Salud, Ciencia y Tecnología. 2023; 3:407
doi: 10.56294/saludcyt2023407

REVIEW

Nanoparticles in Growth Factor Therapy: A Promising Approach for Tissue Regeneration

Nanopartículas en la terapia con factores de crecimiento: Un enfoque prometedor para la regeneración de tejidos

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Cite as: Sharma Udayashankar Sulibele U, Sharma V, Ahmad I. Nanoparticles in Growth Factor Therapy: A Promising Approach for Tissue Regeneration. Salud, Ciencia y Tecnología. 2023;3:407. https://doi.org/10.56294/saludcyt2023407

Received: 08-04-2023 **Reviewed:** 30-04-2023 **Accepted:** 12-06-2023 **Published:** 13-06-2023

Editor: Fasi Ahamad Shaik

ABSTRACT

Nanoparticles (NP) are being explored as a promising approach for growth factor therapy in tissue regeneration. Growth factors play a critical role in tissue regeneration by stimulating cell growth, proliferation, and differentiation. However, the use of conventional growth factor therapy is limited by their short half-lives, rapid clearance from the body, and difficulties in delivering them to the target site. To overcome these challenges, nanoparticles have been used to encapsulate growth factors, providing a sustained and localized delivery system. The aim of this article focuses on the most recent advancements in Growth Factor Therapy (GFT), where tissue generation (TR) and cell therapy depend heavily on iron oxide nanoparticles (IONPs). Additionally, the presence of magnetic fields can use mechanotransduction to drive cell differentiation into a particular cell type or to specifically route IONP-labeled cells to the site of action. Further research is needed to fully understand the safety and efficacy of using nanoparticles in therapeutic applications, but their potential to revolutionize tissue regeneration and provide better treatment options for patients suffering from various diseases and injuries is significant.

Keywords: Nano Growth Factor Therapy; Nanoparticles; Iron Oxide Nanoparticles; Tissue Regeneration.

RESUMEN

Las nanopartículas (NP) están siendo exploradas como un enfoque prometedor para la terapia con factores de crecimiento en la regeneración de tejidos. Los factores de crecimiento desempeñan un papel fundamental en la regeneración tisular al estimular el crecimiento, la proliferación y la diferenciación celular. Sin embargo, el uso de la terapia convencional con factores de crecimiento se ve limitado por su corta vida media, su rápida eliminación del organismo y las dificultades para hacerlos llegar a la zona diana. Para superar estas dificultades, se han utilizado nanopartículas que encapsulan los factores de crecimiento, proporcionando un sistema de administración sostenido y localizado. El objetivo de este artículo se centra en los avances más recientes en la terapia con factores de crecimiento (TFG), en la que la generación de tejido (TR) y la terapia celular dependen en gran medida de las nanopartículas de óxido de hierro (IONP). Además, la presencia de campos magnéticos puede utilizar la mecanotransducción para impulsar la diferenciación celular en un tipo de célula concreto o para dirigir específicamente células marcadas con IONP al lugar de acción. Es necesario seguir investigando para comprender plenamente la seguridad y eficacia del uso de nanopartículas en aplicaciones terapéuticas, pero su potencial para revolucionar la regeneración de tejidos y ofrecer mejores opciones de tratamiento a pacientes que sufren diversas enfermedades y lesiones es significativo.

Palabras Clave: Nanoterapia con Factores de Crecimiento; Nanopartículas; Nanopartículas de Óxido de

Hierro; Regeneración Tisular.

INTRODUCTION

Diagnostic imaging makes extensive use of particulate materials like NPs because of their versatility as molecular imaging agents.[1] To favorably influence regeneration on its own, when combined with the context of magnetic forces to encourage a desired division of cells.[2]

Figure 1 depicts nanoparticles, which have a lot of potential for improving the effectiveness of growth factor therapy. Proteins are used in growth factor therapy to encourage tissue repair and regeneration, but their efficiency is frequently constrained by their brief half-lives and quick elimination from the body.

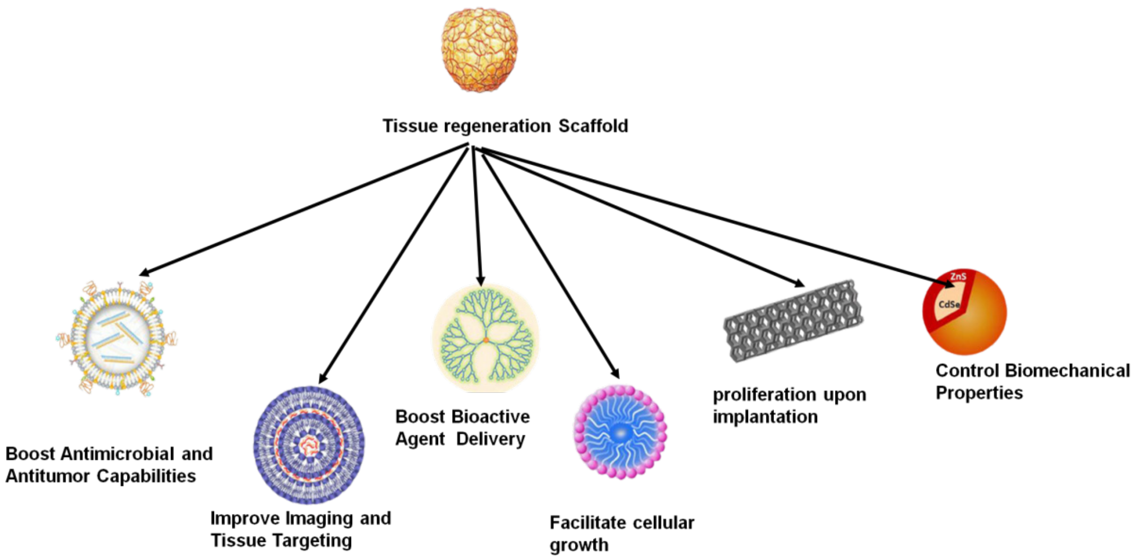

Figure 1. Implementation of nanoparticles in growth factor therapy

The use of adhesive bonding and synthetic sealants in place of sutures and staples during surgical operations has gained popularity in recent years. Conventional methods of wound closure also have several potential drawbacks.[3]

As an alternative to sutures or to support them by removing stress localization and enabling load transfer between the cracked surfaces, an adhesive covers the whole contact region. Although specially formulated tissue adhesives for wound healing are becoming more and more common in a variety of therapeutic settings, they have substantial inherent drawbacks including rejection, infections, toxicity, and excessive swelling. Additionally, under wet or humid conditions, the performance of adhesives is drastically reduced. For many years, the design and regeneration of innovative biomaterials have drawn heavily on inspiration from nature.[4]

NP has been researched as a potential growth factor therapy delivery method and to encourage tissue development, repair, and regeneration, development factors are used in tissue treatment. However, the effectiveness of growth factor therapy is constrained by the clearance from the site of action.[5]

Nanoparticles can assist in overcoming the limitations by protecting the growth factors from deterioration and clearance and delivering them to the target site in a controlled manner. Incorporating growth factors into nanoparticles also allows for their release pH or temperature changes, the presence of enzymes, or a combination of the three. Some of the types of nanoparticles that have been investigated for growth factor administration include liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles.[6] Studies have shown that growth factor therapy, including tissue regeneration (TR), bone regeneration, and wound healing, can be more effective when administered via nanoparticles. To enhance the design and formulation of growth factor delivery systems based on nanoparticles and to evaluate the efficiency and safety of the systems in clinical settings, additional research is needed.[7]

Recent research on tissue regeneration aimed to provide individualized treatments for each patient, encouraging the regeneration, remodeling, and development of the injured tissue. With the use of technique, biomaterials can be created for in vitro research, and creation of bio-scaffolds can be used for in vivo transplantation as well as drug screening.[8]

The Research investigated the use of two-phase systems with scaffolds embedded in growth factor-loaded

https://doi.org/10.56294/saludcyt2023407

nanoparticles has tremendous promise since it can deliver numerous growth factors sequentially and offers sustained release over a therapeutically relevant timescale.[9]

Zheng et al.[10] focused on the most recent developments in the use of scaffolds, hydrogels, or nanosheets made of 2D nanomaterials that are designed to repair cartilage, bone, and skin tissues. Reviews of further uses, such as the therapy of brain diseases, the regeneration of spinal cord tissue, and the restoration of skeletal and cardiac muscles are also offered. We examine the difficulties and potential of 2D nanomaterial applications in GFT. The case study provided a summary of TR's growth factor delivery. Some fundamental difficulties and design strategies relevant to material carriers are provided to accomplish certain technical goals. Recent advancements highlight the importance of regeneration and materials science in growth factor delivery techniques for GFT.[11] The essay summarized the most recent developments and solutions providing the idea for feasible conventional methods.[12]

Neves et al.[13] applications in dentistry, bone TR mediated by growth factor and anti-inflammatory medication therapy, and cancer therapy utilizing anticancer drugs and/or gene release. The essay presented and covered all of the subjects, giving readers a thorough understanding of the key advantages and therapeutic potential of calcium phosphate carriers. The research reviewed recent developments in MSC membrane-coated nanoparticle therapy and drug administration are intended to serve as a guide for the future design and therapeutic use of membrane carriers.[14]

The case study reviewed the state-of-the-art in bone regeneration technologies as well as prospects for nanocomposites-based bone tissue regeneration therapies.[15] The Research focused on current Mesenchymal stem cells (MSCs) based therapy strategies and is broken up the main topic of the next section. In conclusion, the article reviewed the largely covered the existing strategies for creating successful GFT using MSC-based nanocomposite materials, including their benefits and limitations.[16]

The case study was harvested through a non-intrusive method in large quantities. Through bioactive substances, such as growth factors and cytokines, adipose-derived stem or stromal cells (ASCs) can be driven into an osteogenic lineage. Additionally, its secretome—specifically extracellular vesicles—have been associated with the healing of fractures. The article's objective is to provide a thorough understanding of ASCs for bone TR and bone regeneration.[17] The aim of this article focuses on the most recent advancements in Growth Factor Therapy (GFT), where tissue generation (TR) and cell therapy depend heavily on iron oxide nanoparticles (IONPs).

DEVELOPMENT

Focusing, Analysis, and Functionality of IONP

Numerous different IONPs have been created for biomedical applications during the past few decades. However, only a handful of synthesis techniques, such as physical, chemical, or biological ones, are used to create the raw materials. Less than 10 % of all IONPs are produced through physical or biosynthetic means, while the bulk of IONPs is produced chemically, mostly through coprecipitation, micro emulsion, and hydrothermal synthesis.

Formulation and uses of IONP

Typical techniques for producing IONPs on a chemical, physical, and biological basis. The fundamental morphologies of iron oxide-based NPs (orange and green: coating materials; blue: iron oxide core). Typical inorganic and organic components for NP application. The typical therapeutic and diagnostic IONP-mediated techniques employed in biomedical research, as depicted in figure 2.

Cardiovascular TR

An expanding role of nanotechnology is being played in the creation of non-conventional cardiovascular regeneration. Particularly, IONPs have significantly expanded cardiovascular research and experimental therapeutics. They do this by enabling multimodal imaging, which helps with illness diagnosis, pathological process monitoring, and therapy, as well as by acting as carriers for therapeutic molecules figure 3 shows the production of substances and components for cardiovascular regeneration, involving the operational fabrication or restoration of, for instance, blood vessels, heart valves, and myocardium, has advanced significantly over the years, albeit primarily through experimentation.[18]

Thrombolysis

The common ailment of thrombosis has a high death risk since it can lead to other illnesses like myocardial infarction or stroke. Drugs that disintegrate clots by catalyzing therapy necessitates may have negative side effects. Therefore, attempts are being made to create methods that will allow thrombolytic medications.

Vascular Grafts and Stents

Cardiovascular grafts consisting of biomaterials are becoming more biocompatible and effective, although this process is moving extremely slowly toward the clinic. There are numerous explanations for this. One requirement is proven and verified in clinical studies which have a variety of nanostructures as a result of the various materials that have so far shown potential

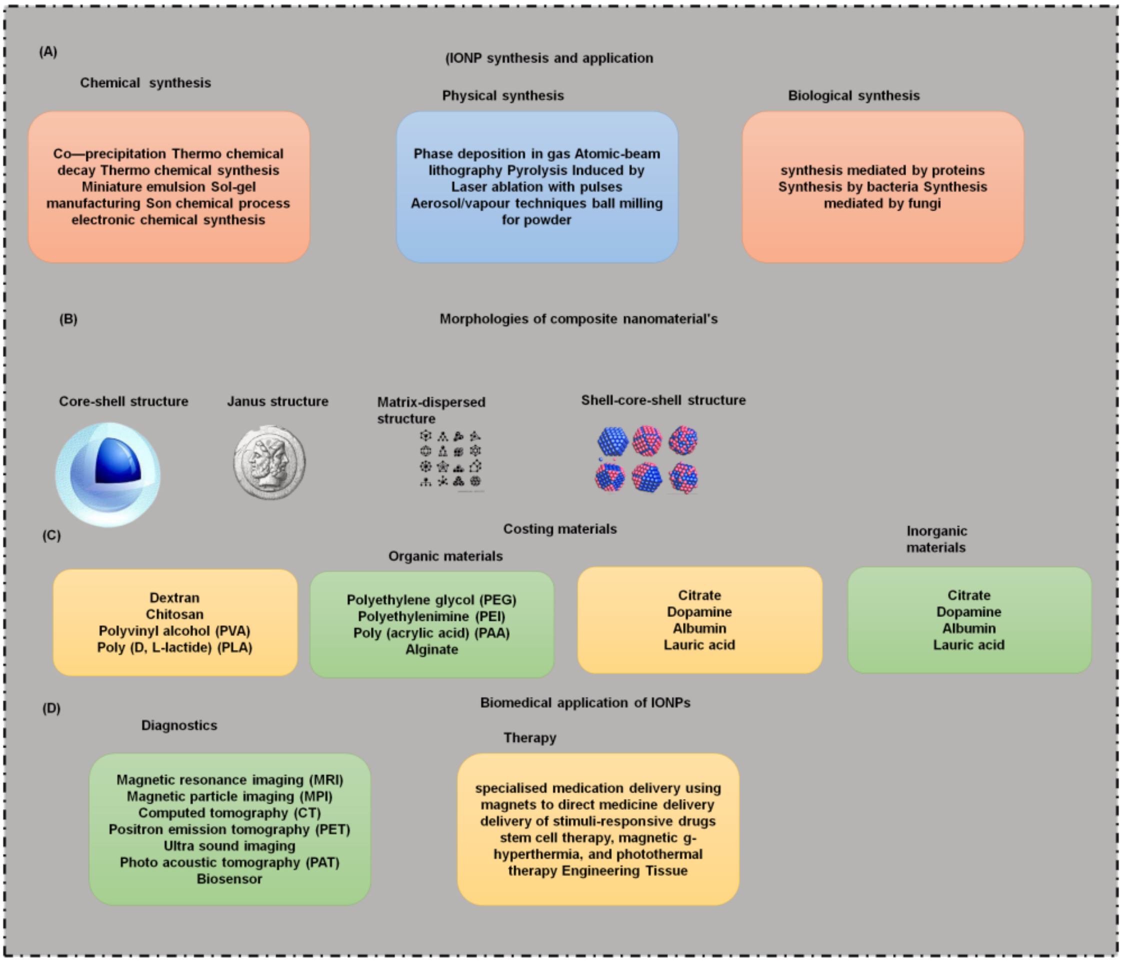

Figure 2. Applications of IONP

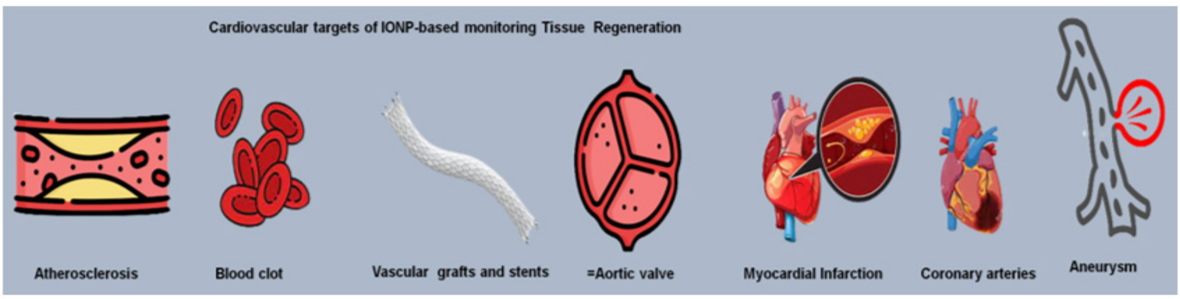

Figure 3. Potential targets for cardiovascular tissue creation and regeneration with IONP assistance

Maintenance of Grafts and Stents Using IONP-Based MRT

Magnetic Resonance Imaging (MRI) has revealed that embedding IONPs into the scaffold itself or coating is an effective way to visualize tissue-engineered vascular grafts (TEVG) function and location. In a further study that added to textile fibers made of polyvinylidene fluoride (PVDF), which were then knitted into vascular scaffolds.

A. IONP-Based Advancements of Vascular Scaffolds

For the manufacturing of TEVG, several materials can be used. To give cells as well as release chemicals as necessary to encourage and speed up the development of new tissue.[19]

B. Atherosclerosis

Despite enormous diagnostic and therapeutic advancements, atherosclerosis continues to be a major public health issue that calls for the creation of fresh approaches. These novel strategies increasingly depend on molecular knowledge of the illness, enabling targeted molecular imaging and therapy based on GFT. IONPs that may transport diagnostic or therapeutic substances by way of specialized surface coating and functionalization are of particular interest since they enable site-specific and targeted delivery. Numerous types of research have been conducted in the interim. The most common of these is contrast-enhanced MRI, and results show that, in comparison to other contrast agents like gadolinium.(20)

C. Hard and Connective Tissue Regeneration

The use of IONPs in pertinent stem cell therapy and TR projects to treat bone and cartilage abnormalities is discussed in the chapter that follows. Work that takes advantage of work that employs IONPs carriers will be taken into consideration.(21)

MRI-Assisted Stem Cell Therapy for Cartilage Regeneration

IONPs are a frequently used labeling agent that can efficiently and quickly label most cells in vitro without significantly impairing their ability to proliferate or differentiate. This labeling enable use in tissue creation or regeneration. In this respect, it was examined how IONPs (ferucarbotran) affected human, neonatal, and adult chondrocyte chondrogenic differentiation, viability, morphology, and proliferation. While stable nanoparticles don't seem to affect adipogenesis or osteogenesis, and these only harmed chondrogenesis when intracellular iron levels were high, the negative impact increased and remained unaffected.(22)

Magnetically-Based Targeted Cell Therapy for Cartilage Regeneration

An additional promising is similar to the potential of increasing stem cell proliferation, differentiation, and migration. The method created magnetic gelatin nanocapsules loaded with transforming growth factor (TGF-β1).(23)

D. Tissue-regenerated Cartilage

Collagen is a popular based scaffold that can integrate the study demonstrated that the structures are not only highly biocompatible with many cell types but can also be quickly, effectively, and steadily labeled with ultra-small IONPs(24) which depicts the potential sites for IONP-assisted TR and TR in the PNS and CNS in figure 4.

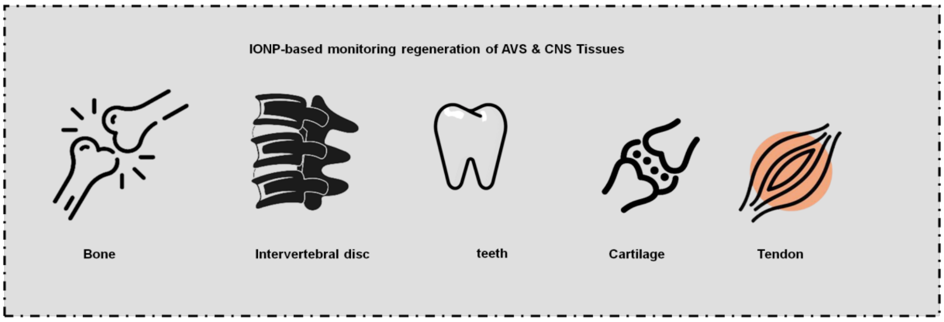

Figure 4. Potential targets in the peripheral and central nervous systems for IONP-assisted TR

Central Nervous system (CNS)

The treatment of brain and spinal cord injuries has a lot of potentials when nanotechnology and stem cells are combined. Current research uses a variety of various cell therapy and TR strategies to treat CNS nerve tissue damage.

Peripheral Nervous system (PNS)

- *Dorsal Root Ganglia:* dorsal root ganglia (DRG) sensory neurons relay information from bodily inputs that cause emotions of touch, pain, muscle tension, and temperature to the CNS.(25)
- *Sciatic Nerves:* to restore damaged peripheral nerves, autologous nerve transplantation is a recognized treatment. There are promising methods for replacing missing nerves using biomaterials or biomaterials combined with cells, owing in part to the scarcity of donor's nerves.
- *Optic Nerves:* the most frequent causes of blindness are disorders of the optic nerve, including glaucoma and diabetic retinopathy.
- *Spinal Cord:* despite extensive studies into potential treatments, there is currently no proven therapy to help patients regain their lost functions.

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- *Brain:* the human brain is the central nervous system's primary organ, and it is considered to be the most complex and crucial organ in the human body. Its functions encompass control and coordination of all bodily processes, ranging from thoughts and emotions to movements and sensations. The brain comprises billions of neurons that communicate with one another through electrical and chemical signals.

E. Other Soft Tissue Regeneration

Ear : functional restoration of inner ear injury, including sensor neuronal hearing loss, is thought to be amenable to stem cell transplantation. Therefore, it would be most beneficial if the course of therapy could be accurately followed and observed.

Eye: stem cell therapies for the treatment of degenerative eye disorders have been studied for a long time. Loss of eyesight may result from corneal edema, opacification, or damage to the corneal endothelium. In a feasibility study, it was found that IONP labeling did not affect corneal endothelial cells (CECs) and that first magnetic exposure had a considerable favorable impact on cell viability. The findings point to IONP-loaded CECs as a viable therapy for ocular damage.

Nose: olfactory damage may also be treated by intranasal administration using external magnets, it was possible to improve the migration of magnetized MSCs in a mouse model with olfactory impairment.

Vocal Fold: treatment of voice abnormalities, such as damaged vocal folds, is a difficult task for GFT. By adding IONPs, the vocal fold fibroblasts from rabbit laryngeal heads magnetized themselves. The same team also proved the viability of magnetic cell guiding and the potential creation of structures while characterizing the cellular consequences of IONP uptake.

Salivary Glands: stem cell or TR approaches may be used to make up for under function as a result of autoimmune illnesses or radiation therapy of cell treatment using extremely tiny IONP-labeled and acinar-like cells could restore the function of injured salivary glands; however, the acinar-like cells shown more therapeutic potential. These cells displayed different magnetic bioprinting may be used to produce epithelial organoids that resemble salivary glands from NP-labeled stem cells.

F. Techniques for creating iron nanoparticles

There are many ways to make iron oxide magnetic NPs with the proper surface chemistry, including wet chemical, dry procedures, and microbiological methods. a thorough analysis of synthesis techniques to assist researchers working in this area in selecting the best synthesis techniques. The following three techniques can be used to create iron nanoparticles, in brief: Applications for Super Paramagnetic Iron Oxide Nanoparticles (SPIONs) include biomedical research and clinical medicine. They are specifically employed as contrast agents in magnetic resonance imaging (MRI) to improve the visibility of tissues or organs. The SPIONs can also be functionalized with specific molecules to bind to particular receptors on the surface of cells, enabling the targeted delivery of medicines.

Physical methods

Physical methods refer to the techniques or procedures that rely on the physical properties of a substance, such as its size, shape, density, solubility, or melting point, to separate, analyze, or modify it. Some common physical methods are:

- *Electrochemical Decomposition:* a process in which an electric current is passed through a substance to cause a chemical reaction that breaks down the substance into its constituent parts.
- *Sonochemical:* a chemical process in which high-frequency sound waves are used to induce chemical reactions or physical changes in a substance. Thermal Decomposition: A process in which a substance is heated to a high temperature, causing it to break down into simpler substances.
- *Coprecipitation:* a process in which two or more substances are simultaneously precipitated from a solution, resulting in the formation of a mixed precipitate.
- *Hydrothermal:* a process in which a substance is subjected to high temperature and pressure in a liquid or supercritical fluid, often leading to the formation of new compounds or materials.
- *Microemulsion:* a thermodynamically stable mixture of two immiscible liquids (typically oil and water), stabilized by an interfacial layer of surfactant molecules and often used as a reaction medium or template for the synthesis of nanoparticles or other materials.

Comparatively, Electrochemical Coprecipitation only achieves a 27 %, whereas Electrochemical Decomposition, Sonochemical, Thermal Decomposition, Hydrothermal, and Microemulsion of 4 %, 15 %, 8 %, 25 %, and 21 %, respectively. It suggests that the suggested technique is more effective than the one already in use which are shown in table 1.

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Methods	Percentage
Electrochemical Decomposition	4
Sonochemical	15
Thermal Decomposition	8
Coprecipitation	27
Hydrothermal	25
Microemulsion	21

Table 1. Comparison of physical methods

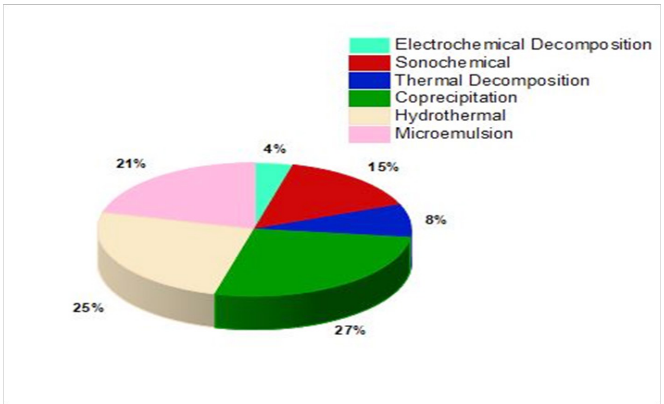

Figure 5. The synthesis of SPIONs by physical methods

Physical approaches suffer from the inability to control particle size since they are intricate processes. This method, illustrated in figure 5, produces iron nanoparticles by condensing a vapor of iron atoms or ions onto a substrate.

Chemical preparation methods

Chemical preparation methods refer to procedures or techniques that rely on chemical reactions or interactions between substances to synthesize or modify a desired substance or material. Some common chemical preparation methods are:

- *Aerosol:* a suspension of fine solid or liquid particles in a gas, typically air.
- *Gas Phase Deposition:* a method of synthesizing thin films or coatings by depositing gaseous precursors onto a substrate and causing them to react or condense to form a solid product.
- *Electron Beam Lithography:* a process of patterning thin films or surfaces by using a focused beam of electrons to selectively remove or add material.
- *Pulsed Laser Ablation:* a method of synthesizing nanoparticles or thin films by irradiating a target material with a high-intensity pulsed laser, causing it to vaporize and condense onto a substrate.
- *Laser-Induced Pyrolysis:* a method of synthesizing carbon-based nanomaterials by irradiating a precursor material with a laser, causing it to break down into smaller units that reassemble into the desired product.
- *Power Ball Milling:* a method of grinding and mixing materials by using a high-energy ball mill to impact and shear the particles, resulting in the formation of smaller particles or the synthesis of new materials.

Table 2. Comparison of Chemical methods

Methods	Percentage
Aerosol	38
Gas Phase Deposition	17
Electron beam lithography	2
Pulsed laser ablation	16
Laser-induced Pyrolysis	13

Comparatively, Aerosol only achieves 38 %, whereas Gas Phase Deposition, Laser-induced Pyrolysis, Electron beam lithography, Pulsed laser ablation, and Power ball milling of 17 %, 13 %, 2 %, 16 %, and 14 %, respectively. It suggests that the suggested technique is more effective than the one already in use which are shown in table 2.

The size, composition, and even the form of the NPs can be controlled by using straightforward, controllable, and efficient chemical production processes. Iron oxides can be produced by incorporating a base into the co-precipitation process, as shown in figure 6. The size, shape, and content of the chemically generated iron NPs are all influenced by the type of salt used, the ratio, and ionic strength.

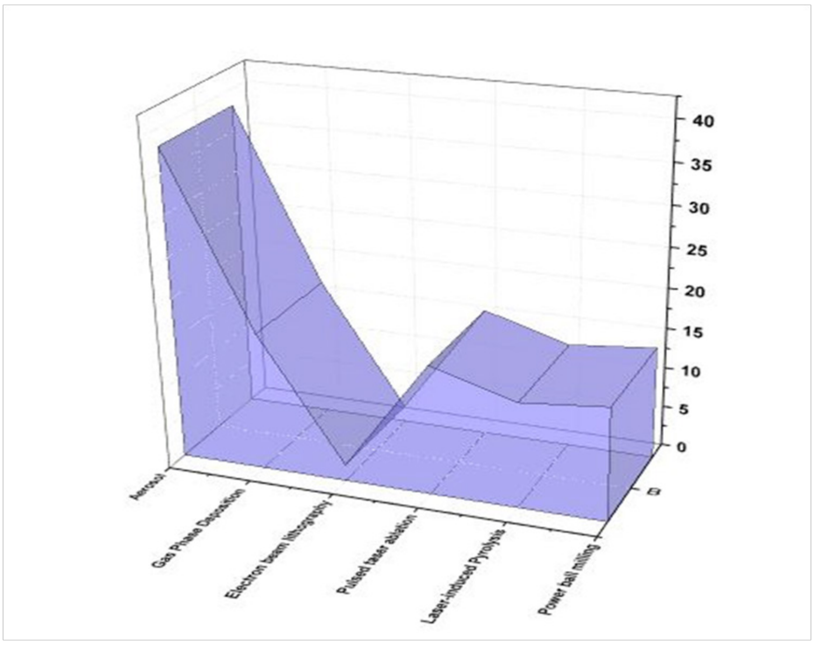

Figure 6. The synthesis of SPIONs by chemical methods

Biological methods

Biological methods refer to the techniques or procedures that rely on the use of living organisms, such as plants, animals, fungi, and microorganisms, to modify or transform a substance or material. Some common biological methods are:

- *Plant:* plant refers to the process or interaction in which a plant plays a role in facilitating a certain activity or communication between organisms. For example, some plants release chemicals that attract pollinators or repel predators, which can benefit both the plant and the interacting organism.
- *Fungi:* fungi refer to the process or interaction in which fungi play a role in facilitating a certain activity or communication between organisms. Fungi can have a symbiotic relationship with plants, forming mycorrhizal associations where the fungi help the plant absorb nutrients from the soil. Fungi can also have a parasitic relationship with plants, causing diseases or damaging plant tissues.
- *Bacteria-Mediated:* a process in which bacteria are used to modify or transform a substance or material. Bacteria can produce enzymes or other metabolites that can catalyze chemical reactions or modify compounds, making them useful for various applications such as biodegradation, bioremediation, and bioprocessing.
- *Protein-Mediated:* a process in which proteins are used to modify or transform a substance or material. Proteins can have a wide range of functions and activities, such as catalysis, binding, and structural support, making them useful for various applications such as biocatalysis, biomaterials, and biotechnology.

Table 3. Comparison of Chemical methods

Methods	Percentage
Plant	3
Fungi	12
Bacteria mediated	20
Protein mediated	65

Comparatively, Protein mediated only achieves a 38 %, whereas Plant, Fungi, and Bacteria mediated 3 %, 12 %, and 20 % respectively. It suggests that the suggested technique is more effective than the one already in use which are shown in table 3.

Figure 7 illustrates how plants or plant extracts are used to create iron nanoparticles. The plant extracts contain a variety of biomolecules, including flavonoids, terpenoids, and phenolic chemicals, which act as reducing and capping agents for the synthesis of NPs.

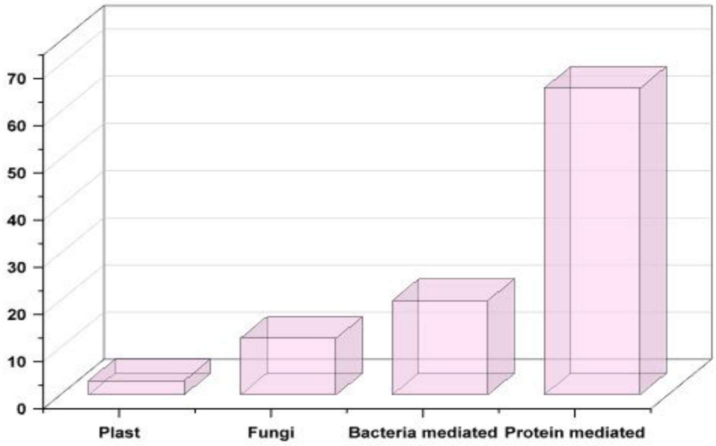

Figure 7. The synthesis of SPIONs by biological methods

CONCLUSIONS

The use of nanoparticles in growth factor therapy holds significant promise for tissue regeneration. The ability of nanoparticles to control the release of growth factors in a sustained and localized manner, along with their ability to enhance the stability and bioactivity of growth factors, makes them an attractive option for therapeutic applications. Moreover, the use of nanoparticles has also been demonstrated to overcome the limitations associated with conventional growth factors therapy, such as short half-lives and rapid clearance from the body.

Numerous developments in the creation and application of nonmaterial for medical purposes have been reported in recent years. We concluded that the use of nanoparticles in growth factor therapy holds immense promise for tissue regeneration.

By encapsulating growth factors in nanoparticles, the efficacy of growth factor therapy can be enhanced through targeted delivery, sustained release, and improved stability. This approach has shown great potential in preclinical studies, demonstrating enhanced tissue regeneration in various applications including bone, cartilage, and muscle regeneration. IONPs can be tailored to any specific application where cellular effects are regulated by loading and delivering bioactive chemicals, in addition to the possibility of IONP-based scaffold visualization in the field of TR.

There are various opportunities, particularly in the field of cell treatment, to positively influence the therapeutic result. Overall, the use of nanoparticles in growth factor therapy has the potential to revolutionize tissue regeneration and provide better treatment options for patients suffering from various diseases and injuries. Further developments in this field may lead to the creation of novel therapies that could transform the way we treat tissue injuries and diseases.

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FINANCING

No financing.

CONFLICT OF INTEREST

None.

AUTHORSHIP CONTRIBUTION

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