Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i6.6589

NANOPARTICLE-ENHANCED REGENERATIVE MEDICINE: A COMPREHENSIVE REVIEW ON APPLICATIONS, ADVANCES, AND DRUG DELIVERY SYSTEMS

Palwasha Tehseen[1], Umair Mahmood[2*], Fatima Gulzar[3], Rabia Afzal[4], Aisha Ghaffar[5], Iqra Nawaz[6], Isma Rafiq[7], Mahpara Jabeen[8], Aqsa Abbas[9], Rimsha Saleem[10]

[1,3,4,5,9,10]Department of Chemistry, University of Agriculture Faisalabad, Pakistan
[2]Department of Biochemistry, University of Agriculture Faisalabad, Sub-Campus Toba Tek Singh, Pakistan
[6,8]Department of Chemistry, University of Sialkot, Pakistan
[7]Department of Chemistry, Government College University Faisalabad, Pakistan

***Corresponding Author:** Umair Mahmood, Email: umair.mahmood@uaf.edu.pk
*Department of Biochemistry, University of Agriculture Faisalabad, Sub-Campus Toba Tek Singh, Pakistan

Abstract
Nanoparticle-enhanced regenerative therapies represent a paradigm shift in healthcare, using nanoparticles distinct capabilities to boost treatments for tissue repair and regeneration. The historical development, wide range of applications, and methodological complexities of nanoparticles integration in regenerative medicine are examined in this study. Through a thorough analysis of the literature, we are able to demonstrate the revolutionary potential of nanoparticles in enhancing regenerative processes, ranging from tissue engineering and targeted medication administration to imaging. Thematic studies highlight the adaptability and promise of nanoparticles in addressing medical needs by revealing applications across therapeutic modalities. An emphasis is placed on a rigorous approach that includes a thorough study design, selection criteria, and data analysis techniques to guarantee the integrity and dependability of the findings. The complex relationship between nanoparticles and regenerative processes is elucidated through findings and discussions, which also highlight significant turning points and the development of nanoparticle drug delivery systems as a pillar of regenerative medicine. This review concludes by summarizing the revolutionary field of nanoparticle-enhanced regenerative medicines and predicting a time when injured tissues would not only be mended but also effectively and precisely regenerated, bringing in a new era of individualized and regenerative healthcare.

Keywords: Regenerative medicine, Nanoparticles, Tissue Engineering, drug delivery system

1. Introduction
The need for tissue engineering and regenerative medicine (TERM) solutions is multiplying because of the numerous problems associated with tissue and organ transplantation, including the scarcity of donors, the requirement for immunosuppressant, and the low success rate (rejection of the transplant). Since there was no such thing as blood type at the end of the 15th century, blood transfusions have been the basis of regenerative medicine [1]. Later, bone marrow transplantation was developed as a

solution to this issue, and it eventually became a widely used medical procedure. Regenerative medicine is the science of using in vitro design and in vivo use to replace or repair damaged or diseased tissue or organs. Weitzman DH et al.1 proposed integrating platelet-rich plasma (PRP) in fibrin glue in 1997, it can be regarded as a new field of medicine. Marx et al.'s 1998 study provided evidence that PRP could stimulate jawbone regeneration.

Stem cells have sparked a lot of curiosity in the area and offer an excellent medium for growing tissues. By initiating and promoting the restoration of sick or damaged tissue, the rapidly expanding interdisciplinary field of regenerative medicine holds great promise for advancing our understanding of biological mechanisms and enabling individualized treatments for a wide range of ailments [2]. During the same time limit, it was found that a portion of bone marrow-derived stem cells could restore various mesenchymal tissues or organs. Consequently, the foundation of regenerative medicine lies in the utilization of either multipotent stem cells or biological products such as platelet-rich plasma (PRP) or its gel formulation known as platelet gel (PG). These materials not only provide support but also act as a guide to help stem cells achieve spatial reconstruction.

Regenerative medicine is a rapidly expanding international field. It has combined the fields of biology, materials science, and engineering to create and produce synthetic structures that mimic natural tissues and organs as models, miniature organs, and implantable systems [3]. Aside from being able to supply bioactive chemicals, this scaffold should also have the right amount of mechanical strength and flexibility in tracking cellular activity. Nanoparticles (NPs) enable highly regulated scaffold properties, including mechanical strength and the release of biologically active substances [4]. The synthesis of NPs and their myriad uses are integral to the processing technology of nanotechnology [3]. The two colloidal and solid forms of NPs can be generated, with diameters ranging between 10 and 1,000 nm.

NPs find extensive uses in the manufacturing of sensors, photovoltaic devices, and biological fields, particularly vaccine adjuvant and drug delivery. Traditional methods in regenerative medicine have evolved due to the influence of nanotechnology, transitioning towards more advanced and efficient systems. In addition to NPs, other microscopic levels materials such as nanostructures and microfibers substrates have played significant roles in this transformation surfaces have been utilized to control cell function in this field. NPs offer a range of applications, such as simultaneous therapeutic and imaging systems, embedding novel biomaterials within scaffolds with superior spatiotemporal control, regulating the release of multiple bioactive agents, including growth factors to direct stem cell fate and morphogenesis, adjusting scaffold mechanical strength for hard tissue applications, and improving biocompatibility and reducing toxicity through tissue-specific delivery. NPs can be made from a variety of materials, including metals, ceramics, and synthetic and natural polymers. Due to their unique properties and compositions, featuring a large area of coverage, good penetrating capacity, and changeable interface qualities, They are one of the most popular candidates in the TERM field for imaging, mechanical strength enhancement, bio-ink supplements, antimicrobials, and bioactive agent carriers [3].

The application of nanotechnology has drawn more interest in recent years to enhance existing methods for tissue and organ regeneration. Specifically, nanoparticles have unique characteristics that can help the science of regenerative medicine progress. Solid colloidal particles with diameters typically ranging from 10 and 200 nm provide a considerable deal of flexibility in terms of component setup, size, and surface chemistry. Nanoparticles can be used as therapeutic agents or as carriers for the transfer of medications, genetic material, or growth factors (GFs) because of their size and surface chemistry [5].

In October 2013, a small group of world-renowned regenerative medicine specialists convened in Xi'an, China, for a confidential session to explore these obstacles and provide solutions. The "Xi'an Papers," a compilation of these people's statements that were prepared before the meeting, are available here as an additional file called heXianPapers.pdf. Many significant issues were brought up, some more frequently than others. This Focus article, which centers on manufacturing paradigms, identifies some of the most pertinent and urgent issues in the translation of regenerative medicine

methodologies and components [6]. The practice of regenerative medicine will advance due to a number of factors. Initially, careful control over the behavior of stem cells whether generated or isolated from adult tissue is frequently necessary to improve their safety profile and efficacy following transplantation.

Traditional and straightforward methods in TERM have changed because to the influence of nanotechnology, moving toward more sophisticated and effective systems. In addition to NPs, other nanoscale technology-produced materials like microfibers and nano structured surfaces were also employed that control functions of cell in TERM fields. Applications of NPs in TERM include utilizing imaging and therapeutic systems simultaneously, embedding novel biomaterials with superior spatiotemporal control within scaffolds, modulating the release of multiple bioactive agents, especially growth factors to direct stem cell fate and morphogenesis, adjusting the mechanical strength of scaffolds for applications in hard tissue, and reducing toxicity and enhancing biocompatibility through tissue-specific delivery as shown in figure 1.

NPs can be made from a variety of materials, including metals, ceramics, and synthetic and natural polymers. Because of their compositions and unique advantages such as their high surface area and tunable surface properties they are among the most popular candidates in the TERM field for imaging, mechanical strength enhancement, as supplements to bioink, and as carriers of bioactive agents and antimicrobials [5]. Nanoparticles hold great promise for enhancing conventional tissue engineering materials. The distinct characteristics of nanoparticles have contributed to the enhancement of diverse tissue growth beyond current capabilities.

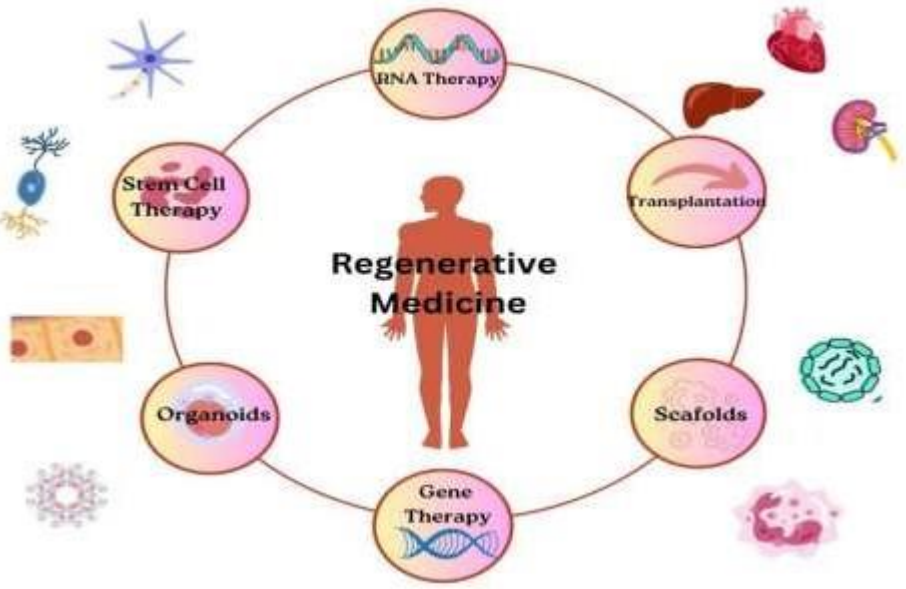

Figure 1: Overview of Regenerative Medicines.

The aggregation states or interactions of nanoparticles with biomolecules in vivo may alter how hazardous they are to people. However, it is evident from the frequently contradictory findings of recent research that this is insufficient to provide a definitive response on the toxicity of nanomaterials [7]. To properly answer the question of whether nanoparticles should be employed in biomedical applications, extensive studies of the effects of nanomaterials on the environment and human health are required [8]. Worldwide, there is a great deal of research being conducted on the key elements of regenerative medicine. To convert fundamental science into reliable clinical products, special efforts are being made to address the challenges that the field is currently facing. This article's scope is to converse about the latest advancement in nanotechnology for regenerative medicine and focused on investigating the potential benefits of nanoparticles in the area of regenerative medicine. It seeks to comprehend their function in Tissue regeneration and repair, investigate their modes of action and make suggestions for further study and application in this area.

2. Fundamentals of Nanoparticles In Regenerative Medicine

The last 23 years have seen a dramatic increase in the number of publications in the field of regenerative medicine. Nanotechnology is also making inroads into biomedical research, and because of its versatility and potential for functionalization, it could improve and speed tissue regeneration. The materials utilized have an enormous variety of shapes and compositions, ranging from particle items to structures of fibers or nanopatterned interfaces [9]. NPs and other particulate matter are specifically utilized in diagnostic applications due to their ability to facilitate multidimensional and multipurpose diagnostic imaging. Materials such as polymers, metals, ceramics, and their various composites are capable of being utilized to produce NPs, depending on the purpose [1]. A growing body of research explores nanotechnology's role in regenerative medicine as shown in figure 2.

Nanotechnology offers superior control over biomaterial properties compared to conventional methods. Nanostructures with tissue-mimicking abilities create durable scaffolds, while scaffolds containing stem cell seeds aim to regenerate bones, contingent on stem cell availability. Nanofibers, mimicking natural cardiac tissue, are under intense study for wound healing with growth factors. Biodegradable scaffolds with multiple growth factors show promise for skin tissue regeneration. Though nascent, nano-ophthalmology aims to preserve and restore. Nanotechnology's potential in regenerative medicine promises to revolutionize tissue repair and regeneration [10]. Nevertheless, there are still several challenges to be overcome. Creating the perfect nanomaterials that can communicate with damaged or sick cells and tissues to start the regeneration process is one of them. Additionally, there's the task of engineering ECM proteins to function precisely like natural ECM proteins of tissue within the internal environment. Moreover, there's critical and rigorous choice of a fresh matrix of polymers /nanomaterials mixto enable the creation of scaffolds with superior biomimicking ability. This involves optimizing their chemical composition and structure [11].

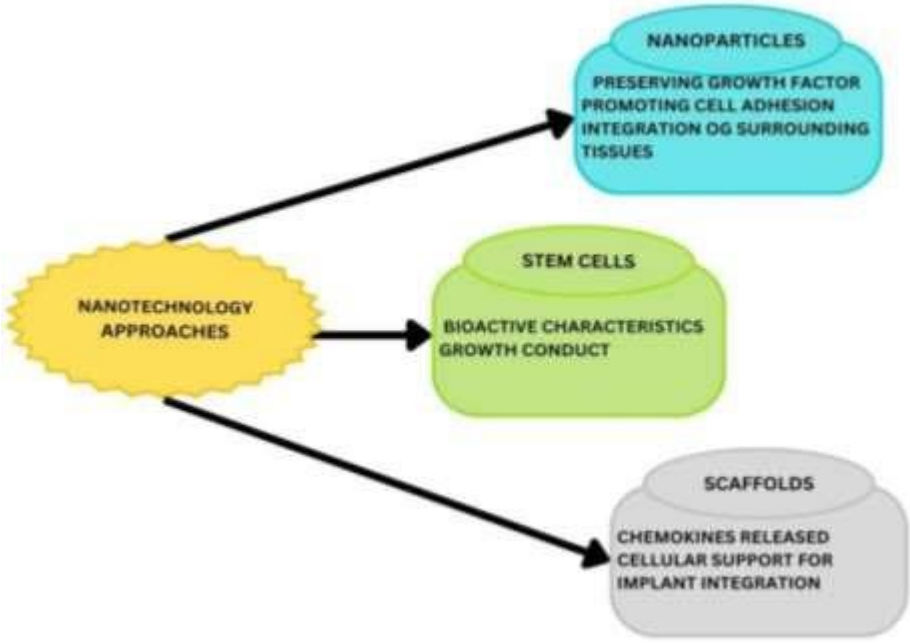

Figure 2: Nanotechnology approaches in regenerative medicine [3].

To get around these limitations, scaffolds that already exist will need to be improved. Since regenerative medicine is still in its preliminary stages, there is great concern about the safety of using nanomaterials in human health. Before applying these nanomaterials to humans, extensive research on their toxic effects should be done. Lastly, Direct interaction between medical professionals and researchers is essential to comprehending the fundamental processes that underlie relationships among cells and biomaterials at the nanoscale and being Capable of transferring research results via lab to their bedside [12].

3. Applications of Regenerative Medicine

Stem Cell Therapy

By promoting pre-clinical research studies, multipotent mesenchymal stem cell (MSC) transplantation has shown its potential as a regenerative medicine therapy alternative [13]. MSCs have been employed in clinical trials with the goal of treating chronic illnesses and autoimmune disorders by resetting immune systems through their potential as regenerative agents, immunosuppressive, and immunomodulatory as shown in figure 3. The secretion of multiple cytokines, including anti-inflammatory factors like iNOS, IDO, PGE2, TSG6, HO1, and gelatins, cytokines like TGFβ, IL-10, CCL2, IL-6, and IL-7, and chemokines such as CCL5, CXCR3, CXCL9-11, IL-6, and CCR5, is responsible for MSCs' immune-regulating abilities. MSCs release potential angiogenic proteins such as TGFβ, PDGF, and VEGF [14]. For both laboratory-based scientific investigations and pre-clinical studies, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy (ISCT) has established standards to define "multipotent mesenchymal stromal cells" (MSC). The designation of mesenchymal stem cells (MSCs) hinges on meeting three specific criteria.

Firstly, MSCs must demonstrate plastic adherence, typically observed when they are cultured in flasks for tissue culturing under normal settings. The second thing, MSCs must express specific surface antigens, as determined by flow cytometry. These antigens include CD105, CD73, and CD90, with high expression levels (≥95%) and minimal or absent expression (≤5/2%) of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA class II. Lastly, MSCs must exhibit the capability to differentiate into osteoblasts, adipocytes, and chondroblasts under standard in vitro differentiating conditions. It's noteworthy that adherence to these criteria is paramount for ensuring consistency and comparability across MSC studies.

Table 1: Here is a listing of tissue-engineered and cellular products that have been approved by the FDA, along with current proposed treatments [10]

PRODUCTS	COMPANY NAME	APPROVED FOR TREATMENT
FUCASO	Innovent Biologics & Iaso Biotechnology	Relapsed or refractory multiple myeloma
Holoclar	Chiesi Farmaceutici	Moderate to severe limbal stem cell deficiency due to ocular burns
CLEVECORD (hematopoietic progenitor cell, Cord Blood)	Cleveland Cord Blood Center	Diseases of the hematopoietic system which can be hereditary, acquired, or brought on by myeloablative therapy
Lantidra	Celltrans	Adults with type 1 diabetes who are unable to approach target glycated hemoglobin (average blood glucose levels
GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen)	Organogenesis Incorporated	llogeneic cellularized scaffold product indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults
LaViv (Azficel-T)	Fibro cell Technologies	Improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults
HEMACORD (Hematopoietic progenitor cell, cord blood)	New York Blood Center	Diseases of the hematopoietic system which can be hereditary, acquired, or brought on by myeloablative therapy
Temcell	Temcell	Acute radiation injury, chronic obstructive pulmonary disease, Crohn's disease, acute graft-versus-host disease, Type I diabetes, and myocardial infarction
Hematopoietic progenitor cell, Cord Blood - MD Anderson Cord Blood Bank	MD Anderson Cord Blood Bank	Diseases of the hematopoietic system which can be hereditary, acquired, or brought on by myeloablative therapy

Due to the angiogenic properties of autonomous adipose tissue-derived mesenchymal-stem cells (MSCs), patients with atherosclerosis renovascular disease (RVD) can experience a substantial rise

in kidney tissue oxygenation, cortex blood flow, and stabilization of the glomerular filtration rate (GFR) for as long as three months. [15]. Patients with type 1 diabetes mellitus may benefit from the anti-inflammatory properties of autologous hematopoietic stem cells by having a lower percentage of T-cell proliferation, lymphocytes, and white blood cells [16]. Additionally, these trials highlight the anti-inflammatory effects of MSCs, manifested by inhibition of T cell proliferation and lowered impression of pro-inflammatory markers. Notably, the anti-inflammatory attributes of these MSCs have exhibited improvements in various parameters such as lung function, skin thickness scores, levels of pro-inflammatory cytokines, and anti-Scl70 autoantibody titers in individuals with disorders linked to systemic sclerosis [17].

Although clinical trials have shown promising results, utilizing MSCs in medical practice presents several challenges. These include low rates of engraftment, variability in immunomodulatory responses, and potential limitations in the field of regenerative medicine [18]. While current clinical trials demonstrate consistent but modest anti-inflammatory benefits with MSC treatments akin to earlier pre-clinical trials, there exists substantial heterogeneity among these trials. Discrepancies, such as differences in cell transplantation quantities, cell culture conditions and methods, characterization, and cell types, hinder clarity of interpretation of the outcomes. This trial marks the inaugural showcase of the potential applicability of MSCs originate from induced pluripotent stem cells (iPSCs) across various clinical targets.

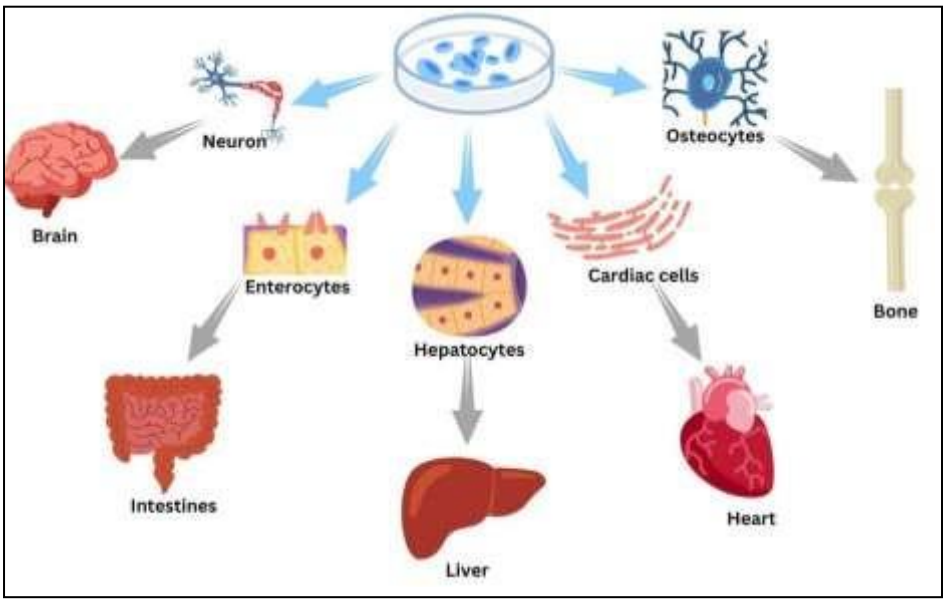

Figure 3: Careers in Stem Cell Research and Regenerative Medicine.

Wound Healing

Numerous circumstances can lead to wounds, including surgery, trauma, pathologic disorders like diabetes or vascular illnesses, or extrinsic stimuli like pressure, burns, and cuts. These kinds of harm are categorized as either acute or chronic wounds based on the underlying causes and outcomes. A structured and suitable healing process is typically followed by acute wounds, leading to the long-term restoration of anatomical and functional integrity [19]. Conversely, chronic wounds are unable to reach the best possible levels of functional and anatomical integrity. The nature, degree, and condition of the host and environment are all factors that influence and are related to pathological processes and healing. The course of wound healing may be impacted by systemic variables, including patient age, the existence of vascular, metabolic, and immunological disorders, as well as continued medication therapy.

Regenerative medicine aims to improve the healing process by using a multidisciplinary approach that addresses weaknesses in the physiological process of wound healing as well as issue solving through reparative approaches [20]. Studies in regenerative medicine offer several ways to encourage

and fasten the healing of wound: Biomaterials, growth factors, and have the capability to be employed straight to facilitate regrowth in either direction to modify the Conditions associated with wounds, speeding up recovery. This interdisciplinary strategy creates new opportunities for tissue regeneration in the future. To link medical professionals with scientific engineering backgrounds with business teams and steer innovative technologies toward a secure and efficient deployment, collaboration is essential [21].

To integrate patient needs with readily available technologies, one approach involves reviewing and analyzing the criteria established by different fields individually. These criteria can then be grouped together and assessed in clinical settings. In clinical practice, safety is a top issue. Regenerative medicine-related disorders and therapies need to be taken into consideration when doing a best-fit risk analysis. Given the wide variations in skin tone in various body regions, the lesion site ought to be the focus of both functional and cosmetic concerns.

A crucial element is the prompt clinical availability of these treatments, particularly in cases of acute injury or injuries that pose a life-threatening risk to the patient. The financial aspect is also significant; the expenses of new technology must be justified by high-quality results. Finally, considering the intricacy of its structure and function, it should be acknowledged that there is currently no perfect answer for skin regeneration. Nonetheless, cross-disciplinary cooperation offers a genuine chance to enhance therapeutic management of challenging wounds.

Osteoarthritis Treatment

The most prevalent type of arthritis is called osteoarthritis (OA), which is defined by morphological and physiological alterations including bone remodeling, osteophyte production, inflammation of the joints, and loss of joint function. In OA, the articular cartilage is the primary structure that is impacted; however, the entire joint is affected. Owing to its avascular and aneural characteristics, cartilage has a limited ability to regenerate, which limits the joint's capability for repair. Patients with OA have a considerable decline in their quality of life due to pain, restricted joint movement, and diminished function. Ocular arthritis (OA) is quite common in the world, which means that medical resources and socioeconomic expenses related to managing and treating OA are always rising [22]. Even though OA has a negative socioeconomic impact, patients currently have very few treatment options, and the majority of therapy techniques involve symptom control.

To do this, a number of techniques are used to lessen the patient's symptoms and slow the degenerative process's advancement. The main treatments include exercises, pharmacologic therapies, thermal therapies, self-management programs, intra-articular (IA) inject able treatments (e.g., hyaluronic acid and steroids), and surgical techniques [23]. The path physiology of OA is becoming more understood, and this includes the roles of signaling molecules, growth factors, and cytokines. This has led to new insights into cartilage regeneration and treatment.

Osteoarthritis cartilage regeneration has been given new life by tissue engineering and regenerative techniques based on biomaterials, cells, and other bioactive molecules [24]. Stem cell and platelet-rich plasma (PRP) injections, chondrocyte transplantation, and surgical techniques including micro fracture and autologous chondrocyte implantation (ACI) are the most often utilized restorative techniques for treating cartilage abnormalities. Surgical techniques like micro fracture and ACI have several drawbacks. ACI is associated with problems such as insufficient fusion, delamination, and graft failure, and its success rate varies.

ACI is not a practical solution for OA due to the extensive joint involvement and the inflammatory environment [25]. Aside from the fact that there are currently few long-term data on ACI, implanted chondrocytes may undergo undesired differentiation or death in the osteoarthritis environment, which could reduce therapy efficacy. The micro fracture (MF) technique, which is frequently employed to regenerate cartilage in OA patients, yields varying and inconsistent results in terms of cartilage repair quality [26]. The mechanical qualities of the "fibro cartilage" that develops during the MF procedure are much lower than those of normal articular cartilage.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) have demonstrated promising outcomes in the treatment of bone, tendon, and cartilage due to their capacity to develop into these tissues constituent cells [27]. MSCs have a high potential for multidirectional differentiation and reproduction. They also interact with the immune system to promote immunoregulation, migrate to the injury site to improve peripheral tissue tolerance, prevent the release of inflammatory factors, promote tissue repair, and increase the activity of injured cells. Neurogenic pain and down regulation of the pain pathway in general can be mitigated by reduced inflammation in the osteoarthritic joint. The inflammatory components of OA may benefit from these MSC characteristics. Through paracrine activity, which decreases cell death and inflammation while promoting cell proliferation and mobilization, MSCs also control chondrogenesis. MSCs use paracrine processes to deliver various signaling molecules to the body, such as extracellular vesicles, cytokines, and growth factors.

Through the absorption of local endogenous stem cells, stem cells can reduce synovial activation and mend cartilage damage by establishing a repair microenvironment. Additionally, the rat model using IA MSCs showed a decrease in apoptotic chondrocytes, indicating the anti-apoptosis impact of MSCs in the therapy of OA [28]. The best settings for MSCs to differentiate into chondrocytes are those that exclude serum, such as hydro gels, scaffold materials, and micro-mass. During the chondrogenic differentiation process, MSCs produce cartilaginous matrix constituents. In addition to interacting with chondrocytes or MSCs, this extracellular matrix (ECM) reconstruction can control tissue morphogenesis and remodeling as well as cell survival, differentiation, and migration.

Recent reviews and meta-analyses have shown conflicting findings. Migliorini et al. [29] observed gains in the McMaster and Western Ontario assessments as well as the visual analog scale (VAS). University Osteoarthritis (WOMAC) scores at six and twelve months of a systematic evaluation of knee OA treatment with stem cell injections. Additionally, they reported that the patients' Lequesne and Knee injury and Osteoarthritis Outcome Score (KOOS) scores improved and that their average walking distance increased. The authors came to the conclusion that bone marrow concentrate (BMC) knee OA might be a possibility based on the evidence that was available. As a result, every clinical and functional outcome saw a notable improvement.

Additionally, they noted that patients' results were noticeably better when they received treatment early in the degeneration process. Individuals with early- to moderately-advanced OA are thought to be suitable candidates for MSCs. The study by Harrel et al. [30] highlighted that the efficacy of MSCs can be impacted by the severity of OA. Autologous MSCs improved clinically and radiographically in mice with mild OA two months after IA injection, but in animals with severe OA, the benefits did not materialize until six months later. In a recent meta-analysis of 13 randomized controlled trials, Dai et al. [31] revealed no significant difference in the VAS, WOMAC pain, function, and stiffness scores for MSCs compared to placebo.

Cartilage Tissue Engineering

Tissue engineering links the production of biological replacements that preserve, enhance, or restore tissue function with the concepts and practices of biology and engineering. In tissue engineering, the right cells are seeded into a biocompatible scaffold. There are now two tissue engineering methods available. One involves implanting the construct into the joint after creating functioning tissue in vitro. The alternative method involves short-term cultivation, immature implantation, and in vivo maturation of the construct in its natural habitat. Tissue engineering has received a lot of interest in relation to cartilage healing because of its biological characteristics and low capacity for endogenous repair [32].

Scaffolds

Numerous scaffolds have been studied for tissue engineering cartilage. They can be categorized based on their chemical composition, structure (massive, porous, foams, viscous liquids, and hydro gels), or nature (protein, polysaccharide, synthetic, or natural). The following fundamental characteristics

of the perfect scaffolds must be present. To inhibit inflammatory and immunological reactions, they must be biocompatible and provide a three-dimensional environment that is conducive to the preservation of a differentiated chondrocyte phenotype. To facilitate the flow of chemicals and nutrients, they need also be permeable. They should be bioactive to permit the uniform and regulated release of growth factors and sticky to allow the fixing of cells in the lesion.
Lastly, they should be biodegradable to allow for long-term integration into host tissues and injections able to permit less invasive surgery.
Hydrogels are perhaps the most promising options due to their structure and characteristics, considering the possibility that cartilage tissue engineering will be successful both in vitro and ex vivo [33]. However, in medical settings Chains of artificial or naturally occurring absorbent macromolecules make up hydro gels. A reticulated hydro gel is formed as a result of chemical changes brought about by cross-linking agents (glutaraldehyde, radiation, pH, or temperature) [34]. The high percentage of water in the macromolecular network replicates the properties of the cartilaginous ECM's three-dimensional environment. The network density of hydro gels can be changed to change their porosity. Another benefit of hydro gels is that they may be injected, which allows for minimally invasive surgery [35], which lowers morbidity and the length of hospital stay. In order for these inject able scaffolds to take on the appropriate shape after being implanted, they must also be able to expand in volume. Preclinical research is being done to assess the mechanical characteristics of hydro gels.

Culture Conditions and Morphogens

Chondrocytes' differentiated phenotype can be preserved through three-dimensional culture. Furthermore, when dedifferentiated chondrocytes are cultivated in three dimensions, they regain their original phenotypic [36]. Only a portion of the molecular mechanisms underlying the processes of dedifferentiation and re-differentiation are known, although a crucial integrins' potential role has been suggested. Culture systems that are mechanically active and regulated are called bioreactors. The optimal bioreactor should boost ECM production, feeding, and oxygenation while providing the tissue with mechanical stimulation akin to in vivo circumstances.
Normal AC formation and regeneration depend on the physiological strain placed on the joint [37]. Both in vivo and in vitro chondrocyte behavior is influenced by mechanical stimulation. Nonetheless, it is generally agreed upon from in vitro mechanical loading experiments that dynamic compression boosts matrix synthetic activity while static compression promotes PG depletion, harms the collagen network, and reduces the synthesis of collagen matrix proteins. The selection of the optimal stimulation parameters is currently being assessed. Growth factors are among the morphogens that are primarily used to either differentiate MSC toward a chondrocytic phenotype or to maintain a chondrocytic phenotype. The maturation of chondrocytes and the creation of cartilage are influenced by several growth factors [38].

Gene Therapy

Gene therapy, which employs cells to produce therapeutic proteins in situ, is being studied with interest, even though most research is focused on developing growth factor delivery systems [39]. This kind of treatment attempts to promote the expression of genes involved in tissue regeneration processes in the context of cartilage tissue engineering. Potential candidates include genes encoding for different members of the TGF super family (e.g., TGF-b, BMPs), IGF-1, Sox family (e.g., -5, -6, and 9), FGF-3, and SMADs. Though gene therapy is still in its early stages of clinical application, it will need to undergo more in vitro and in vivo testing before it can be added to the list of treatments available for osteoarticular conditions.

4. Traditional Methods

Iron oxide Nanoparticles in Regenerative Medicine

Iron oxide nanoparticles (IONPs) are one of the most promising materials at the nanoscale; they ought to be functionalized with other bioactive substances, embedded in composites, and bound or taken up

by cells [40]. IONPs have become increasingly prevalent in drug delivery cases. Directed drug delivery is made possible with the influence of external magnetic fields or by utilizing specific binding proteins like antibodies. These approaches enable targeted delivery of therapeutic agents to be desired sites, improving treatment efficacy while minimizing off-target effects [41]. Stem cells, when loaded with IONPs, can differentiate into a wide range of cell types including myoblasts, adipocytes, chondrocytes, osteoblasts, and neuron-like cells. This versatility makes them valuable tools for tissue engineering and regenerative therapies aimed at repairing or replacing damaged tissues and organs [42].

Bone Regeneration

A key objective of regenerative medicine is the reconstruction of bone tissue. Stem cell differentiation under control and the creation of bone scaffolds using various materials are promising strategies. The utilization of iron oxide nanoparticles (IONPs) has been demonstrated to not only facilitate MRI imaging for visualizing the therapeutic process in addition to encouraging cell differentiation, enhance ontogenesis and enable targeted delivery of drugs or cells to the desired site through the application of magnetic fields. This multifunctional capability of IONPs enhances the efficacy and precision of therapeutic interventions in various biomedical applications [43].

IONPs have long been known to stimulate tissue repair, though the precise underlying mechanisms remain unknown. Wang et al. have demonstrated, through the use of gene microarray assays and bioinformatics analyses, that treatment with IONPs strongly regulates the gene expression of human bone marrow-derived mesenchymal stem cells (BM-MSCs) and activates the classical mitogen-activated protein kinase (MAPK) signaling pathway. This activation, in turn, regulates downstream genes and promotes osteogenic differentiation [44].

Following systemic injection into rat veins, Schulze et al. examined the effects of amino-polyvinyl alcohol (PVA)-coated IONPs on BM-MSCs. They discovered that these nanoparticles aggregated in the bone marrow, increasing the BM-MSCs' metabolic activity and rate of migration. Because of this, the particles have a lot of potential for bone marrow MRI imaging and may also prove helpful in the future for regenerative medicine applications [45]. Mechanotransduction is another way to favorably affect cell differentiation [46].

Peripheral and Central Nervous System Regenration

Numerous pathologies of the central nervous system(CNS) and peripheral nervous systems(PNS), including neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), ischemic stroke, amyotrophic lateral sclerosis (ALS), spinal cord injury, and multiple sclerosis (MS), have been treated with Progenitor and stem cells, in addition to developed cells such as adult neurons, Schwann cells, and astrocytes [47]. Patients with damaged neural tissue may benefit greatly from the application of nanotechnology in tissue engineering, drug delivery, and diagnostics. Hence, after implantation, transplanted cells can be tracked and monitored by employing IONP-labeling techniques for various cell types, including stem cells, astrocytes, and microglia. These techniques enable precise visualization and tracking of cell behavior and distribution in vivo, offering valuable insights into therapeutic outcomes and mechanisms [47].

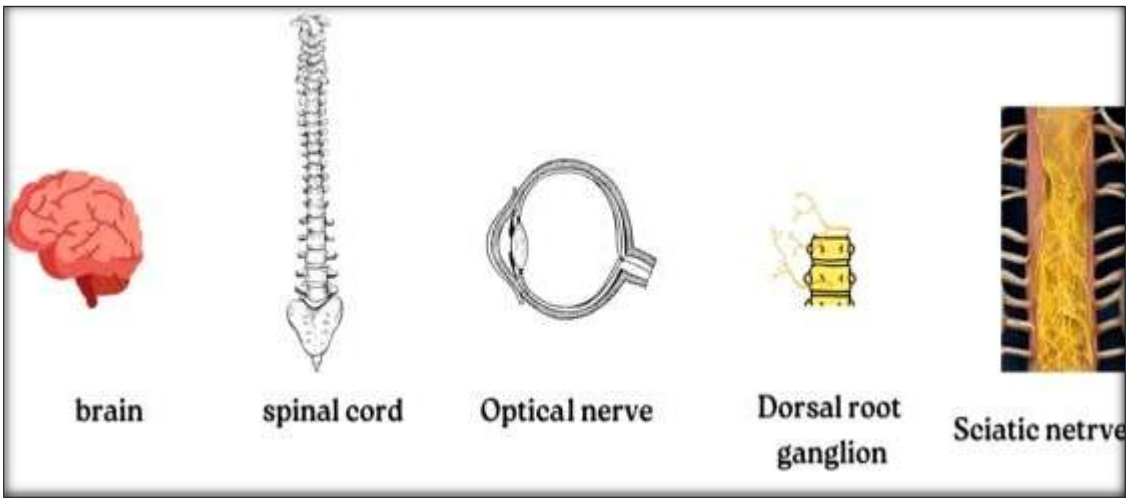

Figure 4: Potential targets in the peripheral and central nervous systems for IONP-assisted tissue engineering and tissue regeneration [48]

Furthermore, through specific nanoparticle functionalization, such as surface modification, IONP-loaded cells and IONPs can facilitate delivery of therapeutic biomolecules. This capability enhances the efficacy and precision of therapeutic interventions, including medicines, proteins, DNA, and siRNA, as well as neurotrophic factors. External magnet fields can be used to efficiently enrich IONP-loaded cells and functionalized IONPs at the site of injury in order to direct axonal development or facilitate neuronal healing [49].

Ultimately, scaffolds composed of diverse nanomaterials can be used to control hemostasis, prevent glial differentiation, encourage neuronal growth, and act as structural support. They can also be used to simulate or induce the production of an extracellular matrix. In this case, IONPs can be added to the biocomposite to enhance cellular differentiation, induce a certain neurite outgrowth or surface topology, or be employed for diagnostic purposes [50] The subsequent sections showcase more intriguing methods for treating CNS and PNS injuries, such as using stem cell therapy or nanomaterials as scaffolds for tissue engineering.

Figure 4 illustrates potential targets for IONP-assisted tissue engineering and PNS and CNS tissue regeneration. This tracking capability allows for the monitoring of therapy progress, assessment of functional recovery, and stem cell injection to the location of damage, among other applications. By offering ECM-like matrices or designing fiber scaffolds to regenerate axons, the usage of biomaterials can aid in regeneration. Moreover, using IONPs can improve regeneration capacity. Still, the particular NPs must be carefully chosen because they may cause negative reactions, even if they seem harmless under normal circumstances [51]. However, it has been demonstrated that IONPs can promote neuroregeneration through a variety of mechanisms; Indeed, nanoparticles possess unique properties that can positively impact various aspects of biomedicine. These capabilities open up exciting possibilities for the development of advanced therapies and biomedical applications [52].

Other Soft Tissue Regeneration

In regenerative medicine, treating voice problems such as vocal fold loss presents a significant difficulty. There are currently very few tissue-engineered or surgical methods available for the restoration of these problems [53]. In the interim, work is being done to construct the Vocal fold structures made with cells supplied with IONP. Vocal fold fibroblasts were obtained from rabbit laryngeal heads by Dürr et al., and IONPs were used to produce their magnetization. The same team described how IONP uptake affected cells and showed that magnetic cell guidance was feasible. They also hinted at the possibility of creating magnetic tissue-engineered three-dimensional vocal fold structures [54].

Acute renal damage combined with chronic kidney disease results in a significant death rate. The only available treatments at this time are kidney transplants and dialysis. Tissue engineering and

regenerative medicine, on the other hand, may be able to lessen treatment-related complications such organ shortages, transplant failure, and many more. In addition to applying effective cell-based techniques for repairing renal tissue, renal tissue engineering holds promise as a potential avenue for restoring normal kidney function in the future. Despite the intricate structure and function of the kidney, the use of nanomaterials in nephrology may offer advantages. This includes the manufacturing of renal medication nanotherapies, tracking the progression of chronic kidney disease, and detecting renal function. While this area hasn't been extensively studied yet, it presents exciting possibilities for improving kidney health and treatment outcomes [55]. MRI research demonstrated that induced pluripotent stem cell-derived mesenchymal stem cells (iPS-MSCs) were directed towards the renal parenchyma of animals with chronic kidney disease (CKD), successfully shielding the kidney from CKD damage.

The mortality rate of chronic liver disease has notably increased in recent years, imposing a significant financial and health burden. While liver transplantation remains the most effective treatment for end-stage liver fibrosis, its application is limited by immunological rejection and a shortage of organ donors. Stem cell therapy, including the use of iron oxide nanoparticles (IONPs), is an emerging option with expanding potential. While it is still unreliable to observe IONP-loaded cells for an extended period of time, multiple studies have shown that IONP-labeled cells can safely monitor liver therapy. For example, it has been demonstrated that bone marrow-derived mesenchymal stem cells (BM-MSCs) can decrease liver fibrosis and early hepatic dysplasia and can also speed up the recovery of the liver after hepatectomy. In a different study, MSC localization was improved by overexpressing human hepatocyte growth factor (HGF) in MSCs, which when combined with IONP labeling, aided in liver repair in a rat model of hepatic fibrosis.

Functionalized IONPs have also been demonstrated to have benefits for liver regeneration [56]. It is well known that fibroblast growth factor 2 (FGF2) has antifibrotic properties and can encourage tissue regeneration in fibrotic illnesses. Unlike free FGF2, FGF2-IONPs enhanced early hepatic fibrogenesis in vivo in the acute carbon tetrachloride-induced liver damage mouse model, as reported by Eftekhari et al.To enable magnetic-based EC accumulation on hepatocyte monolayers, Ito et al. (2004) used human aorta endothelial cells (ECs) coated with cationic magnetite liposomes. This innovative method was one of the first to use iron oxide nanoparticles (IONPs) to create 3D liver tissue that resembled vivo, producing a multilayered, heterotypic structure [57].

The authors found a considerable increase in albumin secretion and improved adsorption of heterotypic cells when they compared "magnetic force-based tissue engineering" (MagTE) to single cell cultures or co-cultures without a magnet. A different area of regenerative medicine was covered by Li et al. when they discussed the creation of biocompatible prosthetic bile conduits by tissue engineering. Using gelatin methacryloyl (GelMA) hydrogel and polycaprolactone (PCL) as the outside coating, they used 3D printing to produce a tubular composite scaffold with exceptional mechanical capabilities. To improve biocompatibility and enable MRI monitoring, ultra-small iron oxide nanoparticles (IONPs) were frequently used. The scaffold could be practically completely colonized and used as an artificial bile duct for implantation in the body by co-culturing with mesenchymal stem cells produced from bone marrow (BM-MSCs) [58].

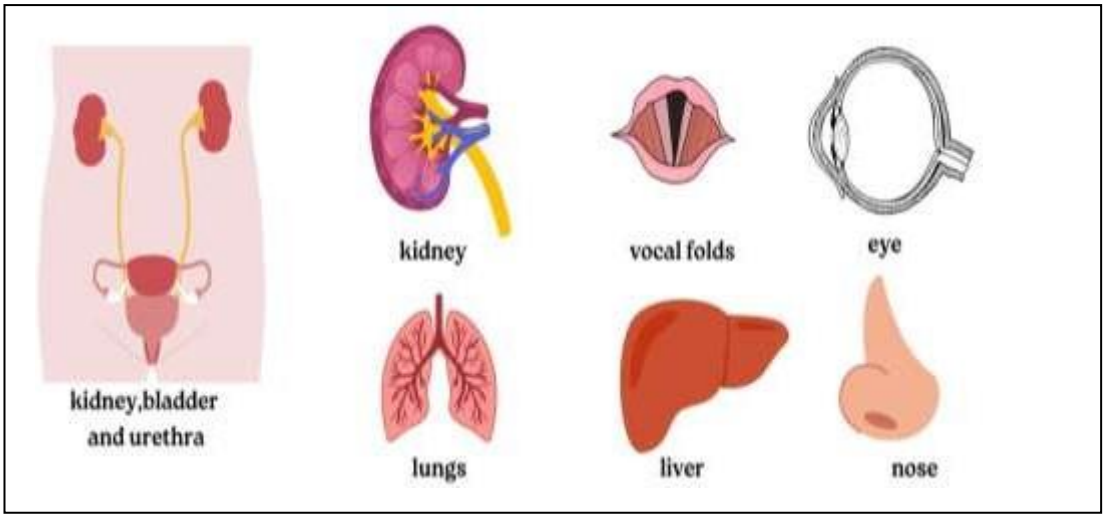

Figure 5: Potential targets for different soft tissue regeneration and tissue engineering supported by IONP

Cerium Oxide Nanoparticles

The goal of tissue engineering is to build structures out of scaffolds and cells in an effort to replace or restore missing organs and tissues without the need for expensive, time-consuming, and infrequently available organ transplants. Tissue-engineered implants are made biocompatible, closely mimic the extracellular matrix of the body, create a biomechanical niche that is physiologically relevant, and provide access to biological components necessary for successful tissue regeneration because of their nanoscale design. The creation of biocompatible nanomaterials, such as carbon nano tubes, nanoporous scaffolds, nanopatterned surfaces, nanofibers, nanowires, and NPs, is made easier by recent advancements in nanotechnology. Certain types of nanomaterials have specific uses in tissue engineering and regenerative medicine [59].

For instance, NPs are primarily used as carriers for the precise and regulated release of anti-inflammatory, antioxidant, and growth factor medications. Moreover, nanopatterned surfaces can be integrated into scaffolds to regulate various properties including mechanical characteristics, hardness, and biodegradation [60]. To create nanoporous materials, methods like etching, sol-gel processing, and electrochemical reactions are used. These materials exhibit enhanced surface area, activities associated with diffusion of pore size, superior cell integration and protein adsorption. For tissue engineering, particularly bone tissue engineering, they are a potential option, because of their effects [61].

Researchers have demonstrated that redox-cycling alone is responsible for all antioxidant activities in CeONPs, contradicting the earlier theory attributing antioxidant capabilities to oxygen vacancies and redox-cycling between cerium in 3+ and 4+ states. As a result, the biological activities of CeONPs, particularly in tissue regeneration, are explained by the surface ratio of Ce3+ to Ce4+. The delicately regulated balance between oxidants and antioxidants is maintained by human tissues and organs to sustain their activities. Oxidants are substances capable of generating reactive oxygen species (ROS), while antioxidants have the ability to prevent the oxidation of other molecules and scavenge these radical species [62].

Redox processes are generally thought of as being triggered by oxidants and antioxidants, or as reduction and oxidation events, respectively. However, Several natural antioxidant mechanisms are advantageous to every cell, including the thioredoxin system, glutathione (GSH) system, protective enzymes and different vitamins like superoxide dismutase (SOD) and catalase (CAT). These systems are redox-sensitive and capable of restoring the redox balance as needed. Numerous transcription factors regulated by redox conditions, such as the nuclear factor erythroid 2-associated factor 2 (Nrf2), also known as hypoxia-inducible factor (HIF), are involved in this process.

GSH and SOD are abundant in mitochondria, where aerobic metabolism occurs, while vitamin E is primarily located in the the plasma membrane. When there is stress from oxidation is present, cells are unable to maintain homeostasis because the production of oxidants, such as reactive oxygen species (ROS), increases excessively in comparison to the production of endogenous antioxidants [63]. A prolonged and substantial increase in reactive oxygen species (ROS) can cause the main cellular macromolecules to deteriorate, including lipids, deoxyribonucleic acid (DNA), and proteins. However, evidence indicates that a brief and moderate increase in ROS is essential for redox signaling, which plays a critical role in various processes such as inflammation and angiogenesis.

The future trajectory of clinical practice has been linked to therapeutic techniques that aim to activate redox-regulated transcription factors, such as HIF and Nrf2, as reported. On the other hand, CeONP's thermodynamic efficiency of redox cycling between 3+ and 4+ states on its surface and its noteworthy ability to absorb and release oxygen are responsible for the vast range of activities observed in it. Hence, a crucial component of research dealing with the possible application of CeONPs is the designed biomaterials of these perspectives [64].

For instance, Passi et al. devised a multifunctional carrier based on silk fibroin, combining the administration of imaging agents with antioxidants. Initially, silk fibroin nanoparticles (SFSNPs) containing the antioxidant sulforaphane were fabricated through a one-step desolvation process. Subsequently, self-assembling CeONP-CD@SFSNP nanocomposites were growing by linking cationic CeONPs with polyethylenimine (PEI)-passivated carbon dots (CDs) at the surface-level of these anionic nanoparticles via electrostatic interactions [65]. To generate positively charged CDs, mulberry leaves (Morus indica) were utilized as a green carbon source, with branched polyethyleneimine (bPEI) employed as a passivating agent.

The resulting CDs emitted green fluorescence, serving as molecular probes, although CeONPs was incorporated to enhance the capacity of antioxidant owing to their unique redox characteristics. The effective trapping size of the nanoparticles averaged 365 nm, with the sulforaphane content reaching 65.21%. The generated CeONP-CD@SFSNP nanocomposites allowed for the imaging of lung cancer cells under oxidative stress caused by H2O2, while also significantly reducing ROS levels. In this instance, sulforaphane activated the Nrf2 pathway, and CeONPs' mixed valency SOD and CAT mimicking activities enhanced antioxidant activity.

In addition, CDs increased the action of antioxidants. The entire nanozyme may be useful for treating a variety of lung conditions, including chronic obstructive pulmonary disease [66]. The capacity of these nanocomposites to mitigate oxidative stress may facilitate tissue regeneration processes. It is important to remember that Nrf2 activation serves as the molecular target for redox control. Because they work together to decrease oxidative damages and stimulate the Nrf2 pathway, these nanocomposites can serve as an excellent illustration of an inventive approach to reestablishing the oxidant and antioxidant balance required for tissue regeneration. Regarding the second chemical target, the HIF pathway, Nethi et al. employed functionalization techniques to enhance the CeONPs pro-angiogenic potential.

To achieve this, they conjugated hydrophilic, biocompatible, and antifouling moieties, specifically (6-(2-[2-[2-ethoxy-methoxy]-ethoxy]-ethoxy)-hexyl) triethoxysilane, with aqueous, dispersible CeO2 and trivalent metal (Sm) ion-doped CeO2 (SmCeO2) nanoparticles. When these nanoconjugates were added to treated endothelial cells, ROS levels were either optimized or decreased. Therefore, in a chick embryo model, functional nanoconjugates of SmCeO2 were found to stimulate the formation of blood vessels and promote endothelial cell proliferation [67]. Traditional methods have several drawbacks due to which researchers move towards advance techniques. Magnetic nanoparticles typically degrade and leach; they are not biocompatible and clump together due to the magnetic dipole-dipole attraction. These factors result in low stability and dispersity, which restricts their application. Without surface architecture, the colloidal suspension of magnetic nanoparticles is readily oxidized in air and vulnerable to losing its magnetism [68].

5. Advancement in Nanoparticle-enhanced Regenerative Medicine

Multidimensional Bioprinting of Tissues and Organs

In the present day, regenerative medicine has made great strides, and transplants of organs, including the liver, kidney, skin, and heart, are commonplace. Regenerative medicine is also frequently used to treat congenital defects [69]. This can be attributed to the development and understanding of stem cells, stem cell-based cell therapy/treatment, body parts, engineered organs [organs-on-chip, bioink-based organogenesis (material that mimics the physical characteristics of extracellular matter, such as tissue firmness, cross-linking process, thickness, bulk transfer attributes, e.g., transparency and diffusion)-based the organogenesis process], growth regulators or developers, biological materials, 3D/4D scaffold or bioprinting technology devices, prosthetics, bioreactor-scale organogenesis, and grafting (allo, auto, xenogenic), which separately or in combination have simulated tissue engineering products and devices to serve as practicable solutions.

The development of multidimensional tissues, organs, and organ systems is well established. Subsequently, the concept of printing multidimensional structures with cells emerged, advancing 3D bioprinting. The most popular types of 3D cell culture process are hydro gel in addition to premade scaffolds. To put it briefly, 3D or 4D systems are thought to be a workable substitute for in vivo organization. The US Food and Drug Administration (US FDA) has recognized and approved a number of multidimensional printing items, orthopedic devices, including medical instructions, implants, and customized restorative tools. Even with the majority of multidimensional printing techniques available today, medical applications have primarily involved the utilization of stiff, inanimate structures intended to serve as structural or space-filling prosthesis. The main characteristics of multidimensional printing technologies to create novel patient-specific goods are demonstrated by the most recent developments in the style and producing nonliving implantable multidimensional printed designs.

The fourth dimension of cell and tissue culture is an advanced dimension in regenerative medicine that has been created by the combined advancements in tissue engineering and micro fluidics. Some limitations, such creating hollow structures to create vascular constructs with multistage vasculatures and to create the right milieu for cell development, differentiation into thick 3D structure, and proliferation, still apply to three-dimensional organogenesis. Tissue engineering in the field of regenerative medicine research could be greatly impacted by 4D bioprinting, which could lead to more specialized and targeted methods that are simpler to implement in clinical settings. Numerous obstacles have been encountered in the multidimensional bioprinting for biological components. Their challenges include, but are not limited to, developing processes for growing and stem cells developing functional cells, maintaining the micro- and macro scale regulation of mechanical abilities, and artificial materials (metals, ceramics, and plastics) transitioning to biological functional materials.

Bioprinting Techniques

The most fascinating bioprinting technologies leverage the self-montage and auto sorting capabilities of cells, which can be classified into three main categories according to the principles: Bioprinting using extrusion, droplet, and laser assistance [70]. Each bioprinting method is unique and has pros and cons for printing speed, resolution, deposition speed, bioink compatibility, usability, cost, commercial availability, and basic biocompatibility. In extrusion-based bioprinting, the bioink is drawn into cylindrical filaments by using mechanical or pneumatic potential energy to resolve surface tension-induced droplet formation. This method differs from laser-based bioprinting, which uses laser technology to print cells precisely and efficiently on a substrate. Methods based on photopolymerization and methods depending on cellular transmission are the two main categories into which they can be separated. Finally, utilizing thermal, electrical, or acoustic energy to deposit and assemble microscopic bioink droplets layer by layer, droplet-based bioprinting prints the cells inside of them. Droplet-based bioprinting can be divided to these categories: bioprinting with micro valves, bioprinting with inkjets, electro hydrodynamic jetting, and acoustic droplet ejection.

Applications of Multiple Bioprinted Tissues

Recently, fascinating multidivisional in vitro models that are capable of accurately recapitulating the path physiology of particular objectives have emerged: engineered tissue/organ equivalents. In order to create new, live tissues for use in medicine, scaffolds and cells are frequently used in tissue engineering procedures. Despite major breakthroughs in synthetic tissue design, the inability of such standard approaches to build structures with specific architecture terrain and the spatial arrangement of cells has fuelled the quest for new alternatives. [71]. Multidimensional bioprinting a helpful method for creating multidimensional tissue/organ analogs is. A revolutionary era in the development and manufacturing of medical equipment is made possible. It is frequently applied to create multidimensional scaffolds by layer-by-layer deposition. Typically, a dispensing mechanism is used to deliver biomaterials to various space points, resulting in a scaffold with a precisely regulated design.

The manufacture of tissue-engineered constructs has benefited greatly from the excellent precision and repeatability of three-dimensional bioprinting at the manufacturing resolution. To replace products treated with biocompatible materials like natural and synthetic polymers, recently developed biodegradable metals, or organic and inorganic ceramic materials, techniques like stereo lithography, targeted laser sintering, fused deposition modeling, precision extrusion deposition, and 3D printing are used [72]. The integration of multidimensional printing technology with tissue engineering provides enhanced capabilities for the quick production of regulated tissue scaffolds with adjustable mechanical and structural topography, internal morphology, and porosity. By charging the specific medication or protein molecule, customized multifunctional physiognomy has been improved to direct the cellular environment.

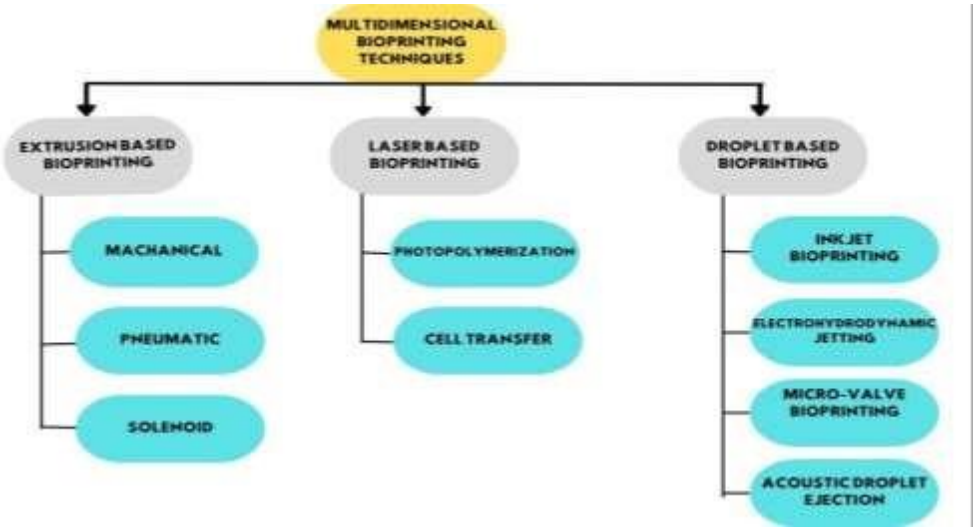

Figure 6: ioprinting Techniques [73]

Despite its many benefits for the biological growth of tissue scaffolds, interdisciplinary printing is limited, particularly in cases when challenging transplantation or organ application is required. Cell placement is necessary. It can be challenging to align cell placement for the seeding arrangement when building the scaffold. On the other hand, several cell kinds and classes are ordered and link with one another in a typical tissue and organ system in complex way. Large-density seed cells present additional challenges since they are limited to adhering to the scaffold's surface and are unable to penetrate the scaffold to access biomaterial within. Because biomaterials from scaffolds frequently take up a lot of room, cells are unable to proliferate to a suitable quantity.

The development of thick tissue and organs depends on the presence of a vascular network, which facilitates the efficient interchange of media necessary to keep the cells stable, oxygenated, and functionally viable [74]. These difficulties have prompted scientists to develop bioprinting methods, which involve enclosing cells in high densities and suitably printing and patterning them to create anatomically realistic tissue structures.

Cancer Treatment by Using Multidimensional Model

In comparison with 2D or monolayer culture, these models (3D or 4D) are more effective in treating both early-stage and late cancer. Due to its lack of structural architecture, the two-dimensional monolayer has important constraints. Multidimensional models can depict the various elements of a tumor microenvironment, including angiogenesis, hypoxia, necrosis, and cell adhesion topology, in an appropriately concise manner. Carrel adopted a multidimensional model for the first time in 1912. Carrel successfully raised explants from a chick embryo and maintained its viability for a duration of three months. By growing the tissues on a sponge matrix substrate, Leighton further enhanced the Carrel method. Subsequent research employing these model systems to treat cancer or tumors aided in the advancement. Histoculture, a far more sophisticated method of 3D culture, offers a number of benefits, including 3D growth, the preservation of structure and organization, customized cancer therapy by drug sensitivity testing, tumorigenicity, and in vitro differentiation of cancer stem cells (CSCs) [75].

The integration of sophisticated computational and mathematical techniques along with the recent development of novel innovations like micro fluidics may help overcome obstacles like development and repeatability. To be a definitive tool for regenerative medicine, such model systems still have a long way to go. In the future, screening the population for cancer may be a common procedure that offers an alternative for accurate and timely cancer diagnosis. Human beings are opposed to radiotherapy and chemotherapy [76] .

6. Theoretical and Clinical Investigation

Multidimensional organ cultures, such as 3D and 4D, are used in drug development, personalized medicine, mutagenesis, carcinogenesis, and drug screening. This is because, in contrast to single or monolayer cell culture systems, multidimensional organ cultures create a reproduction of the biological environment, which helps the model grow and interact with its atmosphere in all directions, improving the model's ability to imitate an in vivo cellular compartment. They are also able to replicate reliable results. These systems or models can be applied to patient care research as well as graduate student training in medicine.

One of the main problems is that, even in vivo situations like vascular pressure without leakage or aneurysm formation the created replica does not satisfy its cent percent criterion. Still, some of them are effective in tests including animal experiments. Secondly, the choice of biomaterial is crucial since it has to meet acceptable physiological criteria or function as a gold standard for a clinically acceptable biomaterial template. To create a successful translational product, interdisciplinary subjects must be original and possess high-caliber in-depth knowledge of several domains. Even so, TE has overcome obstacles to produce a number of successful products. The next difficulty is an industrial collaboration that complies with international standards or is certified [73].

Table 2: List of the companies dealing in field of regenerative medicine worldwide [73]

COUNTRY	COMPANY NAME	SPECIFIC FIELD
Australia	Living Cell Technologies	Regenerative medicine
USA	Regen BioPharma	Regenerative medicine, , small molecule cell therapy
USA	Histogen	Regenerative medicine
USA	Cellf BIO	Regenerative medicine related therapy for fecal incontinence
USA	Mesoblast	Regenerative medicine
European Union	Tikomed	Regenerative medicine
	Celixir	Regenerative medicine
Israel	Cellect Biosciences	Regenerative medicine
South Korea	MEDIPOST	Stem cell technology, Regenerative medicine
New Zealand	Living Cell Technologies	Regenerative medicine
Malaysia	Stempeutics Research Sdn. Bhd.	Therapeutics, regenerative medicine therapy

7. Nanoparticle Delivery System In Regenerative Medicine

Delivery Systems for Nanoparticulates For effective periodontal tissue regeneration, nanoparticles improve the in vivo efficacy of bioactive compounds by facilitating simple penetration, improving drug-release kinetics, and enabling regulated distribution. There are numerous types of Nanoparticulates delivery systems [77], such as micelles, liposome's, polymeric, solid lipid, inorganic, nanotube, dendrimer, and solid lipid nanoparticles. On the other hand, Nanoparticulates delivery strategies for periodontal tissue regeneration include.

Liposomes

Since liposomes have a bilayered structure, are biodegradable, biocompatible, non-toxic, and immuneogenic, they are widely known to be excellent drug delivery methods [78]. The polar head groups of liposomes are structurally oriented towards both the inner and outer aqueous phases, granting them the unique capacity to deliver molecules having diverse solubility. It has been shown that therapeutic biomolecules for periodontal regeneration can be delivered by the physical action of ultrasonography. plasmid DNA delivery technique into the gingiva [79], which could aid in the management of periodontitis. After developing "Bubble liposomes," a helpful carrier for delivering drugs or genes, Suganos et al. investigated the possibility of combining Bubble liposomes with ultrasound to transfer genes into gingival tissues. An effective method for transferring plasmid DNA into the gingiva was made possible by the combination of bubble liposomes and ultrasonography, which may aid in the treatment of periodontitis. Due to their combination of hydrophobic and hydrophilic properties, negatively charged liposomes are considered versatile tools in the realm of drug delivery systems [80].

A unique pH-activated nanoparticle called TMC-Lip-DOX NPs was created by Hu et al. using a liposome, doxycycline, and quaternary ammonium chitosan, also known as N, N, N-trimethyl chitosan. The results showed that TMC-Lip-DOX NPs had outstanding biocompatibility with hPDLSCs, could effectively prevent biofilm development, free mixed bacteria, and had good promise for treating periodontal inflammation. it's crucial to concentrate on the macrophage states of activation in bone regeneration because numerous studies have revealed that these cells can regulate inflammation resolution and healing by inhibiting proinflammatory stimuli, removing dead cells by efferocytosis, and enhancing neovascularization, which is necessary for tissue regeneration [81].

Since the structure and functionality of liposomes are quite similar to those of the biological environment, the drug payload of liposomes acts on macrophages by depositing lipid components at specific sites. This explains why, The suppression of TNF-α release in macrophages by 2% minocycline hydrochloride liposomes was shown to be much more effective than that of periocline and minocycline hydrochloride solution. This is crucial for reducing the damaging effects of cytokine-mediated tissue damage in periodontitis. minocycline hydrochloride liposomes synthesized by Liu et al. capable of targeting specific locations within macrophages, as liposomes present feasible objects for phagocytosis by natural macrophages [82].

The nonflavonoid polyphenol resveratrol (RSV) is well-known for its anti-inflammatory and immunomodulatory properties. In order to stop the spread of inflammation, in their study, Shi et al. created a unique liposomal system containing resveratrol (Lipo-RSV). They found that Lipo-RSV exhibited biocompatibility and was capable of altering the phenotype of inflammatory macrophages, shifting them via turning on p-STAT3 and suppressing p-STAT1, from M1 toward M2-like. Consequently, it led to a reduction in pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. This finding suggests Lipo-RSV can serve as a promising drug delivery system for periodontal diseases that do not necessitate antibiotic treatment. Although liposomes have been largely successful in drug delivery, despite their advantages, polymeric nanoparticles still encounter several challenges, including physical stability and restricted chemical, ,and complexities in optimizing the production process and drug leakage.Fortunately, many of these hurdles can be recovered and further enhancements could be achieved with changing the composition and properties of the vesicles [83].

Polymeric Nanoparticles

The advantageous metabolic and physicochemical features of polymers make them essential components of drug delivery systems. What set them apart from inorganic nanoparticles are properties including their lack of immunogenicity, biological inactivity, and the ability of functional groups to facilitate the covalent attachment of target moieties. Periodontal flaws have been treated with a wide range of polymeric nanoparticle-carriers, both natural and synthetic [84]. Additionally, a variety of techniques have been used to enhance the therapeutic impact of polymeric nano-drug delivery system (DDs), including structural customization, the use of biodegradable polymers in combination, and carrier surface modification to ensure extended retention at the injured areas [85]. These nanoparticles offer numerous advantageous properties such as biocompatibility, antibacterial activity, biodegradability, on-toxicity, and osteoinductive effects [86], Chitosan (CHT), derived from the deacetylation of chitin, stands out as one of the most extensively researched nanometric excipients for treating periodontal defects.

Unlike rigid synthetic polymers such as polyglycolic acid (PGA) and polylactic acid (PLA), chitosan exhibits flexibility in humid environments. Chitosan has been utilized to promote good periodontal tissue repair because of its biodegradability profile, which allows it to be kept in place as a barrier for up to 4-6 weeks. There have been reports on the biodegradation of chitosan membrane manufactured using various methods; after 90 days at room temperature in phosphate buffer saline (PBS), pure chitosan membrane degraded by 15–40% [87]. In a different study, the rate at which chitosan degrades and releases itself can be adjusted for a particular duration in the process of bone tissue regeneration. Chitosan possesses a cationic nature and can produce stable complexes having great number of polyanionic molecules, such as nucleotides, making it a potential carrier for gene delivery without the need for viruses. However, while chitosan may be beneficial for addressing osseous abnormalities, its osteoconductivity requires enhancement for optimal bone regeneration. To improve its bioactivity, chitosan can be combined with other bioactive substances. Recent studies have shown that composite biomaterials incorporating bioactive glasses and biodegradable polymers exhibit favorable osteoconductivity, bioactivity, and biocompatibility both in vitro and in vivo. To facilitate guided bone regeneration, Mota et al. proposed combining chitosan (CHT) with bioactive glass nanoparticles (BG-NPs). Their research revealed that their addition to CHT membranes led to a reduction in mechanical properties but enhanced bioactivity. This enhancement included promoting cell mineralization and metabolic activity, in addition to causing simulated bodily fluid (SBF) to deposit bone-like apatite [87].

Nanogels are tiny, water-loving polymer networks that have gained a lot of attention for delivering drugs. These nanosized gels are popular because they're biocompatible, stable, customizable in size, and can hold a lot of drugs. Plus, their surfaces can be modified for precise and efficient targeting. With diameters under 200 nm, nanogels are excellent carriers for peptides, siRNAs, and medicines. Nanogels can also be added to tissue scaffolds to influence cell behavior, altering the scaffold’s structure, mechanical properties, and texture. Moreover, they help prevent proteins from clumping together or breaking down. For example, proteins within these cross-linked nanogels remain stable even at high temperatures and in the presence of organic solvents. [88].

Alles and colleagues investigated the potential of a drug delivery system using cholesterol-bearing pullulan (CHP) nanogel, with the TNF-α and RANKL antagonist W9-peptide as a model. Their research showed that the CHP-nanogel was easy to use for transporting peptides in living organisms, effectively serving as a carrier for the W9-peptide and preventing it from clumping together. This indicates that CHP-nanogel might be capable of reducing bone resorption by facilitating the controlled delivery of peptides. In addition, He and his team have developed an innovative asymmetric barrier membrane to overcome the shortcomings of conventional membranes, which often do not have adequate bone-forming (osteoconductive) and antibacterial properties.The key component of this barrier membrane is a nanoscale agarose hydrogel, sedimented within agarose to create an asymmetrical structure. These features, combined with the membrane's enhanced biocompatibility and mechanical strength, suggest it could be useful in periodontal tissue engineering. Poly (lactic-co-

glycolic acid) (PLGA), a synthetic biodegradable polymer, is favored for therapeutic drug delivery systems due to its biodegradability, biocompatibility, suitable degradation rates, and adjustable mechanical properties. Its versatility allows for the encapsulation and delivery of a wide range of both water-soluble and water-insoluble compounds. Researchers have explored using PLGA nanoparticles to deliver BMP2 as a key component. Additionally, there's ongoing research to develop a blend of silver nanoparticles, chitosan, and PLGA [89].

Inorganic Nanoparticles and Nanocrystals

The two inorganic nanoparticles that are most commonly studied for the treatment of periodontitis are calcium-containing nano-biomaterials for bone regeneration and metallic nanoparticles with antibacterial and regenerative properties. Inorganic nanoparticles have a number of advantages over organic ones, including long-lasting activity, chemical stability, and resistance to heat. Strontium cation (Sr^{2+}) has been found to inhibit osteoclast activity, facilitating the mesenchymal stem cells (MSCs) differentiation in the bone tissue. Due to its dual biological activity of promoting bone formation (osteoanabolic) while inhibiting bone resorption (anti-resorptive), as a medicinal agent, strontium ranelate has been approved to help with bone rebuilding and manage osteoporosis.Recent research has shown that strontium treatment dramatically boosted the expression of genes linked to osteoblasts and osteogenic-differentiating MSCs' alkaline phosphatase (ALP) [90].

Marins et al. looked at how strontium ranelate affected rats with different levels of estrogen that had ligature-induced periodontitis. Their findings indicated that strontium ranelate partially increased trabecular bone area in both estrogen-deficient and estrogen-sufficient conditions. Particularly, it demonstrated efficacy in preventing rats lacking in estrogen experienced bone loss due to ligatures. Additionally, the compound seemed to exert an anti-resorptive effect by disrupting the production of bone markers. In a related study, Miranda and colleagues examined how strontium ranelate affected the way that tooth extraction wounds healed in rats with various estrogen levels.The optimal nano-DDSs for periodontal regeneration should be able to limit the activity of both bacterial pathogens and favor osseointegration with host tissues. For this reason, a method of adding ceramic-based nanoparticles to polymers has been suggested [91]. To enhance the osteo/odontogenic potential of human mesenchymal stem cells, a separate investigation described the incorporation of phenamil, an activator of the bone morphogenetic protein (BMP), into strontium-doped mesoporous bioglass nanoparticles.

Zamani et al. discovered that these composites might enhance the antibacterial qualities, bioactivity of alginate, and mechanical strength in their investigation into the impacts of adding zinc and magnesium ions into bioactive glasses. This could have main applications in the regeneration of bone tissue. According to reports, silver and zinc-based nanoparticles (NPs) have a major impact on enhancing osteogenic qualities and squelching bacterial activity [92]. However, when these NPs degrade, the body may accumulate heavy metal elements [93]. Magnesium oxide nanoparticles (nMgO) have attracted considerable interest in recent biomedical research focused on periodontal regeneration, thanks to their recognized benefits in promoting osteoinductivity and antimicrobial properties. In a study by Liu et al., it was shown that the osteoinductive effect of magnesium ions, which is dose-dependent, was observed a poly (L-lactic acid) (PLA)/gelatin periodontal membrane along with MgO nanoparticles incorporated in rabbit bone marrow stem cells (rBMSCs) [94].

Conclusion

Regenerative medicine has the potential to completely transform healthcare by repairing harmed tissues and organs using the body's naturals healing processes. Nanoparticles can be used as flexible instruments in regenerative medicine, surpassing the limitations of conventional therapy. Nanoparticles provide a variety of opportunities to enhance regeneration processes, including targeted drug administration, imaging, and tissue engineering. They are the perfect choice for precisely controlling cellular behavior and delivering therapeutic cargo due to their compact size, great surface area-to-volume ratio, and changeable surface chemistry.

Historical turning points show how uses for nanoparticles have developed over time, from preliminary studies to complex drug delivery schemes intended to promote tissue regeneration and repair. Early investigations reveal the fundamental principles established by the field's pioneers, and significant turning points emphasize the revolutionary potential of nanoparticle interventions. Regenerative medicine is starting to rely heavily on nanoparticle drug delivery technologies, which provide precise control over therapeutic payloads to maximize efficacy and reduce side effects. This study concludes by summarizing the revolutionary field of nanoparticle-enhanced regenerative therapies, which is situated at the nexus of cutting-edge research and practical application. Nanoparticle technologies have great promise for transforming patient care and meeting unmet medical needs as we stand on the brink of extraordinary discoveries. Researchers can advance regenerative medicine by utilizing the special qualities of nanoparticles, opening up new avenues for the precise and effective regeneration of damaged tissues in the future.

Reference

1. R. P. Friedrich, I. Cicha, and C. Alexiou, "Iron oxide nanoparticles in regenerative medicine and tissue engineering," *Nanomaterials,* vol. 11, p. 2337, 2021.
2. A. Bayes-Genis, P. Gastelurrutia, M.-L. Cámara, A. Teis, J. Lupón, C. Llibre, E. Zamora, X. Alomar, X. Ruyra, and S. Roura, "First-in-man safety and efficacy of the adipose graft transposition procedure (AGTP) in patients with a myocardial scar," *EBioMedicine,* vol. 7, pp. 248-254, 2016.
3. K. Chaudhury, V. Kumar, J. Kandasamy, and S. RoyChoudhury, "Regenerative nanomedicine: current perspectives and future directions," *International Journal of Nanomedicine,* pp. 4153-4167, 2014.
4. J. Bartunek, A. Terzic, B. A. Davison, G. S. Filippatos, S. Radovanovic, B. Beleslin, B. Merkely, P. Musialek, W. Wojakowski, and P. Andreka, "Cardiopoietic cell therapy for advanced ischaemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 clinical trial," *European heart journal,* vol. 38, pp. 648-660, 2017.
5. M. Fathi-Achachelouei, H. Knopf-Marques, C. E. Ribeiro da Silva, J. Barthès, E. Bat, A. Tezcaner, and N. E. Vrana, "Use of nanoparticles in tissue engineering and regenerative medicine," *Frontiers in bioengineering and biotechnology,* vol. 7, p. 113, 2019.
6. I. Martin, P. J. Simmons, and D. F. Williams, "Manufacturing challenges in regenerative medicine," *Science translational medicine,* vol. 6, pp. 232fs16-232fs16, 2014.
7. Q. Ullah, M. Qasim, A. Abaidullah, R. Afzal, A. Mahmood, A. Fatima, and I. Haidri, "EXPLORING THE INFLUENCE OF NANOPARTICLES AND PGPRS ON THE PHYSICO-CHEMICAL CHARACTERISTICS OF WHEAT PLANTS: A REVIEW," *EPH-International Journal of Agriculture and Environmental Research,* vol. 10, pp. 1-9, 2024.
8. L. Zhang and T. J. Webster, "Nanotechnology and nanomaterials: promises for improved tissue regeneration," *Nano today,* vol. 4, pp. 66-80, 2009.
9. C. Ding, L. Tong, J. Feng, and J. Fu, "Recent Advances in Stimuli-Responsive Release Function Drug Delivery Systems for Tumor Treatment," *Molecules,* vol. 21, p. 1715, 2016.
10. A. Petrosyan, P. N. Martins, K. Solez, B. E. Uygun, V. S. Gorantla, and G. Orlando, "Regenerative medicine applications: An overview of clinical trials," *Frontiers in Bioengineering and Biotechnology,* vol. 10, p. 942750, 2022.
11. A. Porcellini, "Regenerative medicine: a review," *Revista Brasileira de Hematologia e Hemoterapia,* vol. 31, pp. 63-66, 2009.
12. J. S. Rink, M. P. Plebanek, S. Tripathy, and C. S. Thaxton, "Update on current and potential nanoparticle cancer therapies," *Current Opinion in Oncology,* vol. 25, pp. 646-651, 2013.
13. Q. Vu, K. Xie, M. Eckert, W. Zhao, and S. C. Cramer, "Meta-analysis of preclinical studies of mesenchymal stromal cells for ischemic stroke," *Neurology,* vol. 82, pp. 1277-1286, 2014.

14. Y. Shi, Y. Wang, Q. Li, K. Liu, J. Hou, C. Shao, and Y. Wang, "Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases," *Nature Reviews Nephrology,* vol. 14, pp. 493-507, 2018.
15. A. Saad, A. B. Dietz, S. M. Herrmann, L. J. Hickson, J. F. Glockner, M. A. McKusick, S. Misra, H. Bjarnason, A. S. Armstrong, and D. A. Gastineau, "Autologous mesenchymal stem cells increase cortical perfusion in renovascular disease," *Journal of the American Society of Nephrology: JASN,* vol. 28, p. 2777, 2017.
16. L. Ye, L. Li, B. Wan, M. Yang, J. Hong, W. Gu, W. Wang, and G. Ning, "Immune response after autologous hematopoietic stem cell transplantation in type 1 diabetes mellitus," *Stem Cell Research & Therapy,* vol. 8, pp. 1-10, 2017.
17. H. Zhang, J. Liang, X. Tang, D. Wang, X. Feng, F. Wang, B. Hua, H. Wang, and L. Sun, "Sustained benefit from combined plasmapheresis and allogeneic mesenchymal stem cells transplantation therapy in systemic sclerosis," *Arthritis Research & Therapy,* vol. 19, pp. 1-8, 2017.
18. V. Tanavde, C. Vaz, M. S. Rao, M. C. Vemuri, and R. R. Pochampally, "Research using Mesenchymal Stem/Stromal Cells: quality metric towards developing a reference material," *Cytotherapy,* vol. 17, pp. 1169-1177, 2015.
19. E. M. Tottoli, R. Dorati, I. Genta, E. Chiesa, S. Pisani, and B. Conti, "Skin wound healing process and new emerging technologies for skin wound care and regeneration," *Pharmaceutics,* vol. 12, p. 735, 2020.
20. C. Pang, A. Ibrahim, N. W. Bulstrode, and P. Ferretti, "An overview of the therapeutic potential of regenerative medicine in cutaneous wound healing," *International Wound Journal,* vol. 14, pp. 450-459, 2017.
21. K. Safferling, T. Sütterlin, K. Westphal, C. Ernst, K. Breuhahn, M. James, D. Jäger, N. Halama, and N. Grabe, "Wound healing revised: a novel reepithelialization mechanism revealed by in vitro and in silico models," *Journal of Cell Biology,* vol. 203, pp. 691-709, 2013.
22. N. Sahin and H. Yesil, "Regenerative methods in osteoarthritis," *Best Practice & Research Clinical Rheumatology,* p. 101824, 2023.
23. S. L. Kolasinski, T. Neogi, M. C. Hochberg, C. Oatis, G. Guyatt, J. Block, L. Callahan, C. Copenhaver, C. Dodge, and D. Felson, "2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee," *Arthritis & rheumatology,* vol. 72, pp. 220-233, 2020.
24. J. M. Patel, K. S. Saleh, J. A. Burdick, and R. L. Mauck, "Bioactive factors for cartilage repair and regeneration: improving delivery, retention, and activity," *Acta Biomaterialia,* vol. 93, pp. 222-238, 2019.
25. G.-I. Im, "Tissue engineering in osteoarthritis: current status and prospect of mesenchymal stem cell therapy," *BioDrugs,* vol. 32, pp. 183-192, 2018.
26. B. M. Devitt, S. W. Bell, K. E. Webster, J. A. Feller, and T. S. Whitehead, "Surgical treatments of cartilage defects of the knee: systematic review of randomised controlled trials," *The Knee,* vol. 24, pp. 508-517, 2017.
27. L. Kong, L.-Z. Zheng, L. Qin, and K. K. Ho, "Role of mesenchymal stem cells in osteoarthritis treatment," *Journal of orthopaedic translation,* vol. 9, pp. 89-103, 2017.
28. Y. Ju, L. Yi, C. Li, T. Wang, W. Zhang, W. Chai, X. Yin, and T. Weng, "Comparison of biological characteristics of human adipose-and umbilical cord-derived mesenchymal stem cells and their effects on delaying the progression of osteoarthritis in a rat model," *Acta histochemica,* vol. 124, p. 151911, 2022.
29. F. Migliorini, B. Rath, G. Colarossi, A. Driessen, M. Tingart, M. Niewiera, and J. Eschweiler, "Improved outcomes after mesenchymal stem cells injections for knee osteoarthritis: results at 12-months follow-up: a systematic review of the literature," *Archives of orthopaedic and trauma surgery,* vol. 140, pp. 853-868, 2020.

30. C. R. Harrell, B. S. Markovic, C. Fellabaum, A. Arsenijevic, and V. Volarevic, "Mesenchymal stem cell-based therapy of osteoarthritis: Current knowledge and future perspectives," *Biomedicine & pharmacotherapy,* vol. 109, pp. 2318-2326, 2019.
31. W. Dai, X. Leng, J. Wang, Z. Shi, J. Cheng, X. Hu, and Y. Ao, "Intra-articular mesenchymal stromal cell injections are no different from placebo in the treatment of knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials," *Arthroscopy: The Journal of Arthroscopic & Related Surgery,* vol. 37, pp. 340-358, 2021.
32. G. A. Ateshian, "Weaving in three dimensions," *Nature materials,* vol. 6, pp. 89-90, 2007.
33. D. Nesic, R. Whiteside, M. Brittberg, D. Wendt, I. Martin, and P. Mainil-Varlet, "Cartilage tissue engineering for degenerative joint disease," *Advanced drug delivery reviews,* vol. 58, pp. 300-322, 2006.
34. J. L. Drury and D. J. Mooney, "Hydrogels for tissue engineering: scaffold design variables and applications," *Biomaterials,* vol. 24, pp. 4337-4351, 2003.
35. C. Vinatier, D. Magne, A. Moreau, O. Gauthier, O. Malard, C. Vignes-Colombeix, G. Daculsi, P. Weiss, and J. Guicheux, "Engineering cartilage with human nasal chondrocytes and a silanized hydroxypropyl methylcellulose hydrogel," *Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials,* vol. 80, pp. 66-74, 2007.
36. J. Malda, C. Van Blitterswijk, M. Grojec, D. Martens, J. Tramper, and J. Riesle, "Expansion of bovine chondrocytes on microcarriers enhances redifferentiation," *Tissue engineering,* vol. 9, pp. 939-948, 2003.
37. J. P. A. Arokoski, J. Jurvelin, U. Väätäinen, and H. Helminen, "Normal and pathological adaptations of articular cartilage to joint loading," *Scandinavian Journal of Medicine & Science in Sports: Review article,* vol. 10, pp. 186-198, 2000.
38. [38] M. Hirao, N. Tamai, N. Tsumaki, H. Yoshikawa, and A. Myoui, "Oxygen tension regulates chondrocyte differentiation and function during endochondral ossification," *Journal of Biological Chemistry,* vol. 281, pp. 31079-31092, 2006.
39. [39] A. Saraf and A. G. Mikos, "Gene delivery strategies for cartilage tissue engineering," *Advanced drug delivery reviews,* vol. 58, pp. 592-603, 2006.
40. R. P. Friedrich, C. Janko, H. Unterweger, S. Lyer, and C. Alexiou, "SPIONs and magnetic hybrid materials: Synthesis, toxicology and biomedical applications," *Physical Sciences Reviews,* vol. 8, pp. 1435-1464, 2023.
41. I. Cicha and C. Alexiou, "Cardiovascular applications of magnetic particles," *Journal of Magnetism and Magnetic Materials,* vol. 518, p. 167428, 2021.
42. N. Ashammakhi, O. Kaarela, and P. Ferretti, "Pulling and pushing stem cells to control their differentiation," *Journal of Craniofacial Surgery,* vol. 29, pp. 804-806, 2018.
43. Y. Li, D. Ye, M. Li, M. Ma, and N. Gu, "Adaptive materials based on iron oxide nanoparticles for bone regeneration," *ChemPhysChem,* vol. 19, pp. 1965-1979, 2018.
44. Q. Wang, B. Chen, M. Cao, J. Sun, H. Wu, P. Zhao, J. Xing, Y. Yang, X. Zhang, and M. Ji, "Response of MAPK pathway to iron oxide nanoparticles in vitro treatment promotes osteogenic differentiation of hBMSCs," *Biomaterials,* vol. 86, pp. 11-20, 2016.
45. F. Schulze, A. Gramoun, L. A. Crowe, A. Dienelt, T. Akcan, H. Hofmann, J.-P. Vallee, G. N. Duda, and A. Ode, "Accumulation of amino-polyvinyl alcohol-coated superparamagnetic iron oxide nanoparticles in bone marrow: implications for local stromal cells," *Nanomedicine,* vol. 10, pp. 2139-2151, 2015.
46. M. Rotherham, J. R. Henstock, O. Qutachi, and A. J. El Haj, "Remote regulation of magnetic particle targeted Wnt signaling for bone tissue engineering," *Nanomedicine: Nanotechnology, Biology and Medicine,* vol. 14, pp. 173-184, 2018.

47. T. A. Kolagar, M. Farzaneh, N. Nikkar, and S. E. Khoshnam, "Human pluripotent stem cells in neurodegenerative diseases: potentials, advances and limitations," *Current stem cell research & therapy*, vol. 15, pp. 102-110, 2020.
48. R. Friedrich, I. Cicha, and C. Alexiou, "Iron Oxide Nanoparticles in Regenerative Medicine and Tissue Engineering. Nanomaterials 2021, 11, 2337," ed: s Note: MDPI stays neutral with regard to jurisdictional claims in published …, 2021.
49. S. J. Gwak, H. Koo, Y. Yun, J. Y. Yhee, H. Y. Lee, D. H. Yoon, K. Kim, and Y. Ha, "Multifunctional nanoparticles for gene delivery and spinal cord injury," *Journal of Biomedical Materials Research Part A*, vol. 103, pp. 3474-3482, 2015.
50. P. A. Soto, M. Vence, G. M. Piñero, D. F. Coral, V. Usach, D. Muraca, A. Cueto, A. Roig, M. B. F. Van Raap, and C. P. Setton-Avruj, "Sciatic nerve regeneration after traumatic injury using magnetic targeted adipose-derived mesenchymal stem cells," *Acta biomaterialia*, vol. 130, pp. 234-247, 2021.
51. A. Umashankar, M. J. Corenblum, S. Ray, M. Valdez, E. S. Yoshimaru, T. P. Trouard, and L. Madhavan, "Effects of the iron oxide nanoparticle Molday ION Rhodamine B on the viability and regenerative function of neural stem cells: relevance to clinical translation," *International journal of nanomedicine*, pp. 1731-1748, 2016.
52. M. Roet, S.-A. Hescham, A. Jahanshahi, B. P. Rutten, P. O. Anikeeva, and Y. Temel, "Progress in neuromodulation of the brain: A role for magnetic nanoparticles?," *Progress in neurobiology*, vol. 177, pp. 1-14, 2019.
53. S. Lee, S. Seon, K. Park, and J. Ryu, "Vocal fold reconstruction using an autologous pedicled fat flap in a rabbit model," *The Laryngoscope*, vol. 130, pp. 1770-1774, 2020.
54. M. Pöttler, A. Fliedner, J. Bergmann, L. K. Bui, M. Mühlberger, C. Braun, M. Graw, C. Janko, O. Friedrich, and C. Alexiou, "Magnetic tissue engineering of the vocal fold using superparamagnetic iron oxide nanoparticles," *Tissue Engineering Part A*, vol. 25, pp. 1470-1477, 2019.
55. M. L. Soriano, A. Rodríguez-Benot, and M. Valcárcel, "Nanotechnological foundations of a "new" Nephrology," *Nefrología (English Edition)*, vol. 38, pp. 362-372, 2018.
56. A. Eftekhari, A. Arjmand, A. Asheghvatan, H. Švajdlenková, O. Šauša, H. Abiyev, E. Ahmadian, O. Smutok, R. Khalilov, and T. Kavetskyy, "The potential application of magnetic nanoparticles for liver fibrosis theranostics," *Frontiers in Chemistry*, vol. 9, p. 674786, 2021.
57. D. W. Kurniawan, R. Booijink, L. Pater, I. Wols, A. Vrynas, G. Storm, J. Prakash, and R. Bansal, "Fibroblast growth factor 2 conjugated superparamagnetic iron oxide nanoparticles (FGF2-SPIONs) ameliorate hepatic stellate cells activation in vitro and acute liver injury in vivo," *Journal of controlled release*, vol. 328, pp. 640-652, 2020.
58. H. Li, Y. Yin, Y. Xiang, H. Liu, and R. Guo, "A novel 3D printing PCL/GelMA scaffold containing USPIO for MRI-guided bile duct repair," *Biomedical Materials*, vol. 15, p. 045004, 2020.
59. I. Armentano, M. Dottori, E. Fortunati, S. Mattioli, and J. Kenny, "Biodegradable polymer matrix nanocomposites for tissue engineering: a review," *Polymer degradation and stability*, vol. 95, pp. 2126-2146, 2010.
60. I. Haidri, M. Qasim, M. Shahid, M. M. Farooq, M. Q. Abbas, R. Fatima, W. Shoukat, and Q. Ullah, "Enhancing the Antioxidant Enzyme Activities and Soil Microbial Biomass of tomato plants against the stress of Sodium Dodecyl Sulfate by the application of bamboo biochar," *Remittances Review*, vol. 9, pp. 1609-1633, 2024.
61. J. Luo, S. Zhu, Y. Tong, Y. Zhang, Y. Li, L. Cao, M. Kong, M. Luo, Q. Bi, and Q. Zhang, "Cerium oxide nanoparticles promote osteoplastic precursor differentiation by activating the Wnt pathway," *Biological Trace Element Research*, vol. 201, pp. 865-873, 2023.
62. S. Oter, S. Jin, L. Cucullo, and H. D. Dorman, "Oxidants and antioxidants: friends or foes?," *Oxidants and antioxidants in medical science*, vol. 1, p. 1, 2012.

63. H. Sies, "Oxidative stress: a concept in redox biology and medicine," *Redox biology,* vol. 4, pp. 180-183, 2015.
64. X. Chen, C. Guo, and J. Kong, "Oxidative stress in neurodegenerative diseases," *Neural regeneration research,* vol. 7, p. 376, 2012.
65. S. Perveen, I. A. Bhatti, S. Jamil, A. Ghaffar, A. Faiz, and R. Sulaiman, "Carbon Dots: Synthetic Routes, Optical Properties, and Emerging Applications."
66. M. Passi, V. Kumar, and G. Packirisamy, "Theranostic nanozyme: Silk fibroin based multifunctional nanocomposites to combat oxidative stress," *Materials Science and Engineering: C,* vol. 107, p. 110255, 2020.
67. S. K. Nethi, H. S. Nanda, T. W. Steele, and C. R. Patra, "Functionalized nanoceria exhibit improved angiogenic properties," *Journal of Materials Chemistry B,* vol. 5, pp. 9371-9383, 2017.
68. U. S. Ezealigo, B. N. Ezealigo, S. O. Aisida, and F. I. Ezema, "Iron oxide nanoparticles in biological systems: Antibacterial and toxicology perspective," *JCIS Open,* vol. 4, p. 100027, 2021.
69. A. M. Bailey, M. Mendicino, and P. Au, "An FDA perspective on preclinical development of cell-based regenerative medicine products," *Nature biotechnology,* vol. 32, pp. 721-723, 2014.
70. I. T. Ozbolat, K. K. Moncal, and H. Gudapati, "Evaluation of bioprinter technologies," *Additive Manufacturing,* vol. 13, pp. 179-200, 2017.
71. Y.-J. Seol, H.-W. Kang, S. J. Lee, A. Atala, and J. J. Yoo, "Bioprinting technology and its applications," *European Journal of Cardio-Thoracic Surgery,* vol. 46, pp. 342-348, 2014.
72. I. T. Ozbolat and M. Hospodiuk, "Current advances and future perspectives in extrusion-based bioprinting," *Biomaterials,* vol. 76, pp. 321-343, 2016.
73. P. Shankar, J. Jagtap, G. Sharma, G. P. Sharma, J. Singh, M. Parashar, G. Kumar, S. Mittal, M. K. Sharma, and K. Jadhav, "A revolutionary breakthrough of bionanomaterials in tissue engineering and regenerative medicine," in *Bionanotechnology: Emerging Applications of Bionanomaterials*, ed: Elsevier, 2022, pp. 399-441.
74. P. Datta, B. Ayan, and I. T. Ozbolat, "Bioprinting for vascular and vascularized tissue biofabrication," *Acta biomaterialia,* vol. 51, pp. 1-20, 2017.
75. R. M. Hoffman, "Histocultures and their use," *eLS,* 2010.
76. J. M. Lee, P. Mhawech-Fauceglia, N. Lee, L. C. Parsanian, Y. G. Lin, S. A. Gayther, and K. Lawrenson, "A three-dimensional microenvironment alters protein expression and chemosensitivity of epithelial ovarian cancer cells in vitro," *Laboratory investigation,* vol. 93, pp. 528-542, 2013.
77. M. C. Bottino, V. Thomas, G. Schmidt, Y. K. Vohra, T.-M. G. Chu, M. J. Kowolik, and G. M. Janowski, "Recent advances in the development of GTR/GBR membranes for periodontal regeneration—A materials perspective," *Dental materials,* vol. 28, pp. 703-721, 2012.
78. T. M. Allen and P. R. Cullis, "Liposomal drug delivery systems: from concept to clinical applications," *Advanced drug delivery reviews,* vol. 65, pp. 36-48, 2013.
79. M. Sugano, Y. Negishi, Y. Endo-Takahashi, R. Suzuki, K. Maruyama, M. Yamamoto, and Y. Aramaki, "Gene delivery system involving Bubble liposomes and ultrasound for the efficient in vivo delivery of genes into mouse tongue tissue," *International journal of pharmaceutics,* vol. 422, pp. 332-337, 2012.
80. J. Kunisawa, T. Nakanishi, I. Takahashi, A. Okudaira, Y. Tsutsumi, K. Katayama, S. Nakagawa, H. Kiyono, and T. Mayumi, "Sendai virus fusion protein-mediates simultaneous induction of MHC class I/II-dependent mucosal and systemic immune responses via the nasopharyngeal-associated lymphoreticular tissue immune system," *The Journal of Immunology,* vol. 167, pp. 1406-1412, 2001.
81. A. Viniegra, H. Goldberg, Ç. Çil, N. Fine, Z. Sheikh, M. Galli, M. Freire, Y. Wang, T. Van Dyke, and M. Glogauer, "Resolving macrophages counter osteolysis by anabolic actions on bone cells," *Journal of Dental Research,* vol. 97, pp. 1160-1169, 2018.

82. D. Liu and P. Yang, "Minocycline hydrochloride nanoliposomes inhibit the production of TNF-α in LPS-stimulated macrophages," *International journal of nanomedicine,* pp. 4769-4775, 2012.
83. A. Jain, R. Kumari, A. Tiwari, A. Verma, A. Tripathi, A. Shrivastava, and S. K. Jain, "Nanocarrier based advances in drug delivery to tumor: an overview," *Current drug targets,* vol. 19, pp. 1498-1518, 2018.
84. A. Safdar, R. Bibi, I. Ilyas, S. Irum, S. Fatima, R. Sikandar, R. Fatima, and M. Qasim, "Botany, ethnopharmacology, phytochemistry and toxicology of Ricinus communis L. A comprehensive."
85. M. Chi, M. Qi, P. Wang, M. D. Weir, M. A. Melo, X. Sun, B. Dong, C. Li, J. Wu, and L. Wang, "Novel bioactive and therapeutic dental polymeric materials to inhibit periodontal pathogens and biofilms," *International journal of molecular sciences,* vol. 20, p. 278, 2019.
86. S. Ul Hassan, B. Bilal, M. S. Nazir, S. A. R. Naqvi, Z. Ali, S. Nadeem, N. Muhammad, B. A. Palvasha, and A. Mohyuddin, "Recent progress in materials development and biological properties of GTR membranes for periodontal regeneration," *Chemical biology & drug design,* vol. 98, pp. 1007-1024, 2021.
87. A. K. Sah, M. Dewangan, and P. K. Suresh, "Potential of chitosan-based carrier for periodontal drug delivery," *Colloids and Surfaces B: Biointerfaces,* vol. 178, pp. 185-198, 2019.
88. J. C. Cuggino, M. Molina, S. Wedepohl, C. I. A. Igarzabal, M. Calderón, and L. M. Gugliotta, "Responsive nanogels for application as smart carriers in endocytic pH-triggered drug delivery systems," *European Polymer Journal,* vol. 78, pp. 14-24, 2016.
89. S. Gulameabasse, F. Gindraux, S. Catros, J. C. Fricain, and M. Fenelon, "Chorion and amnion/chorion membranes in oral and periodontal surgery: A systematic review," *Journal of Biomedical Materials Research Part B: Applied Biomaterials,* vol. 109, pp. 1216-1229, 2021.
90. S. Peng, G. Zhou, K. D. Luk, K. M. Cheung, Z. Li, W. M. Lam, Z. Zhou, and W. W. Lu, "Strontium promotes osteogenic differentiation of mesenchymal stem cells through the Ras/MAPK signaling pathway," *Cellular Physiology and Biochemistry,* vol. 23, pp. 165-174, 2009.
91. D. Sriranganathan, N. Kanwal, K. A. Hing, and R. G. Hill, "Strontium substituted bioactive glasses for tissue engineered scaffolds: the importance of octacalcium phosphate," *Journal of Materials Science: Materials in Medicine,* vol. 27, pp. 1-10, 2016.
92. R. Sulaiman, A. Ghaffar, S. Perveen, D. Ashraf, I. Tariq, and T. Shakir, "Synthesis, Characterization, and Biomedical Applications of Zinc Oxide Nanoparticles," *BME Horizon,* vol. 1, 2023.
93. M. Waseem, M. Q. Abbas, K. Ummer, R. Fatima, W. Khan, F. Gulzar, M. Qasim, Q. Ullah, and I. Haidri, "PHYTO-REMEDIES FOR SOIL RESTORATION: A DEEP DIVE INTO BRASSICA'S PLANT CAPABILITIES IN CADMIUM REMOVAL," *EPH-International Journal of Biological & Pharmaceutical Science,* vol. 9, pp. 23-44, 2023.
94. A. E. Pazarçeviren, A. Tezcaner, D. Keskin, S. T. Kolukısa, S. Sürdem, and Z. Evis, "Boron-doped biphasic hydroxyapatite/β-tricalcium phosphate for bone tissue engineering," *Biological Trace Element Research,* vol. 199, pp. 968-980, 2021.