REVIEW PAPER

Nanoparticles to overcome bacterial resistance in orthopedic and dental implants

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ABSTRACT

An implant is a device for replacing a damaged or deformed joint, bone, or cartilage. Considering the aging population and developing culture of active lifestyles, orthopedic and dental implants have found their stance as a fundamental component of medical sector, which is envisioned to be continuous. Reducing the rate of failures, particularly in cases of bacterial infection, is a necessity for meeting the extending demands for implants. One of the major risk factors of this field is implant infection, which can reduce the effectiveness of treatment, as well as increase the need for corrective surgery or extend the chances of mortality. Traditional antibiotics are incapable of providing the desired effects due to the difficulties of bacterial resistance. The exertion of nanotechnology-based approaches can overcome most of the limitations and obstacles of implants. Nanostructures and nanoparticles can facilitate the production of implant coatings, provide suitable materials for making implants, and function as carriers for the release of antibiotics. There are a number of different nanostructures available for this purpose. Nanoparticles and microstructures contain a larger number of effective bactericidal properties than smooth surfaces due to their significantly increased level of adhesion. This study attempted to investigate the antibacterial properties of nanoparticles in dental and orthopedic implants.

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INTRODUCTION

The development of implant industry, especially orthopedic and dental implants, is growing at an incredible rate. The application of over 300 000 hip and knee implants, as well as 100 000 and 300 000 dental implants, are reported every year in the United States for replacing or restoring the functionality of injured and damaged tissues [1, 2]. As a matter of fact, the clinical utilization of implant designs throughout the recent years was quiet predictable. The purpose of designing implants is to provide a distinct interfacial layer and a biomechanically effective bone matrix. Despite being an external substance, the applied biomaterials in implants are required to exhibit biological compatibility

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and proper functionality in human system, as well as contain applicable mechanical, abrasion, and corrosion qualities. The progress of biomedical implants in orthopedic and dental implementations can be confined by a deficient bone-implant integration and implant-related infections [3]. Unfortunately, the weak design of some implants demands for improvements and better bone implants. Considering the unexpected outcomes of failures, many implant operations necessitate a corrective surgery to recover from a failed implant. One of the related statistics is about the average life expectancy, since the average lifespan of a joint replacement is only about 10-15 years[4-6]. The long-term fixation of load bearing implants (Especially metal implants) in bony tissues has remained as a challenge. Clearly, the insufficient lifetime of implants will lead to the need for many revision surgeries to remove failing implants, especially during the lives of young patients. Numerous factors contribute to implant failure, which include inadequate initial bone growth on the surface of implant that requires to be integrated into juxtaposed bone, the generation of wear debris by implant articulating components that turn into lodges among the implant and nearby tissue and cause the death of bone cells, and the inducement of implant loosening and eventual fracture by stress and strain imbalances throughout the implant and neighboring tissue, as well as device-related obstacles including insufficient integration, local tissue inflammation, and infection [7-10]. Implant-associated infections has remained as one of the principal causes of failure implications. Biofilm formation is assumed as the most essential pathogenic coincidence throughout the progress of infections, which is instantly triggered subsequent to bacterial adhesion on an implant to provide an efficient protection for microorganisms from the immune system and systemic antibiotics [11]. Post-surgery infections are the most challenging complication of orthopedic and dentistry fields. In the last few decades, the incorporation of antibiotics into bone cements was considered as an attempt throughout primary and revision surgery for preventing and treating orthopedic implant infections. However, not everyone believes in the therapeutic usefulness of antibiotic-releasing bone cements, since the long-term exposure of patients to low dosages of antibiotic-releasing bone cements has led to the current possibility of antibiotic resistance to medicine [12]. The local delivery of antibiotics is clearly more effective in transferring medicines to the affected area without causing any risks of systemic toxicity. [13]. Nanotechnology can overcome these limitations by facilitating the construction of surface structures for cell engineering and enhancing the surface structure of implants to promote osseous integration. Most of the reasons behind implant failures can be surpassed through the amazing potential of nanostructured coatings. In addition, the unique features of nanomaterials can provide the manufacturing of suitable coatings and implants as well [14, 15]. This work attempted to present a summary on the exertion of nanoparticles for controlling and enhancing the rate of implants while focusing on improved antimicrobial purposes. In this regard, we reviewed recent researches on the impacts of nanostructured biomaterials and particles for the antibacterial applications of orthopedic and dental implants to present a robust framework for understanding the basic interactions that control and prevent antibacterial processes.

REQUIREMENTS FOR SUCCESSFUL IMPLANT SYSTEMS

The property requirement of a modern-day implant can be divided into three equally significant categories[16]:

Safety and compatibility

The applied materials in the manufacturing of implants are required to be compatible with human body. Next to orthopedic and dental implants, safety concerns should include all of the implant devices as well. Specifications and standards are meant to assist producers, users, and consumers in providing safety for their products. The reaction of tissues towards the introduction of a foreign material is understandable, however, it is intolerable for the accompanying alterations in mechanical, physical, and chemical features throughout the localized surrounding to cause local detrimental changes or hazardous systemic impacts. Biological, mechanical, and morphological compatibilities are the major compatibility factors that are essential for the bio integration of implants with the receiving hard tissue and the subsequent biofunctionality[17, 18].

appealing balance of mechanical and physical qualities

An implant can achieve promising outcomes by accommodating the needed balance in mechanical and physical features. The kind and action of the particular implant portion can configure the optimization of qualities, which include elasticity, yield stress, ductility, time-dependent deformation, ultimate strength, fatigue strength, hardness, and wear resistance. As a universal requirement, the ability of implants to establish a suitable mechanical unit with the nearby hard or soft tissues must remain activated throughout the entire body. The functionality of a loose (or unstable) implant may be weakened, completely prevented, or result in an excessive tissue response, while causing discomfort and pain for the patients[19-21].

simple fabrication and reproducibility

An appealing device is required to contain a simple fabrication, reproducibility, consistency, and compliance with every technological and biological parameter. Meanwhile, there are possible limitations to be concerned, such as the design of techniques for producing outstanding surface finish or texture, the capacity of materials for obtaining adequate sanitation, and manufacturing costs, as well as having repairing methods for the cases of failure[16, 22, 23].

WHY ARE IMPLANTS NEEDED?

Implants can be defined as devices that are designed for replacing a damaged or deformed joint, bone, or cartilage. Synovial joints, such as the pelvis, knee, and shoulders, can operate as a result of this combined effort. A nourishing fluid is released by articular cartilage, which is a bearing connector tissue responsible for covering the bones of joints[24, 25]. However, these joints are prone to degenerative and inflammatory disorders throughout the common area and lead to the inducement of joint pain and stiffness. The common joint cartilage caries (softening of cartilage) are caused as a result of aging, as well as other disorders such as osteoarthritis (bone inflammation), osteoporosis, rheumatoid arthritis (synovial membrane inflammation), and chondromalacia. Interestingly, 90% of people over the age of 40 suffer from such destructive diseases [16, 26-28]. Degeneration is mainly originated by three factors including the deficiency of joint biomaterial features, overload conditions, and the collapse of common repair mechanisms [29-31]. Although minor surgical procedures are carried out, there is a definitive agreement to provide temporary support for a large number of patients, implicating inefficient Joints for pain relief and long-term mobility as the natural replacement phase. In severe situations, implants can replace or heal human joints. The complicated and elegant construction of human joints is abled to operate in life-threatening situations, therefore, the development of site-specific implants that would be applicable in human body is a major issue for surgeons and scientists [32-35]. Implants are widely exerted in the fields of surgery, orthopedics, and dentistry, while their other applications include ophthalmology, cardiovascular, cochlear, and maxillofacial implementations[36-38].

orthopedics and dentistry implants

Millions of people around the world suffer from degenerative and inflammatory bone and joint diseases. In affluent countries, people aged over 50 years old are accounted for half of all the chronic diseases These disorders are in the frequent need of surgery, as well as total joint replacement in the cases of natural joint deterioration. Furthermore, a variety of bone fractures, low back pain, osteoporosis, scoliosis, and other musculoskeletal issues demand for treatments with the exertion of permanent, temporary, or biodegradable devices. As a result, orthopaedic biomaterials are designed to be implanted as the components of a device in human body to perform particular biological functionalities through the replacement or repairing of various tissues such as bone, cartilage, ligaments, and tendons, which can also act as a guidance for bone repairs in specific situations [39, 40]. A range of orthopedic prosthetic implants are exerted by orthopedists for the purposes of replacing missing joints and bones, or to provide support for a damaged bone. Orthopedists most typically utilize knee and hip prostheses to restore the complete range of motion for patients in a relatively pain-free and short period of time. Prosthetic materials can be incorporated with a healthy bone to replace the sick or damaged bone in some circumstances, whereas prosthesis can completely replace certain parts of a joint bone [41, 42]. The method of tooth extraction subsequent to an immediate implant placement is the most typically applied surgical practice in recent years. The objective of modern dentistry is to revive the normal function, speech, health, and appearance of patients, regardless of stomatognathic system atrophy, disease, or damage. Considering this goal, dental implants can serve as an ideal choice in the cases of patients with a lost tooth (or teeth) due to periodontal diseases, injuries, or other conditions. Subperiosteal implants, endosseous implants with fibrous encapsulation, and endosseous implants with direct bone-to-implant contact (BIC) are included among the implant systems that are utilized for replacing missing teeth. Dental implants (also known as artificial tooth roots) are biocompatible metal anchors that are surgically positioned underneath the gums of jaw bone (also known as medically traumatised bone) to support the artificial crown of places where natural teeth are missing. The healing period of non-union (due to traumatization) bone can range from three to six months or more upon the usage of root form implants (as the closest sample in shape and size to the natural tooth root), which also undergoes the occurrence of osseointegration. The growth of bone in and around the implant provides a strong structural support for the upcoming attached or screw-tightened superstructure [15, 43, 44]. The rate of implants usage in the oral and maxillofacial skeleton is being constantly increased. For instance, the placement of 300,000 dental implants are estimated to occur each year in United States. The application of implants can facilitate a replacement for missing teeth, repair the craniofacial skeleton, provide anchorage during orthodontic treatments, and even aid the formation of new bones in the course of distraction osteogenesis process[45-47].

Risk Factors related to Failure of Dental and orthopaedic Implants

The provision of informed consent is a necessity for every clinical treatment, which refers to the patients permission for taking the proposed treatment subsequent to understanding the nature of illness, procedure description, risks and benefits, and treatment alternatives that include the option of no treatment. Although a written consent does not always stand for a informed consent, but in comparison to discussion and verbal consent, this format is easier to comprehend and recall at a later date, while providing proof for consent considerations. Treatment is contraindicated upon the patients lack of acceptance or agreement with the recommendations. In addition, implant therapy may be unsuitable for patients who are incapable or reluctant to maintain active oral diseases, as well as those with absurd treatment expectations [48-50].

Since their introduction by Branemark in 1970s, dental implants found their popularity as an appealing treatment for missing teeth rehabilitation. Nevertheless, there are limitations to this procedure that include the reports on the rate of dental implant failure ranging from 1% to 19% . Based on the connected abutment, these collapses can be classified in the two categories of early failure and late failure. Early failures take place in prior to applying the functional loading, whereas the progress of late failures can be observed subsequent to the occlusal loading or the first removal of temporary restoration in the cases of immediate implant loading. Early failure refers to the failure of dental implants in maintaining osseointegration, whereas late failure expresses the collapse of either established osseointegration or performance of dental implants. Considering how the early failure is mainly caused by biological complications, the occurrence of late failure can be possibly related to both biological and mechanical complications. Peri-implantitis commonly implicate the resorption of soft and hard tissue, while its inducement is associated with biological difficulties. Mechanical complications may occur as a consequence of incorrect implant loading design and lead to the fracture of implant body, screw body, or implant supra-structure[51-54]. Next to including a larger percentage of bone loss, the time interval between diagnosis and removal of a dental implant in late failure is substantially longer than the cases of early failure. Treatment planning for the entire dentition should be completed in prior to the surgical planning for implant placement. Systemic diseases impose the usual limits on minor surgical operations, which involve implant placement as well. There is a paucity of evidence to support systemic illnesses as a contraindication to oral implant therapy [52, 55].

Uncontrolled hypertension is a condition of blood pressure that regularly reaches higher than 160/90 mm Hg. This disorder requires immediate treatment due to the risks of high blood pressure for the patient, which include the occurrence of stroke, heart failure, myocardial infarction, and renal failure. Patients with a history of heart attack in their last six months should be prevented from implant surgery, while the cases that suffer from angina must be provided with glyceryl trinitrate tablets or sublingual sprays throughout the procedure[48, 55]. implant failure is associated with smoking, diabetes, autoimmune illnesses, osteoporosis, bisphosphonates, periodontitis-related tooth loss, genetic factors, local anatomy, and radiotherapy. Periodontal disease and smoking are considered as crucial risk factors for the late failure of implants [56-61]. Other prevalent late fracture risk factors are categorized into three sections based on (1) patients history (radiation therapy, periodontitis, gritted teeth, and premature implant failure), (2) clinical characteristics, or (3) both (posterior implant position, and bone grade), while considering the question of were there any(4) or (5) doctor's decisions? (low initial stability, more than one implant in the course of surgery, inflammation at the surgical site during the first year, or usage of a cone-type overdenture). It is necessary for the doctors to remain cautious from the initial stages of evaluation up to treatment planning, surgery, and prosthesis selection to reduce the chance of late dental implant failure [62]. A delay in cleaning the infections at surgical site after spinal deformity surgery results in the need for the removal of implant. Patients may be required to repeat the instrumentation and fusion upon the development of exceeding deformity or symptomatic pseudoarthrosis subsequent to the implants removal [63].

Surgical site infections account for nearly 3% and up to one-third, of all the nosocomial infections. The consequences of induced complications by these infections in the implantation of a prosthesis, such as a hip replacement, can be devastating. Joint replacement infections commonly affect 0.5–5% of patients. Nevertheless, providing treatment for these infections in the course of retaining the position of prosthetic remains as a difficulty [64].

Risk factors associated with implant infections

Infection is known as another serious side effect of implant surgery, which can lead to long-term clinical consequences and significantly increase the difficulty and cost of therapy [65]. Biomaterial-associated infection is a common impact of modern orthopaedic surgery with the potential of inducing long-term pain and functional loss in patients. Facing infection in an orthopedic surgery can be a disaster for the patient and the surgeon, while surgical site infections (SSIs) are very common in this kind of surgery. According to current estimations, periprosthetic joint infection complicates up to 2.5 percent of primary hip and knee arthroplasties and up to 20% of revision arthroplasties Prosthetic joint infection (PJI). Although modern facilities and aseptic procedures have reduced the incidence of this obstacle, yet its prevalence remained significant in developing countries. The consequences of this severe condition include increased antibiotic usage, prolonged stay in hospital, repeated debridements, longer period of rehabilitation, and increased morbidity and mortality. Furthermore, eradication is another challenging problem due to the pathophysiology of infection in fracture-fixation devices that is attributed to growing microorganisms in biofilm. The three stages of infection include early (less than two weeks), delayed (two to ten weeks), and late (more than ten weeks) infections[66-69]. Staphylococcus accounts for up to two-thirds of every existing microorganism throughout orthopedic implant infections, which stands as the primary cause behind the two principal forms of bone infections, septic arthritis and osteomyelitis, both of which implicate inflammatory joint and bone damage. Bacterial adherence is recognized as the first and most crucial step of implant infection. This complex process can be affected by various factors such as environmental conditions, bacterial characteristics, material surface qualities, and the presence of serum or tissue proteins [41].

Similar to other body implants, dental implants can collapse by the increasing accumulation of plaque that is mostly generated by the two pathogens of Streptococcus mutans and Porphyromonas gingivalis. The placement of dental implants in the contaminated surgical field of oral cavity can exceed the risk of implant failure [70, 71]. Implant infections are frequently caused by bacterial adhesion, while proliferation Caries and periodontitis are both generated through the bacterial adherence to tooth surfaces. The existing biofilms on the surfaces of dental implant can induce inflammatory lesions in peri-implant mucosa, which can result in the inhibition of osseointegration, leading to the loss of nearby bone substances and in worst-case scenario, cause a total implant failure. According to the majority of case studies, these biofilm-forming bacteria promote colonization on the fixed appliances of prosthodontic therapy, which damages the periodontal tissues. In addition, facing instability or mismatch conditions in the implant-abutment contact is another common cause of failures in dental implant treatments. The presence of microcracksmicrocracks on the joint surface of two-piece implants, which contain variable fluid flow, can facilitate the infiltration of bacteria and inflammatory cells and lead to the inducement of bone resorption in the surrounding area. Periodontitis-associated germs can colonize the bacterium throughout the early minutes of its implantation . This fixture-abutment gap (FAI) is a suitable environment for the growth of bacteria, resulting in a bacterial reservoir and inducing the inflammation of soft tissues at the fixture-abutment junction [72-74]. The production of biofilm is triggered right after bacterial adhesion on an implant, which provides an efficient protection for microorganisms from the immune system and systemic antibiotics. This process is considered as a crucial pathogenic event in the generation of implant-related infections. In the form of bacterial groups, biofilms are accountable for the majority of chronic and recurrent infections. Next to the recurrence of about 65–80 percent of biofilm-related infection cases, the rate of antibiotic resistance is also high among the associated bacteria with biofilms. In laboratory studies, bacteria with antibiotic resistance have displayed a considerably reduced susceptibility to antimicrobials as a result of certain processes such as altered drug absorption, changing drug target, and drug inactivation; these observations were in accordance with the standard view of antibiotic resistance[75, 76]. Considering these facts, it is questionable that is there a way to overcome this problem?

NANOTECHNOLOGY-ENABLED MATERIALS FOR ANTI-INFECTION TREATMENTS IN IMPLANTS THERAPHY

Nanotechnology implicates the investigation and exertion of materials propertied that were dramatically changed in nanoscale (1–100 nm or 10^{-9}–10^{-7} m) or atomic scale. This field has succeeded in exhibiting a great potential in the fields of medical science and biomedical engineering[77]. Polymer nanoparticles, magnetic nanoparticles, liposomes, carbon nanotubes, quantum dots, dendrimers, metal nanoparticles, and non-polymer nanoparticles can be listed among the examples of nanotechnology-based systems that are classified as pharmaceutical nanoparticles[78-81]. NPs are gifted with unique physical and chemical characteristics due to their high surface area and nanoscale size, while their reactivity, toughness, and other features are also affected by their distinctive size, shape, and structure [82, 83]. The accommodation of these properties has created suitable candidates for a variety of commercial, diagnostic, and medicinal applications including catalysis, imaging, cancer therapy, antimicrobial, medicinal, energy-based research, and environmental implementations[81, 83-87]. The ability to study compounds at molecular level has guided the search of materials with exceptional qualities for medical applications. The usage of these unique materials has spawned a new study field known as nanobiotechnology, which can be applied to disease diagnosis, drug design and delivery, and implant design [88]. Considering the aging population and developing culture of active lifestyles, orthopaedic and dental implants turned into one of the staples of medical industry and this trend is expected to be continuous. In response to the exceeding demands for implants, it is necessary to reduce the rate of failures, especially those that are generated by bacterial infection[89, 90]. Potential bacteria carriers include the implant itself, surgical tools, the operating room, and contaminated disinfectants. Implant materials are an appealing location for the adhesion of bacteria, which can compromise the patients immunity and heighten the risk of bacterial infection. The existing bacteria [mostly Pseudomonas aeruginosa (P. aeruginosa), including Staphylococcus aureus (S. aureus), and Staphylococcus epidermidis (S. epidermidis)], tend to adhere to the surface of implants and produce a layer of preprosthetic biofilm with resistance properties to antibacterial treatment. The infection may progress into local inflammation or spread throughout the body and lead to the inducement of a chronic infection. Nevertheless, the early replacement of an implant can prevent amputation or death. [41]. Some of the consequences of this severe condition include prolonged hospitalization, long-term antibiotic therapy, bacterial resistance, the emergence of superbugs, revision surgery, or death. The approach of antibiotics and antibacterial coatings were designed in the last two decades for reducing the chances of revision surgery and rates of infection-related death. The rapid spreading of bacterial resistance to antibiotics over the world has turned into a major public health concern, which seems to be unsolvable due to the numerous resistance mechanisms. Overexpression of relative efflux pump activity is reported to be a common and important source of bacterial resistance. Efflux transporters in the membranes of resistant bacteria may contain a crucial functionality in inhibiting intracellular drug intake and obstructing drug activities. The ineffectiveness of these methods prompted the conduction of research on the design of nano-textured surfaces to mimic the bactericidal

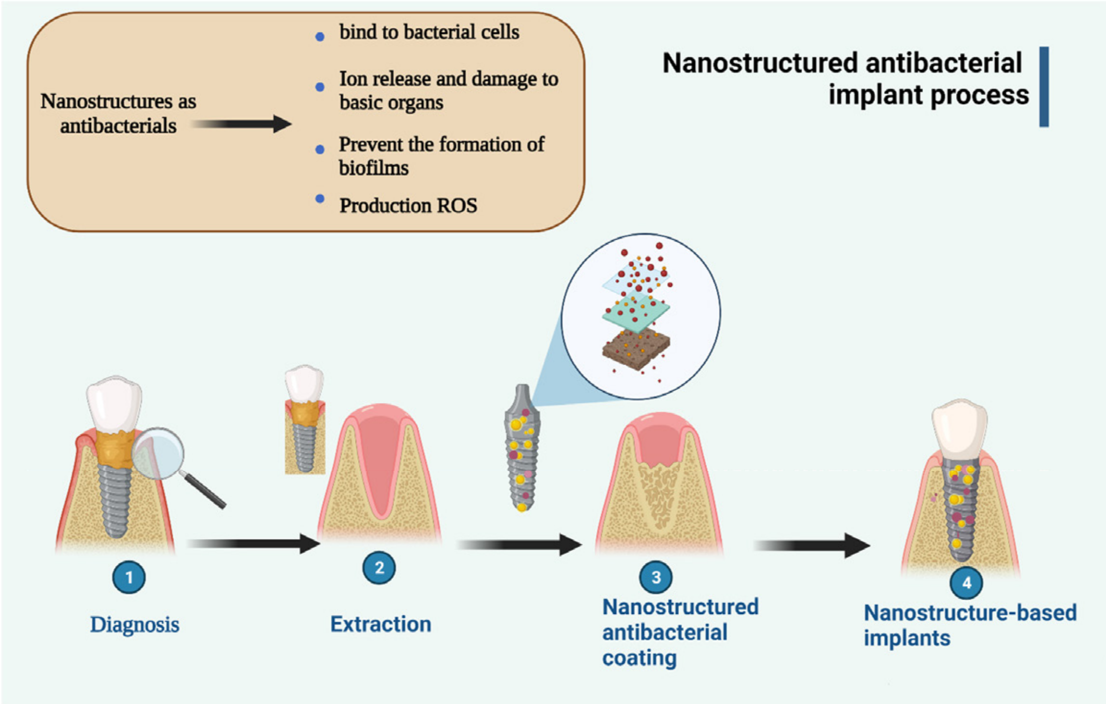

Fig. 1. Applications of nanoparticles in the prevention of bacterial infections in dental implants

capabilities and topographical characteristics of various animal, plant, and insect species [89, 91]. Researches tended to focus on the production of materials with nanostructured surfaces for limiting the growth of bacteria, biofilm formation, and ultimately bacterial infection without causing side effects, with the aim of reducing the chances of requiring revision surgery. Considering their wide application as encapsulating materials, nanoparticles (NPs) have the potential to boost intracellular drug accumulation and efficiently inhibit the activity of transporters [92]. Postoperative infection caused by medical implants emerged as a formidable but crucial obstacle in implant surgery, which sparked a flurry of nanotechnology research. The main applications of nanotechnology in implant therapy include bone replacement materials and implant coatings (production of biocompatible surfaces, for example, by implicating immobilized antimicrobial agents). Aside from antibiotics and nano particle [93, 94], the contact to adhesion area of nano and microstructures is significantly increased, which leads to the generation of more effective bactericidal properties than flat surfaces. The height, radius, and spacing of a structure can affect the bactericidal efficiency of surfaces. Bactericidal or anti-biofouling surfaces have the ability to repel the adherence of bacteria. Moreover, anti-biofouling surfaces can inhibit the inducement of cell attachment due to their surface chemistry or undesirable surface topography, whereas bactericidal surfaces cause the disturbance and ultimately annihilation of cells[95, 96]. Current antibiotic treatments are still incapable of targeting bone infection sites and eventually result in ineffective therapeutic outcomes. However, the design of nanostructures gave rise to the possibility of targeted therapy[97]. As a matter of fact, nanoparticles bind to bacterial cells due to their small size to disrupt and damage their membrane, which consequently results in bacterial cell death. The antibacterial properties of nanoparticles were proved to be effective against Both gram-positive and gram-negative bacteria. These materials can contribute to bacterial death by releasing ions with the ability to attack many parts of bacteria, such as enzymes, DNA, proteins, Cytomembranes, and etc. At the same time, nanoparticles have the potential to boost the production of bacterial reactive oxygen species (ROS) that can cause oxidative destruction in cellular components[98-102] (Figs. 1). Denaturation is the result of nanoparticles interaction with ribosomes in particular, which leads to the inhibition of translation and protein synthesis. Furthermore, the effective interaction of nanoparticles with carboxyl and thiol groups of -galactosidase has the potential to inhibit intracellular biological activities and induce cell death [103]. Nanoparticles can damage the cytoplasmic membrane of bacteria and impair cell respiration by preventing the entry of oxygen to cells, which leads to the suffocation and death of bacteria [104-106].

The weak penetration of these biomolecules is

Table 1 Use of antibacterial nanostructures in orthopedic implants

Types of nanostructure	The role of nanostructure	Application	Reference
silver nanoparticles	-as a coating on hydroxyapatite	-antibacterial activity	[109]
Hydroxyapatite (HA) nanoparticles + silver (Ag) nanoparticles	-as a bifunctional bone scaffold	- hydroxyapatite (HA) to form organic/inorganic composite with suitable levels of bioactivity -silver (Ag) nanoparticles were abled to add antibacterial qualities	[110]
HA/Cu Nanostructures	-as coatings on the surface of titanium	- composite coatings are able to induce the formation of apatite - improve the friction properties - Improve antibacterial activity up to a rate of 97%	[111]
Silver nanoparticles (Ag-NPs)	multifunctional core (Ag-NPs)–shell (pDA)–shell (HAp) nanoparticles (Ag@pDA@HAp-NPs)	- Improved hemocompatibility - reduced the cytotoxicity - obtained long-term antibacterial qualities	[112]
silver (Ag) nanoparticles	-as strawberry-like Ag-decorated barium titanate of polymer scaffold	- improved the electric output functionality of the scaffold - The enhanced surface electric charges caused a notable promotion in proliferation and differentiation of MG-63 cell - The scaffold prevented the growth of Escherichia coli by releasing Ag+	[113]
nano-structured titania +silver nanoparticles	-nano-structured titania coating incorporated with silver nanoparticles	- prevent bacterial adhesion - inhibit post-operation infection in the early and intermediate stages and perhaps even late infection around the implant	[114]
silver nanoparticles+ HA nanocrystals	-produced porous Ti-6Al-4V implants	- enhanced the proliferation and differentiation of pre-osteoblasts - maintain the antibacterial leaching activity	[115]
Silver Nanoparticles	-incorporation of both growth factors and silver (Ag) into hydroxyapatite (HA) coatings on metallic implant surfaces	-improving osteoinductivity and antibacterial properties	[116]
Ag Nanoparticles	-as Bioactive Coating on Ti AlloyIn dental and orthopedic implants	-Improve Osseointegration and Antibacterial	[117]

Continued Table 1 Use of antibacterial nanostructures in orthopedic implants

Types of nanostructure	The role of nanostructure	Application	Reference
nanostructured titania +silver nanoparticles	-as a promising therapeutic material for orthopedic application	- influence on normal bone-implant integration - Long-term antibacterial qualities and the capable of preventing biofilm production	[118]
Nanoparticulate zinc oxide	-as a coating material for orthopedic and dental implants	- prevent bacterial adhesion -generate the growth of osteoblast	[119]
nanostructured hydroxyapatite (nanoHA) +zinc oxide (ZnO) nanoparticles	-as three-dimensional and interconnected porous granules as a template for bone regeneration	- as a template for bone regeneration - restrain biomaterial-associated infections	[120]
zinc oxide nanoparticle	-development of ZnO polymer composites for many applications, including endotracheal tubes, catheterp and implanted biomaterials	- reduction in Staphylococcus aureus proliferation and biofilm formation	[121]
ZnO nanoparticles	-as a multifunctional polypyrrole/zinc oxide composite coating on biodegradable magnesium alloys for orthopedic implants	- The Ppy/ZnO coating displayed suitable cytocompatibility and osteogenic differentiation - efficient in preventing bacterial adhesion and growth	[122]
Zinc Oxide/Poly(Lactic Acid) Nanocomposite	- as Layer Coated on Magnesium Alloys	- Improve Antibacterial Function	[123]
silica/zinc oxide hybrid nanoparticles	- as constructed on titanium implants	- enhancing antibacterial ability	[124]
titanium dioxide nanotubes+ zinc oxide +hydroxyapatite nanoparticles	as a nanoporous coating Multilayered	- a stable and antimicrobial coating	[125]
Poly(lactide-co-glycolide) (PLGA) nanospheres	-as a carrier of vancomycin and gentamicin in Schanz pins	- superior biocompatibility - long-term antibacterial activity	[126]
chitosan nanoparticle	-carrier of ciprofloxacin as a coating on titanium implants	- efficient antibacterial activity	[127]
titania nanotubes	-carrier of gentamicin sulphate (GS) as biomaterials in implant construction	- inhibiting the initial release and peri-implant infection in the field of orthopaedics	[128]
chitosan nanoparticles (CNPs)	carrier of Vancomycin in orthopedic implant	- enhancing antibacterial and antibiofilm	[129]
Silk fibroin nanoparticles	carrier of gentamicin as a coating in titanium-based orthopedic and dental implant	- sustained drug release -Improves osteoblast adhesion, proliferation and differentiation	[130]

Continued Table 1 Use of antibacterial nanostructures in orthopedic implants

Types of nanostructure	The role of nanostructure	Application	Reference
poly(ethylene glycol) (PEG)-based hydrogel	- coatings on osteoarticular Ti implants	- sustainable drug release and maintain an effective concentration for a longer time - efficient strategy for the treatment and inhibition of local bone infections	[131]
chitosan-gelatin/silica	-carrier of gentamicin drug as Versatile bioactive and coating system of titanium implants	- enhancing antibacterial ability	[132]
chitosan/gelatin/silica nanoparticles	-carrier of gentamicin coatings through the electrophoretic deposition on surgical grade stainless steel	- enhancing antibacterial ability	[133]
mesoporous silica NPs	- carrier of the drug vancomycin	- excellent biocompatibility and effective antibacterial	[134]
silica nanocarriers	- carrier of the drug gentamicin	- controlling and extending the release of the antibiotic	[135]
chitosan–Laponite nanocomposite	- carrier of vancomycin as chitosan – Laponite nanocomposite coatings in bone implants	- improved cell attachment - drug-release rate through a longer period	[136]
mesoporous silica nanoparticles	- carrier of gentamicin	- excellent mechanical properties - sustainable drug delivery efficiency - orthopedic surgery to prevent post-surgery infection	[137]
Magnesium Oxide (MgO) and Zinc Oxide (ZnO) nanoparticles	- fabricating nanocomposites for developing artificial bones and biomedical implants	- enhanced antibacterial properties	[138]

Table 2. Use of antibacterial nanostructures in dental implants

Types of nanostructure	The role of nanostructure	Application	Reference
chitosan conjugated silver nanoparticle	- as a prospective coating material of titanium dental implants	-inhibits the adhesion of S. mutans and P. gingivalis - reduce the biofilm formation	[70]
zinc oxide + hydroxyapatite nanoparticles	-as dental implant coating materials	-anti-biofilm activity	[139]
copper + zinc oxide nanoparticles	-as a potential disinfectant material of connections in implant provisional abutments	- increases bactericidal activity via: - exceeded LDH release and intracellular ROS generation - generated the production of cleaved caspase-3 -activating the apoptotic pathway	[140]
Nanocomposite Titania-Zinc Oxide	- as thin films on Si substrates for Dental Implant	- improve the bonding of metallic fixture with bone - inhibit the growth of both Staphylococcus aureus and Escherichia coli	[141]
nanoporous silica nanoparticles	-carrier of chlorhexidine drug - as medical implant coating or as components in dental composite materials	- efficient controlled drug release system for long-term delivery - treatment of biofilm-associated infections	[142]
hydroxyapatite (HAp) nanoparticles	- carrier of gentamicin sulfate (Gs) and ciprofloxacin (Cip)	- efficient inhibition of Pseudomonas aeruginosa bacteria	[13]
cerium oxide–incorporated calcium silicate coatings (CeO2-CS)	-as coatings (CeO2-CS) in dental implants	- strong antimicrobial activity - good biocompatibility - promote the osteoblastic differentiation of osteoblasts	[143]
zinc oxide nanoparticles (nZnO)+ nanohydroxyapatite (nHA)	-as a coating material tobone implants	-improve antimicrobial -biocompatible	[119]
graphene/zinc oxide nanocomposite (GZNC)	- as an effective coating agent for dental implants	- inhibiting *Streptococcus mutans* biofilms	[144]
Zn(O) nanoparticles+ Porous tantalum oxide	- as coating for dental implants	- prevent initial bacterial colonization	[145]
graphene-oxide nanosheets (nGO)+ PMMA	as coating for dental implants	- prevent microbial adhesion - improved mechanical properties - increasing the hydrophilicity	[146]
polymethyl methacrylate (PMMA)+ silk fibroin + polyethyleneimine	-material in dental applications, particularly as denture resins	- improve antibacterial activity - improve mechanical	[147]
	-functional dental restoration material	- enhance both mechanical and antibacterial properties	[148]

Continued Table 2. Use of antibacterial nanostructures in dental implants

Types of nanostructure	The role of nanostructure	Application	Reference
polymethyl methacrylate (PMMA)+ titanium dioxide (TiO2)Np + polyetheretherketone (PEEK)			
calcium fluoride nanoparticles	- dental nanocomposites	- superior mechanical - fluoride releasing	[149]
Zinc Oxide +Calcium Fluoride Nanoparticles	- sealants to develop caries-inhibiting and stress-bearing sealants	- enhance mechanical and antibacterial properties	[150]
calcium fluoride nanoparticles (CaF2-NPs)	- as a coating on dental implants	- inhibition of biofilm formation	[151]
nano-hydroxyapatite	- dental restorative composite (DRCs)	- achieve better interfacial strength - Improve physical and mechanical properties	[152]
hydroxyapatite nanoparticles	-dental materials	- infection control - enhance antibacterial properties	[153]
silver nanoparticles	-as a coating on Ti substrates	- good antibacterial activity against Lactobacillus salivarius	[154]
Poly-l-lysine/Sodium Alginate+ Nanosilver	-as a coating on dental Implants	- prevent bacterial infections - enhance the cytocompatibility	[155]

due to their lack of water solubility, which may be resolvable through the synthesis of antimicrobial nanoparticles for improving their activity[70]. In comparison to native biomolecules, nanoparticles can be more effective as a result of their superior dispersion ability and access to deeper tissues. They can ensure the delivery of biomolecules deep within the body and release the bioactive chemicals at the desired location, succeeding in causing high levels of bactericidal effects upon the release[70, 107, 108]. Tables 1 and 2 present the types of applied nanostructures in orthopedic and dental implants that contain antibacterial properties and can take a role in reducing or preventing infections caused by implants.

CONCLUSION

The presented studies exhibited a perspective of using different nanostructures in dental and orthopedic implants and described their antimicrobial activity. The introduced innovations in this work discovered a new vector of development for the dental and orthopedic materials and composites with the aim of improving the quality of patients lives. The ongoing assessment of researchers on dental and orthopedic nanomaterials is focused on their capability to maintain their antimicrobial effects, low cytotoxicity, and high strength over time. These nanomaterials can lead to promising horizons for having better performances and consequently improve the quality of patients lives.

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CONFLICT OF INTEREST

Te authors declare no conflicts of interest

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