly effective in medical applications.

**Nano-scaffolding** refers to the design and fabrication of nanoscale structures; an advanced medical technique used for regenerating tissues, bones, and even certain organs. These scaffolds are three-dimensional structures composed of extremely fine polymer fibres, typically on the nanometre scale ($10^{-9}$ m). Initially developed by the U.S. military, this technology utilizes a microscopic framework made of polymer fibres to facilitate tissue regeneration. Damaged cells adhere to the scaffold and begin reconstructing lost tissue or bone through small pores within the structure. As new tissue forms, the scaffold gradually dissolves and is naturally absorbed by the body, removing the necessity for surgical removal**.**

Nano-scaffolding technology has shown significant promise in healing burn wounds by supporting skin regeneration. However, while it can aid in the reconstruction of tissues and bones, it has not yet advanced to the point of growing complex organs such as hearts.

Nano-scaffolds are made from either polymeric or inorganic nanofibers, forming a three-dimensional matrix that promotes cell attachment and proliferation. They provide an ideal framework for tissue engineering by mimicking the extracellular matrix, allowing cells to grow and develop in a structured environment. Their biodegradability and bio absorbability enable the gradual replacement of the scaffold by newly formed tissue, making them highly effective for medical applications. Initially designed for military use, Nano-scaffolds technology has since expanded into the broader field of regenerative medicine. It is now widely applied in repairing damaged tissues and organs, offering new possibilities for medical treatments. As research progresses, nano-scaffolding continues to evolve, improving its effectiveness in various biomedical applications.

## History of Nano-scaffolding and Nano-scaffolds:

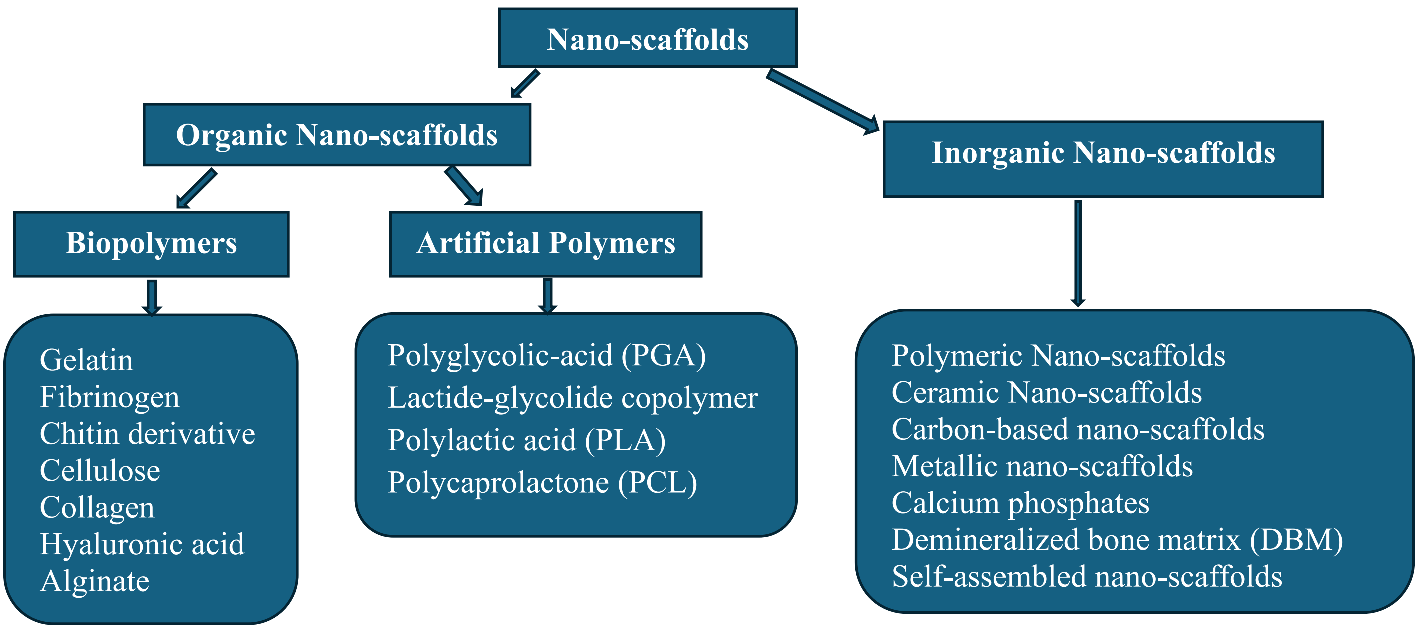
The development of nano-scaffolds began in the 1960s–1980s when researchers explored synthetic polymers and natural biomaterials for tissue regeneration. Early studies introduced biodegradable polymers like polylactic acid (PLA) and polyglycolic acid (PGA) for scaffold design [1]The formal concept of tissue engineering emerged in the 1930s, with advancements in the 1970s and 1980s emphasizing biomaterial scaffolds for cell growth [2] In the 1990s–2000s, nanotechnology improved scaffold properties. **Electrospinning** enabled the production of nanofibers mimicking the extracellular matrix [3]**Hydroxyapatite Nanocomposites**: Used for bone tissue engineering to improve bioactivity and integration with natural bone. And **Carbon Nanotubes (CNTs)** were incorporated into scaffolds for enhanced mechanical and electrical properties.[4]Over the last two decades, bio fabrication and 3D bioprinting have enabled precise scaffold control. **3D bioprinting**, an advancement in additive manufacturing, facilitates the creation of functional tissues for regenerative medicine by integrating engineering, biomaterials, and cell biology. [5]

## Earlier Research:

**Varsha rani *et, al.*** examined about Neurodegeneration and synaptic loss in Alzheimer's disease (AD) impair memory, while neuroinflammation activates microglia and astrocytes, leading to increased pro-inflammatory cytokines. In a scopolamine-induced amnesia mice model, elevated IL-1β, IL-6, IL-10, and TNF-α levels in cerebral tissue indicated their role in AD progression. Treatment with memantine formulations, including nanoscaffolds and stem-cell grafted systems, reduced IL-1β, IL-10, and TNF-α, while IL-6 levels remained high, highlighting its dual role in neuroprotection and degeneration.[6]**Xiaokun Chen *et al.*** investigated spinal cord injury regeneration by integrating nanoscaffolds with stem cell transplantation. Their study highlighted the significant role of inorganic and organic nanomaterials in neural stem cell (NSC)-based therapy for SCI due to their distinct physicochemical properties. They emphasized that advanced 3D bio scaffolds, such as collagen/chitosan and synthetic polymers like PLGA, aid spinal cord repair by facilitating the delivery of signalling molecules, drugs, and growth factors. While natural bio scaffolds provide biocompatibility and biodegradability, synthetic variants offer adjustable mechanical properties, improving SCI treatment approaches.[7]**Li *et al.*** reviewed about cellulose-based Nano-scaffolds for targeted cancer therapy, emphasizing their biocompatibility, tunable surface properties, and controlled drug release. They highlighted how cellulose nanocrystals and nanofibrils enhance drug stability and bioavailability while reducing toxicity, offering a promising approach to personalized cancer treatment[8]. Collectively, these studies showcase nano-scaffolds' growing role in therapeutic delivery, regenerative medicine and cellular engineering (tissue regeneration), highlighting their potential to enhance biocompatibility, cellular interactions, and therapeutic outcomes in future medical advancements.

## Types of nano-scaffolds [9]

Classification efficiently organizes Nano-scaffolds according to their material composition. Nano-scaffolds can generally be grouped based on both their composition and the techniques used for their fabrication.




**Organic Nano-scaffolds:**

- **Natural Polymers:**

  - **Collagen:** A primary structural protein in the extracellular matrix, collagen-based Nano-scaffolds support cell adhesion and tissue regeneration.
  - **Gelatin:** Derived from collagen, gelatin offers biocompatibility and biodegradability, making it ideal for use in drug delivery systems.
  - **Chitin derivative:** Obtained from chitin, chitosan exhibits antimicrobial properties and promotes wound healing.

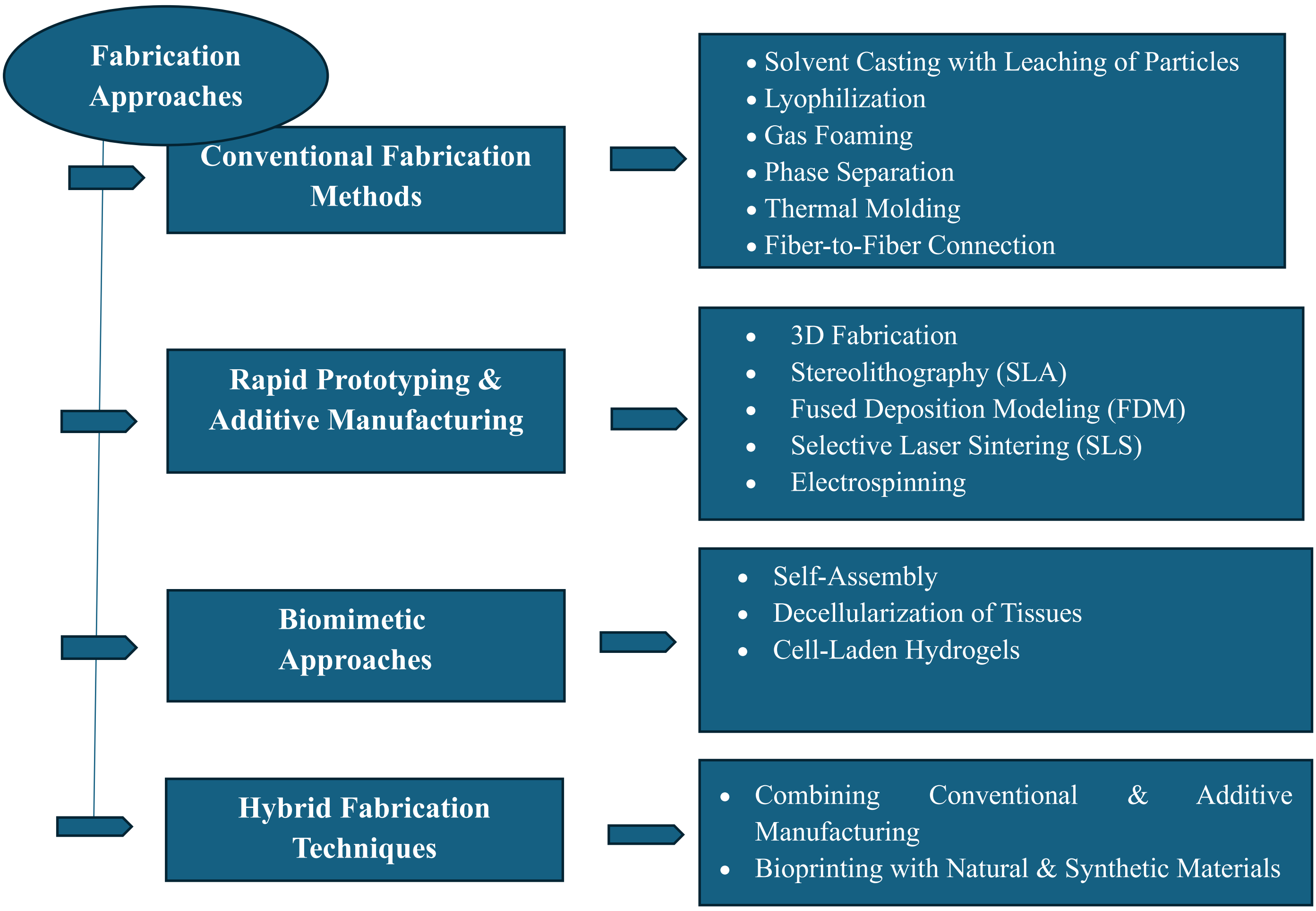
- **Cellulose:** A polysaccharide used to create Nano-scaffolds with high mechanical strength and biocompatibility.
- **Hyaluronic Acid**: A glycosaminoglycan that enhances cell proliferation and migration, beneficial in tissue engineering.
- **Alginate:** Sourced from brown seaweed, alginate forms hydrogels ideal for cell encapsulation and delivery.

- **Synthetic Polymers:**
  - **Polylactic Acid (PLA):** A biodegradable polymer used in Nano-scaffolds for bone and cartilage regeneration.
  - **Polyglycolic Acid (PGA):** Known for its rapid degradation, PGA is employed in soft tissue engineering.
  - **Lactide-glycolide copolymer:** Combining PLA and PGA properties, Poly (lactic-co-glycolic acid) (PLGA) offers tunable degradation rates for various applications.
  - **Polycaprolactone (PCL):** A slow-degrading polymer suitable for long-term tissue engineering scaffolds.

**Inorganic Nano-scaffolds:**

- **Ceramic Nano-scaffolds:**
  - **Hydroxyapatite:** A calcium phosphate ceramic that closely resembles bone mineral, promoting osteointegration.
  - **Bioactive Glasses:** Materials that bond to bone and stimulate tissue growth through ionic dissolution products.
- **Carbon-Based Nano-scaffolds:**
  - **Carbon Nanotubes and Graphene:** These nanomaterials provide exceptional mechanical strength and electrical conductivity, useful in neural tissue engineering.
- **Metallic Nano-scaffolds:**
  - **Silver Nanoparticles:** Incorporated for their antimicrobial properties, aiding in infection prevention.
  - **Gold Nanoparticles:** Utilized for their biocompatibility and potential in photothermal therapy.

## Fabrication approaches: [11,12]



**1. Conventional Fabrication Methods**

- **Solvent Casting with Leaching of Particles:** This approach entails dissolving a polymer in a solvent and mixing it with pore-forming particles (such as salt or sugar). Once the solvent has fully evaporated, the Pore-forming is removed, leaving behind a porous framework.[10]
- **Lyophilization:** Commonly referred to as freeze-drying, this method entails solidifying a polymer solution and then removing the solvent through sublimation under vacuum, resulting in a highly porous structure(scaffold) with interconnected pores.
- **Gas Foaming:** Uses high-pressure gas (e.g., CO2) to create a porous structure in a polymeric scaffold. Upon depressurization, gas bubbles expand, forming interconnected pores without the need for organic solvents.[12]
- **Phase Separation:** Involves the separation of polymer phases through thermodynamic changes, leading to porous structures. Commonly used for fabricating scaffolds with controlled porosity and morphology.
- **Thermal Molding:** Uses heat to mold polymers into specific shapes. The material is melted and then cooled to retain the desired scaffold structure, often combined with porogen leaching for added porosity.
- **Fiber-to-Fiber Connection:** This method involves bonding polymer fibers together to form a fibrous scaffold. The fibers can be randomly arranged or aligned to mimic the natural extracellular matrix.

**2. Rapid Prototyping & Additive Manufacturing**

- **3D Fabrication:** sequential deposition of biomaterials to create scaffolds with precise control over their structure and porosity, making it ideal for producing customized scaffolds tailored to individual patients.
- **Stereolithography (SLA):** Utilizes a laser to selectively harden a photosensitive Polymer(resin), creating highly precise scaffolds with intricate designs.
- **Fused Deposition Modelling (FDM):** A meltable filament is heated and extruding it through the extruder head to build 3D scaffolds in a layer-wise fashion.
- **Selective Laser Sintering (SLS):** Utilizes a beam of light to fuse particulate materials, such as polymers or ceramics, into solid scaffold structures.
- **Electrospinning:** Makes use of a charged field to extract polymer solutions into ultrafine fibrils, creating nanofibrous Frameworks resembling the extracellular matrix
- **3. Biomimetic Approaches**
- **Self-Assembly:** Biomolecules spontaneously organize into nanostructures based on molecular interactions, forming highly ordered and functional scaffolds.
- **Decellularization of Tissues:** Removing cellular components from natural tissues while preserving the extracellular matrix, providing an ideal scaffold for tissue regeneration.
- **Cell-Laden Hydrogels:** Hydrogels embedded with live cells that can support tissue regeneration. These scaffolds provide a biomimetic environment for cell growth and differentiation.

**4. Hybrid Fabrication Techniques**

- **Combining Conventional & Additive Manufacturing:** Integration of different techniques (e.g., electrospinning combined with 3D printing) to optimize scaffold properties.
- **Bioprinting with Natural & Synthetic Materials:** Utilizes specialized (bioinks) made of living cells and biomaterials to construct complex tissue structures with exact control over spatial organization.

**Table 1: Nano scaffold – method of polymer processing and application**

| S.N. | Type | Function | Application | Method of Polymer Processing |
|---|---|---|---|---|
| 1 | **Collegen** | Supports cell adhesion, promotes tissue regeneration | Bone regeneration, wound healing | Freeze drying, electrospinning |
| 2 | **Gelatin** | Enhances cell attachment, biodegradable matrix | Drug delivery, tissue engineering | Solvent casting, freeze drying |
| 3 | **Chitosan** | Antimicrobial, biocompatible | Wound dressing, bone tissue engineering | Co-precipitation, lyophilization |
| 4 | **Alginate** | Hydrogel formation, controlled drug release | Cartilage repair, drug delivery | Ionic gelation, freeze drying |
| 5 | **Polylactic Acid (PLA)** | Provides mechanical strength, biodegradable | Bone scaffolds, sutures | Electrospinning, solvent casting |

| | | | | |
|---|---|---|---|---|
| 6 | **Polyglycolic Acid (PGA)** | Rapid biodegradation, promotes cell growth | Sutures, nerve regeneration | Melt extrusion, gas foaming |
| 7 | **Lactide-glycolide copolymer** | Tunable degradation, drug release control | Drug delivery, regenerative medicine | Solvent casting, nanoprecipitation |
| 8 | **Polycaprolactone (PCL)** | Long degradation time, high mechanical strength | Orthopaedic applications, wound healing | Electrospinning, solvent casting |
| 9 | **Bioactive Glass** | Stimulates osteogenesis, supports mineralization | Bone tissue engineering | Sol-gel processing, melt-quenching |
| 10 | **Hydroxyapatite (HA)** | Mimics bone mineral composition | Bone grafts, dental implants | Biomimetic mineralization, co-precipitation |
| 11 | **Carbon-based Nano-scaffolds** | High conductivity, mechanical strength | Neural regeneration, bone scaffolds | Chemical vapor deposition, electrospinning |
| 12 | **Metallic Nano-scaffolds** | Provides structural support, osteoconductive | Orthopaedic implants, bone tissue engineering | 3D printing, electrochemical deposition |

## Pharmaceutical and Biomedical Application:

### Neural Tissue Engineering

Nano-scaffolds contribute significantly to in neural regeneration by providing a supportive microenvironment to enable neuron growth and repair. They are used to treat neurodegenerative diseases and spinal cord injuries by guiding axonal growth and enhancing synaptic connections. Conductive nano-scaffolds, such as those incorporating carbon nanotubes or graphene, support electrical signalling, which is vital for neural tissue repair. Additionally, scaffolds functionalized with neurotrophic factors have demonstrated improved neural differentiation and recovery in preclinical models, offering potential solutions for nerve regeneration.[13]

### Bone Regeneration

Bone tissue engineering has benefited greatly from nano-scaffolds, which provide structural support and promote osteogenesis. Bioactive scaffolds containing hydroxyapatite, calcium phosphate, or bioactive glass stimulate bone growth and mineralization. These scaffolds can also be loaded with osteo inductive factors to enhance bone regeneration in fractures, osteoporosis, and bone defects. Research indicates that Nano-scaffoldsimprove bone tissue integration, structural strength and cell adhesion, making them best fit for orthopaedic prosthetic devices (like implants) and bone graft substitutes.[14]

### Gene Therapy

Nano-scaffolds have emerged as efficient vectors for gene delivery, ensuring targeted and sustained release of nucleic acids such as DNA, RNA, and siRNA. Their biocompatibility and ability to protect genetic material from degradation make them ideal for gene therapy applications. Functionalized Nano-scaffoldsimprove transfection efficiency, enhance gene expression, and facilitate site-specific gene delivery. Studies have demonstrated their potential in treating genetic disorders, cancer, and regenerative medicine by enabling precise genetic modifications. Advanced nano-scaffold designs incorporating CRISPR/Cas9 systems are being explored for next-generation gene editing therapies[15]

### Drug Delivery

Nano-scaffolds are revolutionizing drug delivery by enhancing precision, bioavailability, and therapeutic effectiveness. These nanoscale carriers ensure site-specific drug targeting, reducing systemic toxicity and improving patient outcomes. Their structural versatility allows the incorporation of various biomaterials, including synthetic polymers, lipids, and inorganic nanoparticles, to optimize drug encapsulation and release. In addition to drug transport, Nano-scaffolds provide sustained and stimuli-responsive release, adapting to environmental factors such as pH or enzymes for controlled dosing. They are instrumental in gene therapy, regenerative medicine, and immunotherapy, offering prolonged drug activity. Advancements in nano-scaffold engineering continue to refine personalized treatment strategies. [15]

CNT Carbon nanotube -based scaffolds allow for controlled and sustained drug release. These features make CNT-integrated nanoscaffolds effective multifunctional drug delivery systems.[16]

### Wound Healing

Electrospun PVA nanoscaffolds aid wound healing by imitating the structure of the extracellular matrix, encouraging celL attachment and growth. Their porous architecture supports the exchange of oxygen and nutrients, which is vital for tissue repair. These nanofibers help retain moisture at the wound site, speeding up the healing process. Due to their biocompatibility and non-toxic properties, they are suitable for direct contact with skin. Moreover, they can be infused with therapeutic agents to boost antimicrobial activity and promote regeneration[17].

## Clinical Translation and Marketed Products:

While Nano-scaffolds have revealed significant potential in early phase studies, their translation into clinical settings has been limited. As of now, there are no widely approved nano-scaffold based products on the market.

However, the broader field of nanomedicine has seen several successful applications. For instance, nanoparticle-based drug delivery systems, such as liposomal formulations (e.g., Doxil) and lipid nanoparticles used in mRNA vaccines, have received regulatory approval and are in clinical use.[18]

## Regulatory Challenges:

The clinical translation of nano-scaffold-based therapies requires overcoming intricate regulatory hurdles. Key obstacles include achieving consistent and scalable production, establishing robust characterization techniques, and conducting extensive safety assessments. Tackling these factors is essential for incorporating nanoscaffolds into routine medical use. Metallic nanoscaffolds, in particular, pose issues such as possible cytotoxic effects from metal ion leaching and inadequate biodegradability, which can compromise their long-term compatibility. Furthermore, their high mechanical rigidity may not align well with the elastic properties of native tissues, potentially limiting their effectiveness in biological integration.[19,20,21]

## Conclusion

Nano-scaffolds have revolutionized medical uses by offering tunable, physiologically well-matched structures for bioactive agent delivery, cellular engineering, and restorative medicine. While significant advancements have been made, constraints such as long-term stability, immune response, and large-scale production remain. Future research should focus on integrating biosensors, improving scaffold durability, and refining fabrication methods to enhance therapeutic outcomes. The combination of nanotechnology and biomedical engineering holds great promise for advancing personalized medicine and next-generation healthcare solutions.

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