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*Review*

# Nanotechnology-Enhanced Orthopaedic Surgery

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**Abstract:** Nanomaterials hold significant promise for the future of orthopaedic implants due to their ability to mimic the nanoscale components of the bone, such as collagen fibrils and hydroxyapatite. Nanomaterials can regulate cell behaviour while offering mechanical strength and biocompatibility, making them ideal for bone repair and tissue regeneration. This comprehensive review explores the key existing and potential applications of nanotechnology in orthopaedics, including bone tissue engineering, drug delivery systems, systems combatting implant-related infections, and the surface preparation of implants to enhance osseointegration. These innovations are poised to revolutionise orthopaedic care by improving implant durability, reducing infection risks, and promoting bone regeneration to deliver personalised treatment and create better patient outcomes.

**Keywords:** orthopaedic surgery; nanoparticles; nanotechnology; bone tissue engineering; arthroplasty



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## 1. Introduction

### 1.1. Traditional Orthopaedic Surgery

Orthopaedic implants are essential tools for fracture fixation and bone regeneration, particularly in promoting growth in immature bone structures. Traditional methods, like autografts and allografts, are still commonly used in 80% of bone defect treatments but face limitations such as bacterial adhesion, restricted cell proliferation, and corrosion resistance issues [1]. A significant challenge with the existing implants is poor osseointegration, leading to implant loosening due to immunological rejection, wear debris, and infection risks [2].

The integration of advanced biomaterials, especially nanomaterials, has emerged as a promising solution, offering enhanced osseointegration, better cellular interaction, and stronger mechanical attachment. By incorporating these materials, modern implants improve both functionality and durability, marking a significant advancement in orthopaedic surgery and improving patient outcomes [3].

### 1.2. Nanotechnology

Microscopic-based cellular and subcellular interventions have been explored as potential adjunctive therapies to the existing macroscopic surgical alternatives. One such promising strategy is nanotechnology, which has a wide range of biological applications in many different domains, including the treatment of orthopaedic-related pathologies [4–7].

Nanotechnology advancements in recent years have made it possible to create materials and structures with features at the nanoscale for biological purposes [8,9]. Nanotechnology works on matter at the nanoscale ($10^{-9}$ m), allowing the development of novel materials and electronics. This technology, which builds up increasingly complex

structures from atomic-sized particles instead of breaking complex materials down into smaller ones, has the potential to deliver medications or other components [10]. Compared to surfaces with micrometre-size features, nanostructured materials exhibiting surface characteristics between 1 and 100 nanometres (nm) show altered and/or amplified biological responses [11]. Studies have demonstrated that protein adsorption, cell adhesion morphology and differentiation, and the synthesis and secretion of extracellular matrix (ECM) components are all impacted by nanostructured surfaces [12]. Numerous applications in the fields of environmental science, biotechnology, molecular biology, and medicine have become possible due to advancements in nanotechnology[13–16]. Medical imaging, drug delivery systems (DDSs), cancer therapy, immunotherapy, and nanofibrous scaffolds for tissue engineering are just a few examples of the advanced techniques that have made it possible to apply nanotechnology to medicine[17–19]. This review provides a thorough analysis of the existing and potential applications of nanotechnology in bone tissue engineering (BTE), arthroplasty, implant-related infections, and DDS within the realm of orthopaedic surgery.

### *1.3. Nanostructures in Orthopaedic Surgery*

Nanomaterials are very promising options for the fabrication of future orthopaedic implants because of their capacity to duplicate or replicate the constituent organs of a normal bone [20,21]. Given that collagen fibrils, Haversian systems, hydroxyapatite (HA), and other components of the bone are nanocompounds (Figure 1), nanotechnology has great potential to be applied in orthopaedic surgery [22].

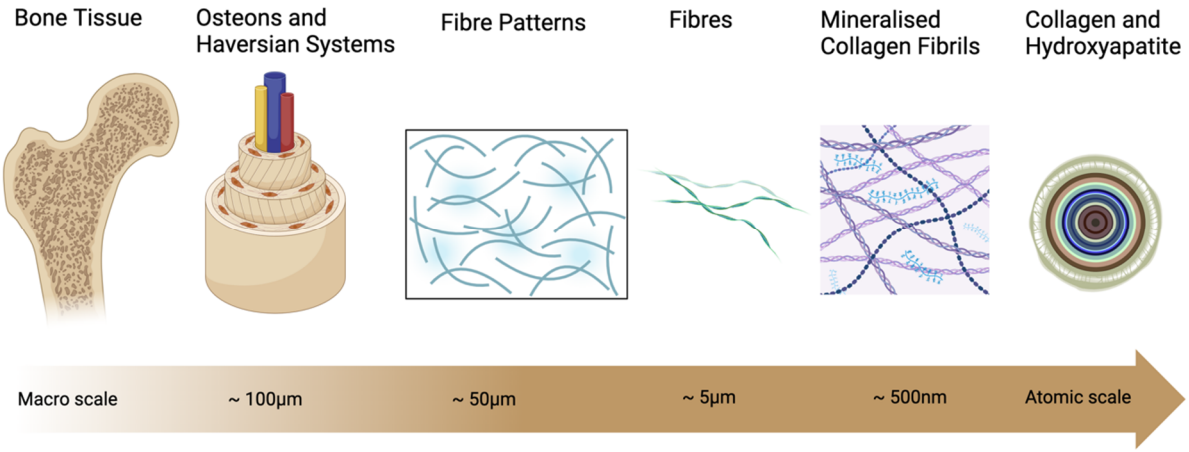


**Figure 1.** Hierarchical structure of bone.

The foundation for the creation of nanostructured materials for orthopaedic applications is found in the structure of the bone, a composite nanostructured tissue composed of HA crystals (2–5 nm thick) and collagen fibrils with a diameter of less than 500 nm. Studies have investigated how bone cells react to artificial nanostructures since bone cells are inherently adapted to nanophase materials [23]. The need for bone substitutes in orthopaedic applications is essential for treating permanent damage to natural, healthy bone. In this context, nanomaterials can be very important since they can control cell migration, proliferation, and differentiation in addition to giving the cell structural support (such as through nanofunctionalised scaffolds) [24,25].

The intricate interplay between biomaterials and host tissue frequently occurs at the microscale during orthopaedic surgery [22]. By employing biomaterials made of nanoparticles (NPs) and nanostructures, the efficiency of such interactions can be greatly increased by nanoscale material alterations. Nanotechnology holds considerable potential for improving the mechanical properties and biocompatibility of orthopaedic implants, making it a valuable tool for orthopaedic research purposes. Superior mechanical strength, increased

resistance to wear and corrosion, the ability for DDS, and the potential to serve as scaffolds for tissue regeneration are all offered by nanostructured implants and prostheses [22,26,27].

As shown in Table 1, the primary uses of nanotechnology in orthopaedics are as follows: (1) BTE for the preparation of scaffolds to treat defects in bone and cartilage; (2) efficient DDS for chemotherapeutic agents and antibiotics; (3) systems combatting implant-related infections; and (4) the surface preparation of prostheses and implants to promote osseointegration (the adhesion of the bone to the implant surface) [3].

**Table 1.** Nanoparticle applications and mechanisms of action in orthopaedics.

| Orthopaedic Applications | Nanoparticle(s) Involved | Mechanism of Action | Reference Number(s) |
|---|---|---|---|
| Bone Tissue Engineering (BTE) | Nano-hydroxyapatite (n-HA)<br>• Gelatine/HA nanocomposite<br>• n-HA/collagen scaffold | • Encourage osteoblast adhesion, proliferation, and differentiation to boost osteoinductivity and osseointegrative capability | [28–32] |
| | Titanium dioxide ($TiO_2$) nanotubes (TNs)<br>• $TiO_2$ (G@$TiO_2$) | • Scaffolds were designed to provide the right amount of internal space and mechanical strength to support the growth of new bone and the exchange of nutrients | [33,34] |
| | Magnetic nanoparticles (MNPs) and magnetic composites<br>• $Fe_3O_4$ MNPs<br>• $Fe_2O_3$ MNPs | • Scaffolds containing MNPs can react to external magnetic fields (EMFs)<br>• MNPs and magnetically responsive scaffolds (MRSs) can administer different peptide agents, and enhance implant stability and the scaffolds' wettability, mechanical qualities, and biocompatibility | [35–40] |
| | Nanocrystalline diamonds (NCDs) and Ultrananocrystalline diamonds (UNCDs)<br>• Titanium (Ti)<br>• Ti alloys<br>• Stainless steel<br>• Tungsten carbide (WC-Co)<br>• Cr-Co substrates | • NCD and UNCD coatings' high hardness and low coefficient of friction give the articulating surfaces of the joint implants remarkable wear resistance<br>• NCD surfaces allow for higher human osteoblast adhesion when compared to titanium surfaces<br>• NCD coatings are more resistant to bacterial colonisation while providing adequate biocompatibility for implant applications with tissue ingrowth and little to no inflammatory response | [41–44] |
| Drug Delivery Systems (DDSs) | Gold NPs<br>• Diclofenac administered with 30 nm gold NPs by iontophoresis | • Nanophase gold DDS significantly reduced the levels of the inflammatory cytokines interleukin-1β (IL1-β) and tumour necrosis factor- α (TNF-α) in tendinopathic tissue | [45] |
| | Nanofibre poly-lactic acid (PLLA)<br>• Bone morphogenetic protein (BMP)-2 delivered by PLLA | • When BMP-2 is delivered by nanofibre PLLA, large calvarial bony defects close quickly and exhibit increased expression of osteoblastic lineage cells | [46] |
| | Polypeptide nanofilms<br>• Polypeptide nanofilm loaded with cefazolin | • Nanofilm-coated surfaces demonstrated noticeably higher osteoblast adhesion, proliferation, and survival when compared to a bare implant surface<br>• Decrease in the bacterial load and an enhancement in the osteoblastic response | [47] |

**Table 1.** *Cont.*

| Orthopaedic Applications | Nanoparticle(s) Involved | Mechanism of Action | Reference Number(s) |
|---|---|---|---|
| Implant-related Infections | Silver NPs (AgNPs) | • By reacting with the phosphorus in the DNA and the sulphur-containing proteins in the bacterial membranes, the silver ions in AgNPs block their function<br>• Silver on a nanometre scale penetrates the bacterial cell wall and firmly attaches to the cell membrane<br>• $Ag^+$ ions in AgNPs bombard the bacterial mitochondria's electron transport chain, resulting in cell death<br>• When silver ions in the bacterial cell are continuously released from AgNPs in a lower pH environment, free radicals are created, oxidative stress is brought on, and the antibacterial activity is increased<br>• AgNPs adhere to the bacteria and break through the cell wall, further killing the bacteria | [48–53] |
| Osseointegration of Prostheses | Silver NPs (AgNPs)<br>• AgNPs with a nanocomposite layer of tantalum oxynitride (TaON)<br>• AgNP-coated bone cement | • Decreases infection rate while exhibiting no cytotoxicity<br>• Strengthens the coating's ability to act as a broad-spectrum antibacterial agent by improving resistance to a variety of microorganisms<br>• Decreases the production of polymer debris | [54–56] |

## 2. Nanotechnology Applications

### *2.1. Bone Tissue Engineering and Arthroplasty Implants*

The most effective surgery for treating joint disorders during the past few decades has been joint arthroplasty, which includes elbow, hip, knee, ankle, and other joints. Even though joint arthroplasty provides pain relief and function restoration with minimal to no impact on daily activities, long-term prosthesis survival remains a concern for these patients. Following joint arthroplasty surgery, osteolysis (Figure 2) is the most frequent long-term consequence [57]. The primary cause of joint arthroplasty failure is the subsequent periprosthetic osteolysis-induced aseptic implant loosening. It could be the result of the implant failing to integrate at first, or loosening after initial integration, and is consequently the primary factor limiting the longevity of present joint arthroplasty prostheses [58,59].

Currently, the mainstay of the surgical management of periprosthetic osteolysis is revision surgery, a very challenging operation. It is associated with poor clinical and functional outcomes, high rates of complications and morbidity, and a significant financial burden on the healthcare system [60]. Another frequent cause of aseptic implant loosening following joint arthroplasty has been identified as the particulate wear particles of various prosthetic material types [61]. Metals, ceramics, and polymers are frequently utilised as orthopaedic biomaterials. These prostheses may produce internal wear particles after implantation as a result of abrasion and corrosion [62]. Once the prosthetic wear particles are released, they can infiltrate the systemic circulation, resulting in systemic toxicity [63]. In addition, they are also locally accumulated in adjacent tissues and spaces, such as the bone and bone marrow [64]. Due to their interactions with peri-implant cell lineages such as bone-forming osteoblasts and their progenitors, mesenchymal stem cells (MSCs) remaining in bone marrow, macrophages, osteoclasts, and fibroblasts; these nondegradable particles may eventually become problematic [65].

Cellular differentiation and osseointegration depend on how the surface of a biomaterial interacts with the surrounding soft tissues and bones when it is incorporated into the human body. MSCs appear to be among the first cell types to become activated when a nanophase biomaterial is introduced into a biological setting [66]. Nanophase implant surfaces and scaffolds have the potential to enhance osseointegration by promoting the differentiation of MSCs and the adsorption of extracellular adhesion molecules that are

crucial for osteoblast function. This is accomplished by replicating the three-dimensional (3D) extracellular and cell surface topography at the nanoscopic level [46,67].

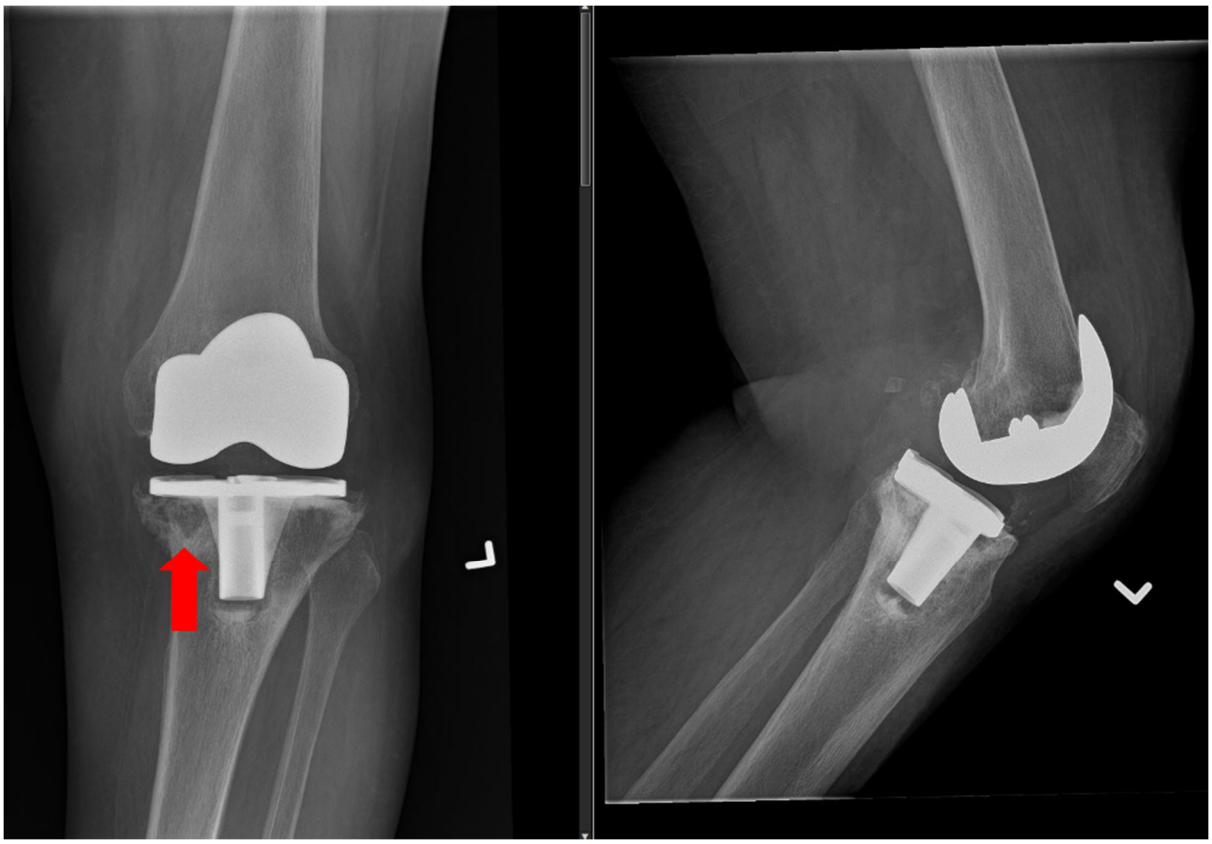

**Figure 2.** Radiographic appearance of osteolysis in the anteroposterior (AP) and lateral radiographs of a 73-year-old female who underwent a revision left total knee replacement (TKR); periprosthetic bone loss is indicated by the arrow.

Without the need for extra osteogenic chemicals, a number of in vitro studies have demonstrated their capacity to regulate and improve osteoblast development and cellular adhesion through the introduction of specially designed nanophase scaffolds [66–69]. Newly formed bone tissue gradually absorbs or replaces the polymer scaffold that facilitates tissue regeneration [70]. In BTE, a variety of scaffolds are extensively employed as 3D constructs with high porosity that facilitate cell adhesion, growth, and migration as well as interactions between cells and biomaterials [71,72]. Additionally, they aid in progenitor cell transit, survival, proliferation, and differentiation [73]. Important behaviours such as osteoinduction and osteoconduction are required for the components of the biomaterial to integrate into the surrounding bone tissue. Bone integrity should also be preserved by the biomaterial [74]. Further crucial factors for biomaterials utilised in BTE include the ease of sterilisation, ease of production, non-thrombogenicity, and stability under various chemical and mechanical conditions [75]. Scaffolds need to be stable and elastic enough to endure the suture site and facilitate the formation of bones with homogenous morphology when they are implanted in the bone defect. A controlled degradation of the implanted scaffold is required in vivo, with or without a low level of toxic or inflammatory side effects [76].

One fascinating area for additional research is the fabrication of specific osteogenic, extracellular nano-topographical surfaces that mimic known biological features. For example, because of its well-known nano-topographical structure, type X collagen is hypothesised to cause endochondral ossification. A replication of this might enable the regulated stimulation of secondary bone healing's endochondral ossification [69]. Numerous materials with nanostructures have been demonstrated to improve osteoblast

performance. These comprise nano-hydroxyapatite (n-HA), titanium dioxide ($TiO_2$), titanium alloy (Ti6Al4V), and nanocrystalline diamond[77–80]. Moreover, a number of in vitro investigations have demonstrated that nanosurfaces exhibit greater osteoid mineralisation than micro-roughened surfaces [81,82].

The goal of the developing field of BTE is to integrate three elements: (a) osteogenic cells that produce the bone tissue matrix; (b) the osteoconductive properties of a biocompatible scaffold that mimics the ECM of the bone; and (c) osteoinductive elements consisting of physicochemical stimuli that influence cell behaviour. A properly constructed bone product shows sufficient vascularisation, does not cause an immune reaction at the defect site, and has no long-term graft site problems [83].

#### 2.1.1. Nano-Hydroxyapatite

In natural bone, HA, which has the chemical formula $Ca_{10}(PO_4)_6(OH)_2$, is the main inorganic component. Its extensive use in biomedical applications is attributed to its excellent biocompatibility and osteoconductive properties [84]. Due to its tiny size, high surface area, and roughness, n-HA is now more often utilised than microscale HA in applications such as coatings and scaffolds for BTE [85]. It is becoming more significant in the remodelling and healing of bones [86]. Numerous research studies report the usage of n-HA in conjunction with chitosan, collagen, polymer, and other bioactive compounds to build a 3D biomimetic composite [28,29]. The inorganic and organic phase composition of natural bone is mimicked in n-HA composite materials including natural or synthetic polymers [87]. When n-HA composite scaffolds have the proper porosity structure, biodegradability, and mechanical properties, they can increase osteoinductivity and osseointegrative capability by promoting osteoblast adhesion, proliferation, and differentiation [29,30]. The osteoblastic MG63 cells had a preference for adhering to the gelatin/HA nanocomposites containing tiny apatite crystals, multiplying, and secreting osteocalcin (OCN) and alkaline phosphatase (ALP). In an effort to create an osteoconductive substance that can inhibit osteosarcomas, adriamycin-encapsulated poly(lactic-co-glycolic acid) (PLGA) NPs have recently been loaded onto a porous n-HA/collagen scaffold [31,32].

#### 2.1.2. Titanium Dioxide Nanotube

The advancement of additive printing technology in recent times has made it possible to create bone tissue scaffolds that combine mechanical, biological, and physical qualities by realising structures with intricate topological features[88–90]. Of these structures, creating and designing triply periodic minimal surfaces (TPMSs) has emerged as a focus of research [91,92]. Nature served as the model for TPMSs, which are continuous, non-self-intersecting surfaces with a zero mean curvature everywhere [93]. Their continuous, smooth surfaces help to lower stress concentrations, which improves mechanical characteristics and promotes cell adhesion and growth. Nevertheless, bacteria may outcompete osteoblasts for adhesion, growth, and colonisation on the implant surface following implantation[94–96]. The scaffold's porous structure interacts directly with bone tissue. When non-fibrous connective tissue surrounds a stable interface created by osteoblasts that win the competition, osseointegration is completed. On the other hand, premature bacterial colonisation might lead to the production of biofilms and implant infection. Thus, for implants used to repair extensive segmental bone lesions in load-bearing locations, mechanical properties, porosity structure, and material surface attributes are all crucial [97].

Titanium dioxide ($TiO_2$) nanotubes (TNs) are stable within the organism and exhibit good tissue compatibility and biocompatibility despite their limited solubility and chemical inertness. $TiO_2$ is thought to be a viable material for bone scaffolding because it stimulates the growth of new bone and increases osteoblast adhesion (Figure 3) [98–100]. To tackle the problem of extensive segmental bone defects, Xiao et al. (2024) created gradient gyroid scaffolds that have $TiO_2$ (G@$TiO_2$) surface modification. The scaffolds' precise proportions of mechanical strength and internal space allowed for the exchange of nutrients and the development of new bone. The G@$TiO_2$ scaffold, which has a gradient structure

and $TiO_2$ surface modification, was shown to have better healing properties in vivo in rabbits than the gradient structure (G) and homogeneous structure (H) and $TiO_2$ surface modification (H@$TiO_2$) scaffolds (Figure 3) [33].

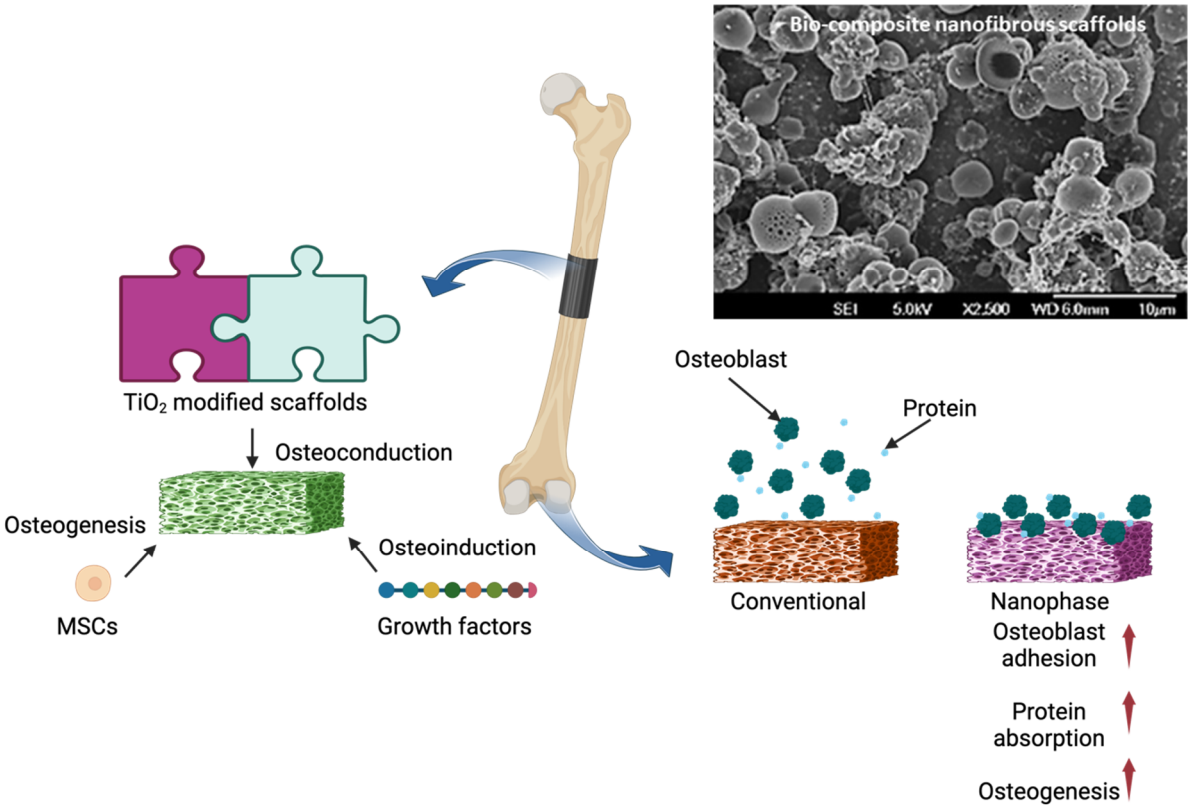


**Figure 3.** Nanomaterial-based scaffolds for bone regeneration; the field emission scanning electron microscope (FESEM) image shows electrosprayed silk fibroin/hydroxyapatite (SF/HA) NPs for BTE.

This study introduces a practical method for fabricating functionalised scaffolds designed to stimulate bone tissue regeneration in the healing of extensive segmental bone defects. Healing has been greatly aided by the gradient structure, especially with the $TiO_2$ surface alteration. After 12 weeks of surgery, a 27% bone volume to tissue volume (BV/TV) ratio was attained in a 20 mm bone defect, or over 30% of the radius's entire length. In addition to providing a photothermal antibacterial action, the surface alteration improved osseointegration even more, which is important in avoiding infections after implantation. These results imply that the scaffolds that were produced could offer an effective substitute for conventional bone grafting techniques, particularly in cases where the defects are significant in size. The scaffold has a dual role of enhancing osseointegration and photothermal anti-infection through synergistic surface alteration. This promotes the quick in vivo ingrowth of bone tissue, which raises the implant success rate. Further work is required in order to assess the scaffolds' long-term durability and biocompatibility in load-bearing regions and investigate the possibility of customising them to satisfy patient-specific criteria including biomechanics and dimensional specifications [33].

Park et al. (2012) found that in both stem cells and bone-forming/-resorbing cells, the cellular response was responsive to $TiO_2$ nanoscaled surface topography [34]. When compared to traditional microroughened titanium (Ti) surfaces, research by Bjursten et al. (2010) revealed that implants with TN surfaces might considerably boost osteoblast adhesion in vitro and bone development in vivo [101]. Furthermore, research findings indicated that MSCs on the surface of TNs had a preference for differentiating into osteoblast-like cells [68,102]. Moreover, it has been suggested that coating Ti with n-HA and TNs might inhibit bacterial colonisation and the development of bacterial biofilms on the implant

surface [103,104]. However, the majority of the aforementioned research focused on how nanofibrous scaffolds influenced a specific cell type. Few studies have examined how TN substrates affect cell-to-cell interactions. It is now commonly acknowledged that tissue regeneration often requires a variety of cell types, and that interactions between these various cell types can significantly aid in the process [105].

2.1.3. Magnetic Nanoparticles and Magnetic Composites

Iron oxide ($Fe_3O_4$) NPs, specifically in the forms of $Fe_3O_4$ and ferric oxide ($Fe_2O_3$), represent the predominant category of magnetic nanoparticles (MNPs). These are widely used in in vivo cell tracking and monitoring and magnetic resonance imaging (MRI) for imaging cancer cells and transplanted tissues, and are usually synthesised using the traditional co-precipitation approach [106]. These particular MNPs have been used by researchers in the biomedical field, particularly for the monitoring of engineered tissues, due to their outstanding biocompatibility and low toxicity. The United States Food and Drug Administration (USFDA) has approved $Fe_3O_4$ for use in clinical settings [107].

The special quality of biodegradable nanofillers' large surface area complements the crucial characteristics of classical scaffolds—such as biocompatibility, physicochemical stability, support for cell adhesion, and cell differentiation. This significantly enhances the BTE technique in tissue engineering and repair [108]. A number of technologies are employed in BTE to develop and introduce efficient nanocomposite scaffolds with regulated size and porosity and a high surface–volume ratio, including the foam replica method, solvent casting and particulate-leaching, phase separation, freeze-drying, gas foaming, rapid prototyping, and electrospinning[109–115]. Unfortunately, most scaffolds are uncontrollable once they are implanted in vivo, and since scaffolds are the only ones that can complete the repair process, the repair will not always be satisfactory. Consequently, the development of composite scaffolds containing MNPs is one of the recommended strategies to accomplish suitable tissue restoration and the potential to influence tissue fate using outside stimuli [70].

Since MNPs themselves are sensitive to external magnetic fields (EMFs), scaffolds containing them are also EMF-responsive. Furthermore, MNPs and magnetically responsive scaffolds (MRSs) have the ability to administer different peptide agents and enhance implant stability and the scaffolds' wettability, mechanical qualities, and biocompatibility [35–37]. Furthermore, MNPs and MRS boost bone cells' osteogenic gene expression and ALP activity [116]. Magnetic nanocomposites (MNCs) that are implantable and functional are thus created by combining the MNPs with nanocomposite scaffolds [117,118]. The magnetic response of these scaffolds is crucial because it enables remarkable advancements in tissue engineering, including the magnetic patterning of cells and the creation of 3D tissue-like structures [119,120].

By creating magnetic scaffolds out of MNP and HA/collagen, Panseri et al. (2012) demonstrated how the presence of MNPs attracts growth factors and cells [121]. $Fe_3O_4$ NPs were also incorporated into macro-porous ferrogel scaffolds to create MNCs with porous structures that were ideal for cell delivery [119,122]. Furthermore, doping HA with magnetic poly(1-caprolactone) and iron results in MNCs that can be used to treat further hyperthermia while also repairing injured tissues [123]. Every particle in the MNP structure has its own magnetic domain. As a result, adding MNPs to scaffolds creates a nanoscale magnetic field that influences the interactions between the scaffolds and cells in the exposed microenvironments. Moreover, it has been shown that a variety of cell surface receptors and associated signalling pathways are influenced by the endogenous force generated by MNPs or EMFs, which changes cell activity toward a specific target [38–40].

Magnetic field stimulation accelerates the process of bone healing by enhancing the integration of scaffolds and host bone, and increasing the calcium content for bone density and new bone creation [124]. It has been demonstrated that to promote tissue regeneration, functionalised MNPs injected near the scaffold can be attracted to the injured site when exposed to an EMF [125]. The inherent magnetic characteristics of MNCs or exposure to distant magnetic fields in conjunction with mechanical support are typically what causes

the control of signalling pathways and various biological responses, the promotion of osteogenic cell differentiation, bone regeneration, and injury repair [126,127]. Hence, when it comes to BTE, MNPs and their nanocomposite scaffolds generally offer a number of benefits over more traditional implants.

MNPs have plenty of benefits and applications, but they have their limitations. A drawback of employing MNPs is their instability and poor solubility in aqueous conditions. It is advised to use a hydrophilic polymer substrate and cover MNPs in order to address this issue and improve their stability [128]. Moreover, steric or electrostatic repulsion should be used to stabilise MNPs in order to stop them from aggregating [129]. The toxicity associated with MNPs' size, shape, and chemistry is another drawback that needs to be taken into account before clinical application. Over time, MNPs may accumulate in tissues and organs, which may result in toxicity and other negative effects [130]. Once MNPs reach the therapeutic endpoint, they must be promptly extracted from the body, whether they are in a polymer substrate or not [131]. Despite the significant therapeutic, restorative, and diagnostic potential of MNPs, further research is necessary to mitigate potential risks to human health. Consequently, a comprehensive pre-evaluation of their biodistribution and biocompatibility is imperative.

#### 2.1.4. Nanocrystalline and Ultrananocrystalline Diamonds

Synthetic diamond coatings with nanoscale diamond grains embedded in amorphous carbon matrices are known as nanocrystalline diamond (NCD) and ultrananocrystalline diamond (UNCD) coatings. These coatings share material characteristics with natural diamonds. The primary distinction between UNCD and NCD coatings is their grain size—NCD coatings have an $sp^3$ content of around 98–99% and grain sizes between 10 and 200 nm, while UNCD coatings have $sp^3$ contents of around 95–98% and grain sizes between 2 and 5 nm [41]. NCD and UNCD are ideal materials for implant coatings because they are wear-resistant, chemically inert, mechanically strong, and biocompatible. These coatings possess exceptional biological characteristics and have demonstrated potential for use in orthopaedic fixation devices and hip joint prostheses [132,133]. The NCD and UNCD coatings' high hardness (80–100 GPa) and low coefficient of friction (0.02–0.05) give the articulating surfaces of the joint implants remarkable wear resistance. Diamond coatings, hence, provide the ability to enhance implant functionality and prolong implant lifespan because of their remarkable resistance to wear and their biocompatible wear components [41].

The use of nanostructured diamond coatings in traditional metallic implants has the potential to greatly enhance their long-term durability and mitigate the unfavourable biological reactions linked to the implantation of metallic biomaterials. Diamond coatings can be deposited on a variety of implant biomaterials, including cobalt–chromium alloys, Ti, Ti alloys, stainless steel, and tungsten carbide–cobalt (WC-Co) [134]. Compared to traditional orthopaedic biomaterials like Ti and stainless steel, NCD coatings have been shown to be more resistant to bacterial colonisation whilst being similarly biocompatible [42,43]. The excellent biocompatibility of NCD coatings for hard tissue applications has been shown in in vitro experiments. When compared to control materials, osteoblasts and human MSCs have demonstrated improved cell adherence, proliferation, metabolic activity, and osteogenic differentiation on NCD coatings. Human MSC adhesion and proliferation were shown to be higher on NCD coatings by Clem et al. (2008) than on Co-Cr substrates. However, the cells cultured on Ti6Al4V deposited more minerals [135]. Human osteoblast adhesion was shown to be higher on NCD surfaces than titanium surfaces [43]. Additionally, adequate biocompatibility for implant applications with tissue ingrowth and little to no inflammatory response has been shown by in vivo investigations using NCD coatings [44]. When considered collectively, the studies demonstrated that diamond has great potential as a material for bone tissue–implant interfaces and that a complex interaction between surface chemistry, texture, nanostructure, and surface potential affects the cellular response to diamond [136].

It is important to take into account the variations in the chemical, physical, and biological environments around the different implants when analysing the bioactive behaviour of the foreign materials placed [137]. The stiffness of the surrounding tissue, the chemistry of the fluids, the presence of various bacterial populations, and the chemical–physical characteristics of the coatings all have an impact on the interactions between the cell and the substrate. This means that the approaches used must make it feasible to adjust the material's mechanical and physical qualities as well as the chemical characteristics of the surfaces coming into contact with the host tissues in order to increase the applicability of diamond-Ti implants in various body regions [138].

Overall, these results point to the significant prospective applications of NPs in orthopaedic implant surfaces due to their enhanced ability to promote osteoid mineralisation and osseointegration.

### *2.2. Nanomaterials Used as Drug Delivery Systems in Arthroplasty*

Precision drug delivery is presently receiving a great deal of attention. In the treatment of tendinopathy, gold NPs have the potential to be successful transcutaneous drug delivery systems (DDSs) for iontophoresis [139]. After tracking for six months, Balfourier et al. (2020) reported that smaller-sized gold NPs (4, 15, and 22 nm) showed comparatively faster degradation when given to primary human fibroblasts, the most widely distributed cells in the body [140]. It was discovered that the oxidation of gold NPs by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) produced reactive oxygen species (ROS), which caused this deterioration. Given that they break down more slowly than previously believed, this questions the current dogma on the longevity of gold NPs in the body. Using a rat Achilles tendinopathy model, Dohnert et al. (2012) demonstrated that the levels of the inflammatory cytokines interleukin 1 (IL1)-β and tumour necrosis factor (TNF)-α in tendinopathic tissue were significantly reduced by diclofenac administered with 30 nm gold NPs by iontophoresis when compared to both untreated controls and diclofenac-only groups. This implies that as a transcutaneous anti-inflammatory drug, diclofenac may be more effective when dissolved in nanophase gold [45].

Nanofibre poly-lactic acid (PLLA) also seems to be a good nanoscopic DDS. When bone morphogenetic protein (BMP)-2 is delivered by nanofibre PLLA, large calvarial bony defects close quickly and exhibit increased expression of osteoblastic lineage cells [46]. The use of NP DDS in joint arthroplasty is now being studied. Li et al. (2010) employed a biodegradable polypeptide nanofilm coating on total joint prostheses to administer cefazolin in a simulated joint arthroplasty environment [47]. They noted a decrease in the bacterial load and an enhancement in the osteoblastic response. *Staphylococcus aureus (S. aureus)* adhered to a bare nanofilm implant surface significantly less than it did to a traditional prosthesis (Figure 4). Furthermore, the *S. aureus* population decreased in a dose-related manner when the same polypeptide nanofilm was loaded with cefazolin and employed as a DDS. Polypeptide nanofilm technology offers the precise regulation of cefazolin release pharmacokinetics, especially critical during the initial two hours post-implantation. This controlled release allows for the targeted delivery of cefazolin, potentially reducing infection risks in the early stages of healing. Furthermore, nanofilm-coated implant surfaces, whether loaded with cefazolin or not, exhibit significantly improved osteoblast adhesion, proliferation, and survival compared to bare implant surfaces. These findings suggest that polypeptide nanofilms provide an ideal surface for enhanced osseointegration, promoting both bone integration and infection prevention in orthopaedic applications [47].

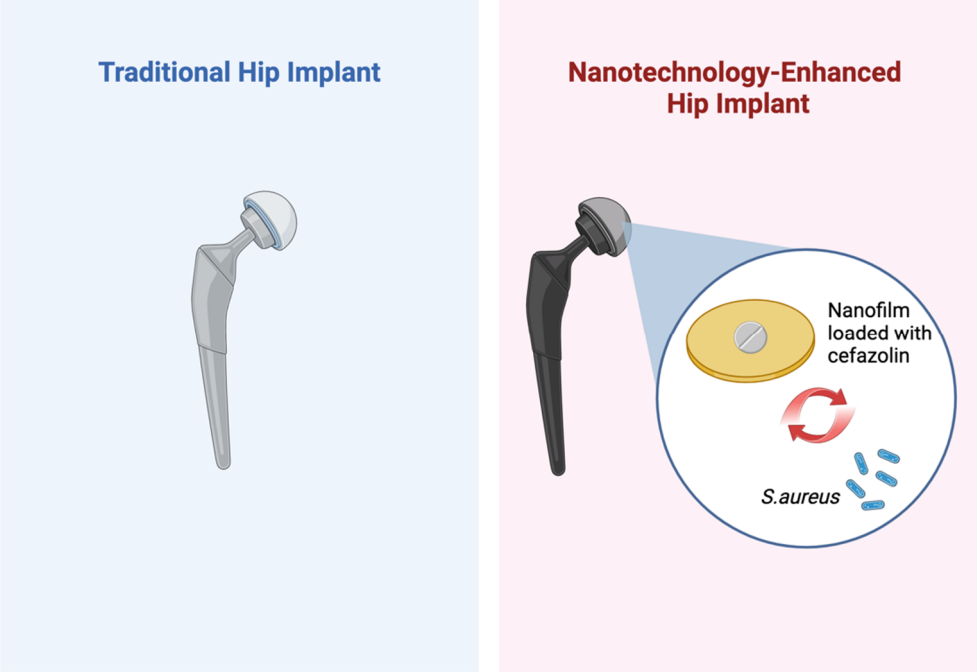


**Figure 4.** Comparison between traditional implant and nanotechnology-enhanced implant; Gram-positive *S. aureus* adhered to a bare nanofilm implant surface significantly less than it did to a traditional prosthesis; *S.aureus* population decreased in a dose-dependent manner when cefazolin was loaded into the DDS.

### *2.3. Nanoparticle Applications in Implant-Related Infections*

Multi-drug-resistant (MDR) bacteria are commonplace nowadays, reducing the resources available for managing illnesses with traditional treatments like radiation and antibiotics. Silver NPs (AgNPs) are excellent antibacterial agents that have been shown to be effective against both Gram-positive and Gram-negative bacteria strains resistant to vancomycin[141–143]. AgNP-released silver ions bind to the thiol (SH) group of the sulphur and hydrogen found in bacterial proteins, preventing the growth of the bacterium [48,144,145]. AgNPs work by disrupting the bacterial electron transport chain system and precipitating the bacterial cellular proteins. They are effective against both anaerobic and aerobic bacteria [146–148]. AgNPs exhibit greater efficiency due to their higher surface area to volume ratio [142,149]. Their mechanisms of action are as follows (Figure 5): (a) by reacting with the phosphorus in the DNA and the sulphur-containing proteins in the bacterial membranes, the silver ions in AgNPs block their function [49]; (b) silver on a nanometre scale penetrates the bacterial cell wall, firmly attaching to and disrupting the cell membrane [50,51]; (c) $Ag^+$ ions in AgNPs bombard the bacterial mitochondria's electron transport chain, resulting in cell death [52]; (d) when silver ions in the bacterial cell are continuously released from AgNPs in a lower pH environment, free radicals are created, oxidative stress is brought on, and the antibacterial activity is increased [48,53]; (e) AgNPs adhere to the bacteria and breaks through the cell wall, killing the bacteria [149].

The antibacterial efficacy of AgNPs is determined by their size, shape, and concentration. A recent study shows that increasing AgNPs' surface area can improve their antibacterial efficacy [150]. At a very low dosage of 20 µg/mL, AgNPs showed 50% inhibitory action against *Escherichia coli* (*E. coli*) and *S. aureus*, two MDRs. It demonstrated the effective suppression of both bacteria at an additional high dosage of roughly 40 µg/mL [151]. In another study, biosynthesised AgNP using marine macroalgae Padina species was found to have good bacteriostatic action against Gram-negative bacteria like *Salmonella typhi* (*S. typhi*) and *E. coli*, and harmful Gram-positive organisms like *Bacillus subtilis*. AgNPs at a dosage

of 1 mg/mL showed increased sensitivity against *Pseudomonas aeruginosa*, with a zone of inhibition diameter of 13.33 ± 0.76 mm, and *S. aureus*, with a diameter of 15.17 ± 0.58 mm, respectively. In contrast, the negative control had a 0.00 mm diameter [152]. A comparison investigation was conducted in another study using polyethylene glycol (PEG)-ylated AgNPs with varying molecular weight and small AgNPs against the principal pathogen *S. aureus*. A total of 12 distinct AgNP sizes, ranging from 29.7 ± 0.02 to 35.5 ± 0.02 nm, were synthesised in three distinct pH ranges—10, 11, and 12. The PEGylated AgNPs had excellent bactericidal activity at a pH of 10, with a zone of inhibition of roughly 29 mm. This occurred as a result of PEG's strong hydrophilic characteristic, which killed the microorganisms and removed additional water [153].

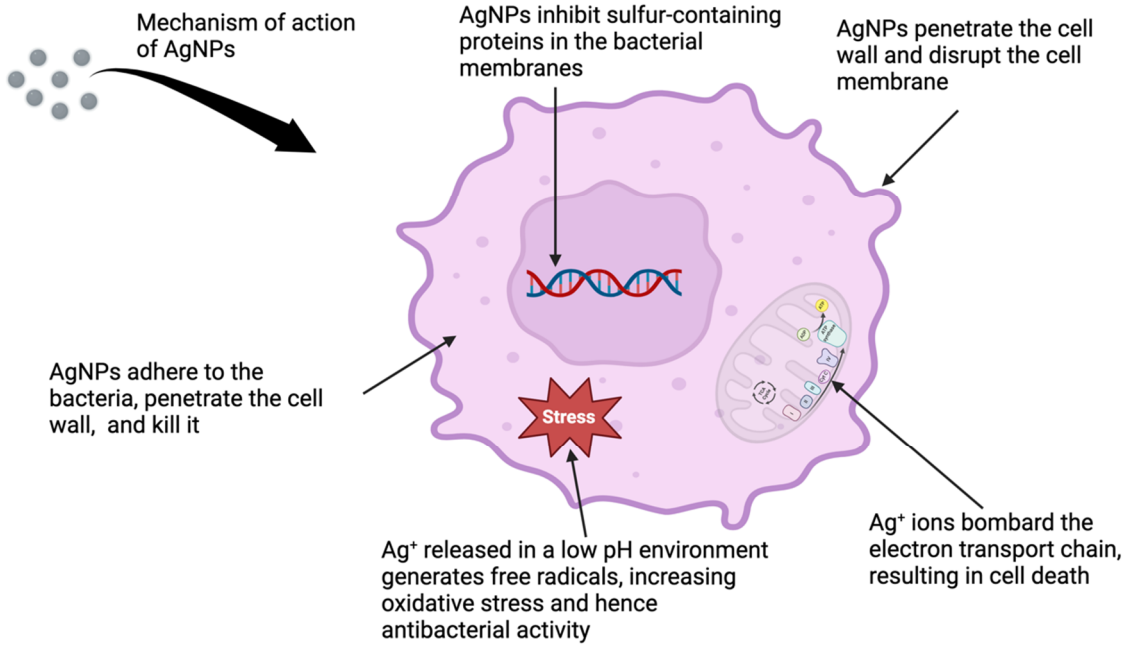


**Figure 5.** Mechanism of AgNPs as excellent antibacterial agents.

By directly interacting with nanomaterial and viral surface proteins, metal NPs such as gold (Au) or silver (Ag) have antiviral activity against a wide range of viruses and lower the infectivity of virally grown cells. Previous studies reported that these metal NPs are potent antiviral agents that combat several viruses, including influenza, Tacaribe virus (TCRV), herpes simplex virus (HSV) type 1, monkey pox, and human immunodeficiency virus (HIV) 1 [154–157]. By preventing the virus's attachment to and penetration of the host cell, AgNPs and polysaccharide-coated AgNPs with sizes ranging from 10 to 80 nm were effective against the *Poxviridae* family virus that causes monkey pox [154]. Through interactions with gp 120, AgNP coated with poly (N-vinyl-2-pyrrolidone) showed antiviral properties against HIV 1 [158]. By rendering the viral particles inactive at the point of initial entry, AgNP at non-toxic concentrations is an efficient way to inhibit the TCRV of the *Arenaviridae* family [159].

As such, AgNPs have a strong anti-inflammatory effect [160]. Researchers employed the aqueous extract of *Selaginella myosurus* to biosynthesise AgNPs, and the results demonstrated a substantial reduction in the paw oedema of Wistar rats at concentrations of 0.1, 0.2, and 0.4 mg/Kg (body weight), respectively [161]. In order to evaluate the anti-inflammatory action in male Wister rats, Shensha et al. (2020) conducted a study on Nigella sativa oil-mediated AgNPs. The results indicated inhibitory concentration at 54.40% (one hour) and 60.30% (five hours) with a dose of 0.3 mg/kg bodyweight [162].

#### 2.3.1. Utilising Silver Nanoparticles to Counteract Orthopaedic Infections

AgNPs have been used in nanomedicine in a variety of creative ways over the past decade [163,164]. One of the most popular approaches to reducing infection-related implant failure rates has been to incorporate these antimicrobial nanoparticles into the outer layers of orthopaedic implants [165]. AgNPs were created and coated in $TiO_2$ nanotubes using electrochemical anodisation in a work [166]. In addition to increasing the surface area available for interaction, the nanorods produced two different sizes of AgNPs: 80 nm outside and 5–10 nm inside. Because of their different sizes, the smaller particles are assumed to have released silver ions in an initial burst, whereas the larger particles released silver ions slowly over a 30-day period, resulting in a logarithmic release of silver. The outcomes showed notable osteoblast cytotoxicity in addition to effective resistance to *E. coli* upon exposure to the modified Ti film. In contrast to the osteoblast-cytotoxic effects previously discussed, a study by Chen et al. (2020) showed AgNPs to have favourable pro-osteogenic effects by regulating M1/M2 macrophages [167]. In their in vivo investigation, the release of 0.2 ppm AgNP over the course of 24 h showed an increase in macrophages' pro-osteogenic M2 expression through the suppression of glucose transporter 1 (GLUT1) expression and the encouragement of autophagy. Reduced AgNP concentrations enhanced trabeculae presence and osteogenesis. With the ability to control infection while promoting osteogenesis, tissue-engineered composite bone graft development, comprising BMP-2 coupled with AgNPs/PLGA, will play a significant role in managing osteomyelitis and infected fracture non-unions [168]. The potential of AgNP-coated external fixator pins to lower infection related to pin tracts is another investigated role [169].

#### 2.3.2. Employing Silver Nanoparticles for Osseointegration

The key to attaining long-term, functional results after arthroplasty is the osseointegration of prosthesis utilised in joint arthroplasty and the prevention of periprosthetic infection. The influence of the host's reaction on the implant is contingent upon multiple factors, including surface topography and surgical methodology. Because of its tribological characteristics, which include resistance to corrosion and inertness, titanium has been the most often used material. The combination of AgNP with a nanocomposite layer of tantalum oxynitride (TaON) strengthened the coating's ability to act as a broad-spectrum antibacterial agent by improving resistance to a variety of microorganisms [54].

Artificial joint replacement is considered the gold standard treatment for arthritic patients. When incorporated into the bones, the usage of bone cements such as polymethyl methacrylate (PMMA) led to a high rate of infection. The only drawback of using ultra-high molecular weight polyethylene (UHMWPE) for artificial joint replacement was the wear and tear and debris production that resulted in inflammation and joint failure in the body. This significant issue was resolved by including AgNPs in bone cement. By covering the implants' exterior with AgNPs, the infection rate was decreased. Therefore, methicillin-resistant Staphylococcus aureus (MRSA) and other bacteria were dramatically inhibited by AgNP-coated bone cement. AgNPs exhibited no cytotoxicity. As a result, this procedure decreased the production of polymer debris [55,56].

## 3. Limitations and Future Work

One of the significant limitations is the stability and solubility of NPs in biological environments, which can affect their efficacy and safety. Additionally, the potential toxicity of NPs, especially when they accumulate in tissues over time, is a concern that requires further investigation. Biocompatibility, long-term durability, and patient-specific customisations also need to be addressed to ensure successful outcomes in clinical settings.

Advancing the design of orthopaedic implants with nanomaterials and nanofabrication techniques to enhance functionality and performance is a critical focus for future research. To achieve optimal outcomes, a comprehensive understanding of the molecular interactions between cells and nanomaterials is essential. Furthermore, the careful evaluation of the biosafety of nanomaterials is needed due to concerns over the toxicity of

NPs generated by wear and degradation. As metals behave differently at the nanoscale than at the microscale, it is vital to thoroughly assess the potential toxicity associated with nanoscale materials to ensure safety and efficacy in biomedical applications. Future work should focus on optimising the stability of NPs, developing more biocompatible materials, and advancing scaffold designs that better mimic bone tissue structures. Furthermore, research into reducing toxicity and improving long-term biocompatibility is crucial to pave the way for widespread clinical adoption.

Expanding research on the advantages, limitations, and current methods of nanotechnology is essential for advancing its application in orthopaedics. Nanotechnology products are inherently complex, making them difficult and costly to manufacture. These high costs can limit accessibility, while lengthy regulatory procedures may slow the transition from research to clinical application. Addressing the issues related to cost, production, and regulatory barriers will help promote the widespread use of nanomaterials in orthopaedics. Although increased funding and research are gradually establishing nanotechnology's role in orthopaedic surgery, ongoing concerns regarding safety and regulation are likely to remain hurdles to its broader and faster adoption.

## 4. Conclusions

Nanotechnology offers a transformative potential in the field of orthopaedics, particularly in DDS, BTE, and implant design. By leveraging the unique properties of nanoscale materials, these innovations aim to enhance biocompatibility, promote bone regeneration, and reduce the risk of infections. With continued advancements, nanotechnology has the potential to revolutionise how we approach bone repair, tissue regeneration, and infection control, ultimately leading to improved patient outcomes and the next generation of orthopaedic implants.

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## Abbreviations

| | |
|---|---|
| 3D | three-dimensional |
| AgNPs | silver nanoparticles |
| ALP | alkaline phosphatase |
| AP | anteroposterior |
| BMP | bone morphogenetic protein |
| BTE | bone tissue engineering |
| DDS | drug delivery system |
| ECM | extracellular matrix |
| EMF | external magnetic field |
| $Fe_2O_3$ | ferric oxide |
| $Fe_3O_4$ | iron oxide |
| FESEM | field emission scanning electron microscope |
| G | gradient structure |
| GLUT1 | glucose transporter 1 |
| HA | hydroxyapatite |
| H@$TiO_2$ | homogenous structure and $TiO_2$ surface modification |
| HIV | human immunodeficiency virus |
| HSV | herpes simplex virus |
| IL1 | interleukin 1 |
| MDR | multi-drug resistant |
| MNC | magnetic nanocomposite |
| MNP | magnetic nanoparticle |
| MRI | magnetic resonance imaging |

| | |
|---|---|
| MRS | magnetically responsive scaffold |
| MRSA | methicillin-resistant Staphylococcus Aureus |
| MSCs | mesenchymal stem cells |
| NADPH | nicotinamide adenine dinucleotide phosphate |
| n-HA | nano-hydroxyapatite |
| Nm | nanometres |
| NOX | nicotinamide adenine dinucleotide phosphate oxidase |
| NP | nanoparticles |
| NCD | nanocrystalline diamond |
| OCN | osteocalcin |
| PEG | polyethylene glycol |
| PLGA | poly(lactic-co-glycolic acid) |
| PLLA | poly-lactic acid |
| PMMA | polymethyl methacrylate |
| ROS | reactive oxygen species |
| SF | silk fibroin |
| TaON | tantalum oxynitride |
| TCRV | Tacaribe virus |
| $TiO_2$ | titanium dioxide |
| Ti6Al4V | titanium alloy |
| TN | $TiO_2$ nanotube |
| TNF | tissue necrosis factor |
| TPMS | triply periodic minimal surface |
| UHMWPE | ultra-high molecular weight polyethylene |
| UNCD | ultrananocrystalline diamond |
| USFDA | United States Food and Drug Administration |
| WC-Co | tungsten carbide–cobalt |

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