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# Potential role of metal nanoparticles in treatment of peri-implant mucositis and peri-implantitis

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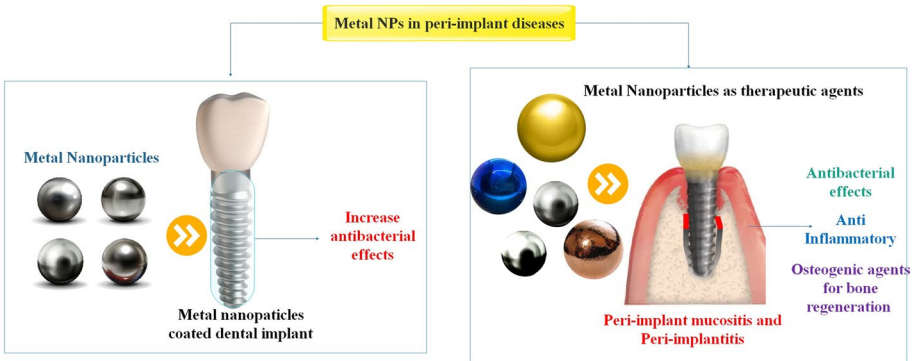
## Abstract

Peri-implantitis (PI), a pathological condition associated with plaque, affects the tissues around dental implants. In addition, peri-implant mucositis (PIM) is a precursor to the destructive inflammatory PI and is an inflammation of the soft tissues surrounding the dental implant. It is challenging to eradicate and regulate the PI treatment due to its limited effectiveness. Currently, there is a significant interest in the development and research of additional biocompatible materials to prevent the failure of dental implants. Nanotechnology has the potential to address or develop solutions to the significant challenge of implant failure caused by cytotoxicity and biocompatibility in dentistry. Nanoparticles (NPs) may be used as carriers for the release of medicines, as well as to make implant coatings and supply appropriate materials for implant construction. Furthermore, the bioactivity and therapeutic efficacy of metal NPs in peri-implant diseases (PID) are substantiated by a plethora of in vitro and in vivo studies. Furthermore, the use of silver (Ag), gold (Au), zinc oxide, titanium oxide ($TiO_2$), copper (Cu), and iron oxide NPs as a cure for dental implant infections brought on by bacteria that have become resistant to several medications is the subject of recent dentistry research. Because of their unique shape-dependent features, which enhance bio-physio-chemical functionalization, antibacterial activity, and biocompatibility, metal NPs are employed in dental implants. This study attempted to provide an overview of the application of metal and metal oxide NPs to control and increase the success rate of implants while focusing on the antimicrobial properties of these NPs in the treatment of PID, including PIM and PI. Additionally, the study reviewed the potential benefits and drawbacks of using metal NPs in clinical settings for managing PID, with the goal of advancing future treatment strategies for these conditions.

**Keywords:** Metal nanoparticles, Peri-implant mucositis, Peri-implantitis, Antibacterial effects, Dental implant

**Graphical abstract**




## Introduction

Although dental implants have demonstrated remarkable efficacy in tooth replacement over the past few decades, with survival rates surpassing 95% over a decade, the longevity of implants is compromised by biological complications [1]. Depending on the population studied and the case definition used, epidemiologic data on peri-implant diseases (PIDs) worldwide show various results. When it comes to dental implants, one common operation is alveolar ridge augmentation [2, 3]. The results of clinical trials comparing the long-term survival rates of implants inserted into pristine bone versus augmented bone remain contentious. Although specific studies have found similar results regarding implant survival rates and marginal bone loss, alternative research has documented substandard outcomes when implants are positioned in augmented sites [4, 5]. PIDs might arise during implant treatment. Peri-implant mucositis (PIM) (23.9–88.0% at the patient level and 9.7–81.0% at the implant level) and peri-implantitis (PI) (8.9–45% at the patient level and 4.8–23.0% at the implant level) have varying prevalences, according to several research. Furthermore, several research concluded that PIM and PI were highly connected with inadequate oral hygiene and maintenance [6, 7]. PIDs are inflammatory disorders caused by biofilms that are characterized by the disintegration of tissue. Mucositis, an inflammation limited to the soft tissues, is the first sign of the condition. It is likely to develop into PI, characterized by bone loss as a host response mechanism to bacterial plaque and its byproduct if it is not well addressed with medication. Remarkably, research has shown that the microbiome present in periodontitis lesions is not the same as the microbial profile PI [8].

Numerous new dental studies have highlighted the possible connections between systemic inflammation and peri-implant health. These include uncontrolled diabetes mellitus, psychological stress, obesity, cardiovascular disease, and infectious diseases like COVID-19. Because PI is an inflammatory condition, it may cause systemic inflammation by increasing the amounts of pro-inflammatory cytokines in the blood, which may have unclear effects on general health [9]. PIM inflammation may also contribute to an individual's burden of vascular disease. The initial indication of peri-implant inflammation necessitates applying a specific periodontal treatment. To

prevent damage to the implant surface, special dental instruments are necessary for implant interventions. These instruments include plastic and titanium (Ti), as well as glycine air-powder abrasion, which is preferable to calcium-carbonate due to the smaller particle size. To guarantee primary and secondary prevention, it is necessary to conduct routine oral and radiographic examinations [10].

Since the presence of a dysbiotic biofilm characterizes every PI, current treatment approaches are predicated on anti-infective theories. Controlling the infection, stopping the loss of bone if feasible without sacrificing aesthetics, and promoting bone regeneration—ideally including implant re-osseointegration—are the primary objectives of treating PI. According to preclinical research, re-osseointegration on an implant surface that has previously been polluted is conceivable but unpredictable. It is acknowledged that non-surgical treatment of PI has variable success rates and produces only modest improvements (in terms of clinical attachment level gain and probing-depth reduction) when compared to baseline, regardless of the kind or method of instrumentation or use of any adjuncts. Specifically, a systematic review found that no non-surgical strategy could be better than any other such approach, even if mechanical debridement combined with adjunct chemotherapeutic measures (antibiotics or antiseptics) may have little additional impact over mechanical debridement alone. Because of this, non-surgical therapy is seen as an essential component of managing PI, even if its ability to control the disease is limited, particularly in instances that are moderate or advanced [11].

Even though topical antibiotic application may theoretically provide additional benefits, there are still some issues that need to be resolved in the non-surgical treatment of PI. For instance, it is still unclear how deep the peri-implant pockets should be to determine whether or not topical antibiotic treatment is appropriate. As a result, the combination of clinical and microbiological indicators may help diagnose and treat PI. Therefore, the microbial investigation and analysis may provide helpful information to advise on selecting the right antibiotic medication, route of administration, and antibiotic regimen before opting to treat PI with supplementary antibiotic treatment. Nonetheless, the need to restrict the use of antibiotics in periodontal treatment arises from the ongoing evolution of bacterial species resistant to antibiotics [12].

Alternatively, for more severe cases, open flap mechanical debridement in conjunction with resective and/or regenerative therapy methods has been more strongly recommended. You may choose between non-augmentation and augmentative therapy when it comes to surgical treatments for PI. Aesthetically undemanding regions with horizontal bone loss may be treated with non-augmentation procedures such as open flap debridement (OFD) and resective therapy [13]. Although bacterial colonization is the cause of PID, the implant's microroughness surface may provide a valuable niche for the collection and growth of potential microorganisms. It is now recognized that the maintenance of long-term stability depends on avoiding/minimizing physiologic bone loss resulting from surgical trauma or the development of supra-crystal connective tissue attachment. Generally speaking, there is a much greater chance of developing peri-implant problems and implant failure later on if the initial bone loss is more than ~0.5 mm. Therefore, it is hypothesized that when bone loss exposes the implant surface to the peri-implant sulcus, bacterial colonies on the implant surface develop and cause inflammation.

Consequently, it is crucial to recognize and use the surgical and prosthetic aspects that may help to minimize early bone remodeling to avoid biological problems [8, 14, 15].

Additionally, long-term evidence demonstrates that although surgical outcomes after PI therapy help prevent additional bone loss and implant failure, they are still unpredictable in reducing inflammation. Both retrospective and prospective trials demonstrated that in situations of further PI collapse, rescue care and implant removal were required [16]. Although dental implant treatments have satisfied successful outcomes, the pathogenesis of the peri-implant tissues (PIT) can still present complications that threaten the long-term survival of implants, such as PIDs. Many studies have reported the varied prevalence of PIM. In addition, compared to PIM, PI is more difficult to manage for the problem of decontamination of the roughened and threaded surfaces on exposed implants and requires more advanced treatment modalities [17].

Scientists discovered that using nanoparticles (NPs) may be a valuable way to address some of the issues that dental implants confront. Their superior physical characteristics and sterilization can ensure the implants' success [18]. A potential replacement, nanodentistry, is expected to have a US$ 1.98 billion worldwide market because of advances in dental technology and increased awareness of oral hygiene. Several nano-formulated medicines are now being developed by researchers to lessen periodontitis, PI, and oral infections. For example, the management of dental health has been the subject of many studies on nanozymes, a form of NP consisting of catalytically active multivalent metal components. Researchers showed that adding antibacterial agents to the nanozymes significantly improved dental conditions, including hypersensitivity, tooth caries, and other bacterial infections. Additionally, it has been shown that metal and metal oxide NPs, such as those made of copper (Cu), zinc (Zn), silver (Ag), and gold (Au), may inhibit a variety of bacterial strains and treat oral health problems. As a result, their bactericidal qualities are often used in nanoformulations to create a synergistic effect between the drug's active ingredients and the NPs [19–21].

Furthermore, coatings for the implant surface may be made from carbon nanomaterials such as carbon nanotubes, graphene and its derivatives, graphene oxide, and graphene quantum dots. Their capacity to be functionalized with suitable chemical groups and their antibacterial qualities make them very helpful for enhancing biocompatibility and encouraging osseointegration [22]. Moreover, Ti nanotubes are employed for improved tissue integration in dental implants, alone or in conjunction with biological agents or medications. Titania nanotubes, graphene, and biopolymers—sometimes laden with anti-inflammatory drugs and extracellular vesicles—have been effectively used in immunomodulation and to prevent implant rejection. The antibacterial qualities of metal NPs, chitosan, and hybrid coatings containing antibiotic agents may be used to avoid PI. Though this research has shown encouraging outcomes, further study is required to evaluate their clinical behavior in people before they can be widely commercialized [23].

However, the primary disadvantage of these methodologies is the possible toxicity and gradual accumulation of the metals [24]. Biomaterials, which encompass dental implants and their associated components, are defined as "any material, whether natural or synthetic, that can be utilized for an extended period to interact with biological systems to enhance or preserve the quality of life of any individual." Currently, Ti is considered the

most beneficial biomaterial in dental implant therapy for connecting the abutment and the implant fastener. Biomaterials have garnered significant interest as potential coatings for dental implant devices due to their ability to transport antimicrobial substances and address biological concerns, including the prevention and treatment of PI [25].

The enhanced antibacterial activity of NPs can be ascribed to their substantial charge density and expansive surface area, which enable them to engage with the negatively charged surface of bacterial cells. Metallic NPs stimulate biomineralization by encouraging the remineralization of dental tissues that have been demineralized (caries-ridden). Moreover, due to the equilibrium of their ions in oral fluid, metallic NPs can overcome obstacles in various oral environments. Academics and clinicians have investigated the ability of numerous nano-formulations to reduce caries [26]. The extensive distribution of PI bone loss presents challenges in effectively managing biological complications that have the potential to compromise the sustained efficacy of osseointegrated implant reconstructions [27]. The tissues around implants have tested positive for metal and Ti particles. Orthopedists have looked at metal particle release as a possible etiologic factor since it causes aseptic loosening around arthroplasties and is linked to implant failures [28]. Emerging knowledge in dental medicine regarding the discharge of metal/Ti particles implies that biomaterials present at the interfaces between the abutment and bone might potentially affect the pathogenesis of peri-implant bone loss [29].

One of the most popular and durable Ti alloys is Ti–6Al–4V. Ti, aluminum (Al), and vanadium (V) comprise over 90% of its composition. For the creation of a medical implant, its many desirable and outstanding qualities are crucial. Among the time-tested, standard methods for treating dental implants, coating techniques rank well in terms of reliability. Surface preparation can significantly enhance the mechanical characteristics of dental implants. Several challenges may arise during the coating process, including technical obstacles in achieving a consistent coating thickness, insufficient adhesion between the coating material and the implant substrate, and more [30, 31]. Bone mineral density, bone development, and trabecular pattern may all be improved by Ti-contained AgNPs without causing injury to the tissues around dental implants [32].

With control over implant properties, greater implant-tissue integration, and local treatment, the nano-engineering of Ti-based dental implants is developing and gaining pace. Anodization performs better than other innovative and clinically used nano-engineering technologies because it is a cost-effective and scalable method of fabricating regulated biocompatible titania nanostructures that enable customization of implant topography, chemistry, bioactivity, and treatment. The authors believe that precisely micro- and nano-engineered dental implants that can satisfy the therapeutic needs of individual patients will be the way of the future for dental implants. The future of dentistry is the fit-and-forget dental implant, which minimizes doctor visits and patient pain by ensuring early stability and long-term success without requiring decontamination, therapeutic administration, or correction. This would help to get a comparable high success rate in both healthy and impaired patient circumstances. Reaching this for a complex dental implant environment (where soft-tissue integration is also required) may open up opportunities for the more significant implant industry, which includes joint replacements, orthopedic implants, and craniofacial implants (Fig. 1) [33].

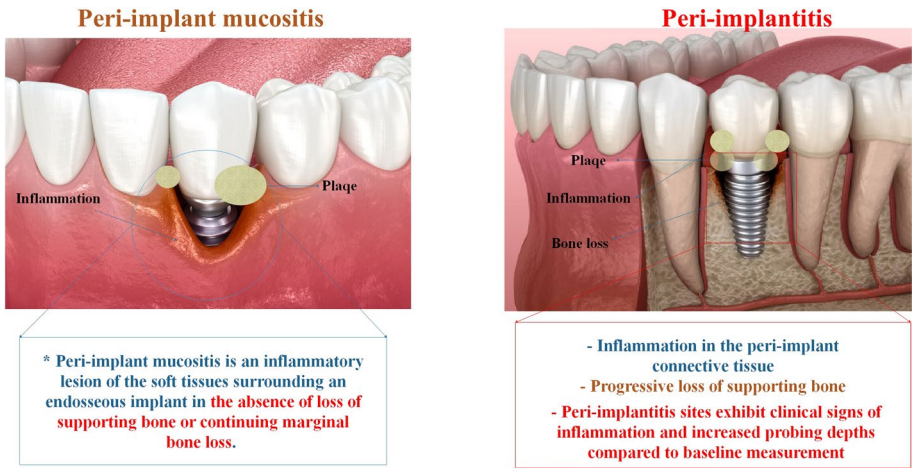



**Fig. 1** The essential characteristics of peri-implant diseases (PIDs), including peri-implant mucositis (PIM) and peri-implantitis (PI), are shown in this image. There are no indications of bone loss in PIM; gum inflammation is limited to the area around the soft tissues of the dental implant. PI is a complex condition that impacts the bone and soft tissue surrounding the implant [34]

It is critical to keep up with the latest advancements in PID prevention and therapy. Therefore, the treatment of PID involves the use of metal NPs such as iron, Zn, Ti oxide ($TiO_2$), Ag, and Au. These NPs may be an excellent substitute for antibiotics in the treatment of PI due to their antibacterial qualities. To lessen the toxicity and improve the effectiveness of these metal NPs in the treatment of PID, several specific research are advised. The critical characteristics of PIM and PI were briefly addressed in this article. Additionally, we look at the potential use of metal NPs in the prevention and treatment of PIDs, including PI and PIM, as well as their therapeutic and antibacterial qualities. For this approach to be used as a significant alternative therapeutic approach in clinical applications for treating PIDs in the future, we have finally examined the current drawbacks and benefits in general.

## Peri-implant diseases

PIDs and condition categorization were introduced. Specific concerns were addressed about soft- and hard-tissue deficits, PIM, PI, and features of peri-implant health. PIM's primary clinical feature is bleeding with light probing. There may also be suppuration, erythema, and/or edema. Because of swelling or a drop in probing resistance, PIM often increases probing depth. Experimental research on humans and animals has provided compelling evidence that plaque is the causative agent of PIM. It is characterized by inflammation of the mucosa around the implant and a gradual loss of supporting bone that follows. In addition to radiographic bone loss, PI locations show clinical symptoms of inflammation, bleeding on probing, suppuration, increased probing depths, and/or recession of the mucosal edge. Regarding the impact of keratinized mucosa on the PIT's long-term health, the research is inconclusive. In epidemiological or disease-surveillance investigations for peri-implant health, PIM, and PI, case definitions were created and used in routine clinical practice [35].

#### Peri-implant mucositis

The initiation of an inflammatory response is causally associated with the experimental accumulation of bacterial biofilms around Ti dental implants. The experimental PIM lesion is characterized by an infiltration of inflammatory cells into the connective tissue lateral to the barrier epithelium. The inflammatory cell infiltration in long-lasting PIM is increased compared to the early experimental PIM lesion, which lasted for three weeks. Biofilm-induced PIM is reversible at the host biomarker level once biofilm control is restored. The clinical indications of inflammation may persist for a period exceeding three weeks. The host-microbe equilibrium is disrupted by biofilm accumulation at the implant-mucosa interface, resulting in an inflammatory lesion that ultimately leads to PIM. Consequently, the therapeutic implication is that the management and prevention of PIM necessitate the adequate clearance of biofilm. It is imperative to understand PIM, as it is considered a precursor to PI [36].

The following were some of the main findings for the researchers: (i) A weighted mean prevalence of 22% for PI and 43% for PIM was found by meta-analysis; (ii) Blood upon probing is a crucial clinical indicator that helps distinguish PIDs from peri-implant health; (iii) Patients with PIM who did not receive frequent supportive care were more likely to develop PI; (iv) smoking was found to be a modifiable risk factor related to the patient and excess cement to be a local risk indicator for the development of PIM, while plaque formation was found to be an etiological factor; (v) It has been demonstrated that patient-administered mechanical plaque control—using powered or manual toothbrushes—is an effective preventative intervention; (vi) Professional intervention, which included mechanical debridement and advice on oral hygiene, resulted in a decrease in clinical indications of inflammation; (vii) No additional treatments (antiseptics, systemic and local antibiotics, air-abrasive devices) were found to increase the effectiveness of professionally performed plaque removal in lowering clinical indicators of inflammation [37]. Research has shown that mechanical non-surgical methods may effectively cure PIM lesions. Furthermore, antibacterial mouth rinses and mechanical therapy for these mucositis lesions enhanced the outcomes. The effectiveness of non-surgical treatment for PI lesions has not been established. Results from the adjuvant chlorhexidine therapy on clinical and microbiological indicators were not very encouraging. However, it has been shown that adjunctive local or systemic antibiotics reduce bleeding both during and after probing. Although some modest advantages of laser therapy for PI have been shown, further study is necessary to evaluate this approach properly. It is essential to conduct randomized controlled studies evaluating non-surgical treatment approaches for PIM and PI [38].

#### Properties of peri-implantitis

Dental implants have emerged as an indispensable component of the dental profession to substitute absent or deteriorating dentition, owing to their exceptional long-term outcomes [39]. Nonetheless, epidemiological studies on PIDs, particularly PI, are increasingly gaining attention within the medical community [40]. PI has been documented to have a prevalence of up to 56%, with reported prevalence rates between 12 and 43%. The variation in reported prevalence can be attributed to the absence of precise diagnostic criteria and case definitions for the diseases [41].

Implant failure is frequently correlated with osseointegration failure. A dental implant is deemed unsuccessful if it becomes dislodged becomes mobile, or experiences peri-implant bone loss exceeding 1.0 mm within the first year and 0.2 mm thereafter. PI may ultimately lead to implant loss due to bone atrophy developing around the site. PI treatment is most effectively achieved when the lost implant-supporting firm and soft tissues are regenerated [42].

It has been discovered that the bacterial flora associated with periodontitis and PI are comparable. *Prevotella intermedia* (*P. intermedia*), *Porphyromonas gingivalis* (*P. gingivalis*), *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*), *Bacterioides forsythus*, *Treponema denticola*, *Prevotella nigrescens*, and *Fusobacterium nucleatum* (*F. nucleatum*) are examples of the Gram-negative anaerobes that are frequently associated with PI. Furthermore, compared to healthy implants, higher concentrations of Gram-positive bacteria, particularly enterococci, were found within PI. It has been discovered that *Enterococcus faecalis* colonizes dental implants to produce PI. A low ratio of facultative anaerobic species to anaerobic species and a high number of Gram-positive cocci, such as *Parvimonas* and *Peptostreptococcus*, are characteristics of biofilms from healthy peri-implant locations [43–45]. PIT in good health is a critical biological barrier against specific pathogens that induce PID. If this tissue is compromised, bacterial contamination escalates to the bone, resulting in its expeditious demise. PI initiation and progression may be significantly influenced by inappropriate implant design, excessive mechanical stress, and corrosion that may result from the connection of a non-noble metal structure to a Ti implant [43].

Probing depth, bleeding on probing (BoP), and bone loss have been utilized to categorize PI into three levels of severity: advanced, moderate, and early. Peri-implant measurements of 4 mm or greater and bone deterioration of less than 25% are considered pre-implants. Probing depths around dental implants that are 6 mm, with bone deterioration ranging from 25 to 50% of the implant length, are classified as moderate PI. On the other hand, a pocket depth of 8 mm, with bone deterioration exceeding 50% of the implant length, is categorized as advanced PI [46, 47]. Adverse biological consequences are usually the outcome, including suppuration, BoP, progressive marginal bone loss (PMBL) beyond physiological remodeling, and ultimately, a catastrophic complication that necessitates implant removal [48, 49].

PI is managed through a combination of conservative (non-surgical) and surgical interventions. The sufficiency of non-surgical therapy in addressing PIDs, whether moderate or severe PI or PIM, may vary. In some instances, a step-by-step approach involving non-surgical treatment followed by surgical intervention may be required [50]. Surgery may be employed to address PI lesions characterized by significant bone loss and pocket formation (greater than 5 mm) after the resolution of the acute infection and the implementation of appropriate oral hygiene practices [51]. Non-surgical and surgical therapies are available to treat PI; however, there is a lack of dependable evidence to determine which interventions are most efficacious [52]. Although the nonsurgical approach demonstrates efficacy in mitigating soft tissue inflammation, including BoP, its treatment efficacy is constrained [53].

The access flap method, also known as OFD, reduces irritation near the implant through direct debridement application and exposure of the implant surface. When

threads protrude from suprarenal bone defects in areas that do not require aesthetic improvement, resective therapy is recommended. Implantoplasty refers to reducing or removing pathological peri-implant pockets, placing an apical mucosal membrane, or recontouring bone around the implant, with or without modification of the implant surface [54]. Besides conventional therapeutic approaches like medication and manual treatment (e.g., using curettes, ultrasonic devices, and air refining systems), contemporary therapeutic methods have emerged to offer innovative alternatives, including photodynamic and laser-supported therapies [55]. An array of conservative and surgical strategies is accessible for managing PIDs. Moderate forms of PI and PIM can be effectively managed with conservative treatments [56].

Antibiotics have been acknowledged for their beneficial role as adjuvants in the clinical management of PI, contributing to intra-oral biofilm control and radiographic bone regeneration. However, systemic administration of antibiotics is frequently associated with adverse effects, including dysbiosis, the development of antibiotic resistance, and gastrointestinal complications [57, 58]. Clinical and microbiological improvements in PI lesions were observed following adjunctive delivery of chlorhexidine gel and locally resorbable antibiotics; however, the use of chlorhexidine caused severe allergic reactions, including oral pain and sensitivity [59].

According to the Javed et al. study, pocket depths were significantly reduced for 1–6 years by systemic and local antibiotic applications (e.g., ciprofloxacin, minocycline hydrochloride, doxycycline, amoxicillin, metronidazole, tetracycline, doxycycline, sulfonamides plus trimethoprim) [60]. When resorbable doxycycline-releasing nanospheres were applied locally over 15 months, Moura et al. saw the same thing [61]. Leonhardt et al. reported an overall success rate of 58% when PI was treated with surgical debridement and a variety of antibiotics and their combinations, including clindamycin, amoxicillin + metronidazole, tetracycline, and ciprofloxacin. Astasov-Frauenhoffer et al. demonstrated the complete inhibitory effects of metronidazole and amoxicillin on the growth of *Streptococcus sanguinis* (*S. sanguinis*), *P. gingivalis*, and *F. nucleatum* when used in isolation from one another. However, the combined efficacy of the two agents was superior to that of metronidazole used alone (Fig. 2) [62].

## Materials used for dental implants

Current dental implants are based on a biological process called osseointegration, in which components like Ti or zirconia link closely with bone. Initially, the implant fixture is positioned to promote osseointegration, and then the dental prosthesis is installed [64]. The physical and chemical properties of implant materials have a significant impact on the clinical outcome and prognosis of implant therapy. The implant's microstructure, surface composition, features, and design elements are among its many well-reported and documented attributes. An excellent implant material should have the following qualities: enough strength, toughness, corrosion resistance, wear resistance, and fracture resistance. The physical characteristics of the material utilized in the implant must be in line with its design principles. Dental implant materials may be categorized according to their biological reactions upon implantation or chemical makeup. The three primary materials used to make dental implants are metals, ceramics, and polymers, depending on their chemical makeup [65].

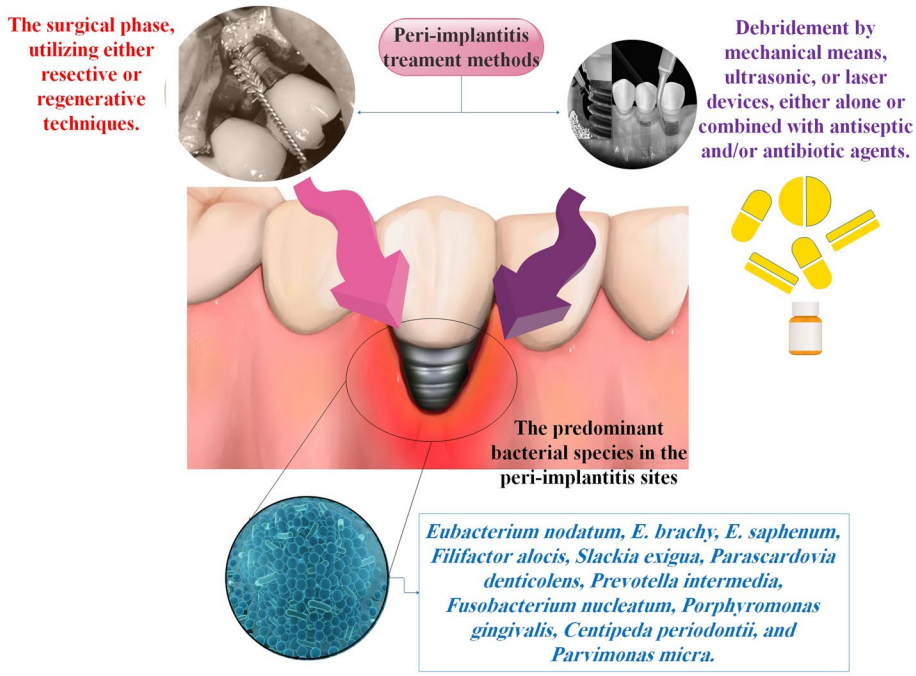



**Fig. 2** This figure shows the types of peri-implantitis (PI) treatment methods. In addition, the treatment for PI consists of two phases: 1. the nonsurgical phase, which uses manual debridement or devices with ultrasonic, laser, or both, either alone or in conjunction with antibiotics and/or antiseptics; and 2. the surgical phase, which uses regenerative or reconstructive procedures [63]

Moreover, the primary materials used to create dental implants are ceramics based on zirconium and metal alloys based on Ti, iron, and tantalum. Simultaneously, during the past 20 years, there has been a significant decline in the number of studies examining stainless steel implants (from 38 to 20%). This decline has been linked to the presence of hazardous impurities in the steel composition as well as the implants' inadequate corrosion resistance and biocompatibility. Concurrently, Ti and its alloys have maintained their top spots (~ 50%) during this time and are now the primary materials used in the manufacturing of dental implants that are sold commercially [66].

Metal implant materials include stainless steel, Au alloys, cobalt-chromium alloys, tantalum, and other materials, in addition to pure Ti and Ti alloys, the most often used types nowadays. Although Ti has better corrosion resistance than stainless steel, 316L stainless steel is a stronger, more affordable, and simpler-to-process alloy that has been employed in implant applications for bone plates and screws. It has not been authorized as a dental implant material because of this. Ti and the majority of its alloys exhibit excellent biocompatibility or tissue compatibility [67]. Under axial loads, Ti exhibits remarkable resistance to deformation. One ideal quality for dental implants is its resistance to the forces exerted while chewing. This suggests that Ti has advantageous properties that enable it to withstand the mechanical forces placed on dental implants during chewing and other oral processes. Its track record of success in dental implant applications further highlights its dependability. Because of zirconia's exceptional biocompatibility, it may be used with oral tissues and lessens the chance of negative reactions or inflammation. Furthermore, zirconia exhibits

remarkable strength and durability that are often compared to Ti implants. Zirconia's exceptional aesthetic features are primarily attributed to its natural white tint, which makes it easy to match with neighboring teeth and improves the overall visual appeal by giving the teeth a more appealing and genuine appearance. Zirconia often has stiffness values that are greater than those of Ti. According to research, zirconia has an excellent degree of stiffness, which means that in dental implant applications, it may provide better structural reinforcement and more resistance to deformation. Zirconia's mechanical strength and structural stability are enhanced by its relatively high mean shear modulus. Increased eigenvalues imply that zirconia may exhibit additional anisotropic properties and varying stiffness at specific orientations. For dental implant applications, other materials are available, such as zirconia and Ti alloys (Ti–Al–2V). Furthermore, although Ti–Al–2V Alloy and Zirconia have unique characteristics, Ti is the material of choice for dental implant treatments due to its well-rounded qualities and well-established history, guaranteeing stability, durability, and biocompatibility [68]. Researchers assessed the biocompatibility of 36 experimental Ti alloys with 5, 10, 15, and 20 wt% of each alloying element as well as nine different kinds of pure metal ingots (Ag, Al, Cr, Cu, Mn, Mo, Nb, V, and Zr). Researchers found that the following was the order in which pure metal cytotoxicity was most influence to least potent: Cu, Al, Ag, V, Mn, Cr, Zr, Nb, Mo, and CP-Ti (in that order). Pure Cu, Al, Ag, V, and Mn had mean cell viabilities, respectively, 21.6%, 25.3%, 31.7%, 31.7%, and 32.7%, far lower than those of the control group. For pure Zr and Cr, the corresponding mean cell viability was 74.1% and 60.6%, respectively. Good biocompatibility was shown by pure Mo and Nb, which had mean cell viability of 93.3% and 93.0%, respectively. All Ti-based alloy groups had mean cell viabilities of more than 80%, except Ti–20Nb (79.6%) and Ti–10V (66.9%). The Ti–10Nb alloy demonstrated superior cell viability (124.8%) compared to CP-Ti. Pure Ag, Cr, Cu, Mn, and V were classified as "moderately cytotoxic" based on the results of the agar overlay test; all other examined pure metals and Ti alloys, except Ti–10V (which has mild cytotoxicity), were classified as "noncytotoxic." The study's findings may be used as a roadmap for the creation of novel Ti-based alloy implant systems [69].

Researchers used spark plasma sintering to fabricate bilayered, single-piece Ti6Al4V-yttria stabilized zirconia (YSZ) dental implants. The bilayered component's Ti6Al4V and YSZ portions function as the fixture and crown, respectively, resolving issues with traditional two- or three-piece implants. The bi-layered component is excellent for dental implants because of its good mechanical qualities and in vitro biological characteristics, such as solid biocompatibility, non-cytotoxicity, good cell adhesion, and hemocompatibility [70].

Ti-Cu sintered alloys (three-weight percent and five-weight percent Cu) were created in this work for use in medical implants. The Ti–Cu alloys were assessed for their antibacterial properties against *P. gingivalis* and *S. mutans* by a variety of methods, including the reactive oxygen species (ROS) staining test, Scanning Electron Microscopy (SEM), inhibitory zone assay, and live/dead fluorescence staining. The findings showed that the composition of α-Ti and $Ti_2Cu$ phases in Ti–Cu alloys rose as the alloy's Cu concentration increased. In a time-dependent way, Ti–Cu alloys showed antibacterial action against both types of bacteria. Ti–3Cu and Ti–5Cu

demonstrated bactericidal rates of 57% and 70% against *P. gingivalis* and 63% and 78% against *S. mutans*, respectively, after 72 h. Within the safe range, the maximum quantity of $Cu^{2+}$ released from these alloys in the first 24 h was 0.3 mg/L. The generation of ROS and the release of Cu ions were proposed as the primary antibacterial processes. All things considered, Ti–Cu sintered alloys show promise as materials for orthopedic and dental implants [71].

Tantalum with pores known as Trabecular Metal (PTTM) has been used in dental implants because of its capacity to raise surface roughness and encourage osseointegration—the process by which bone grows directly into the implant. PTTM has similarities in elasticity and porosity with bone microstructures, being 80% porous. The implant's trabecular portion increases its surface area and encourages osseoincorporation into the bone during ingrowth and growth. Research has shown that tantalum stimulates the process of osteoblastic differentiation, while Ti enhances cell proliferation. It is believed that tantalum's porous structure, which resembles spongy bone, has a role in encouraging bone ingrowth. Because PTTM may promote osteogenesis, wound healing, and neovascularization, it has also been used in orthopedic implants. Using PTTM in dental implants may help to enhance bone integration and the implant's long-term viability [72].

Based on the ceramic system, transparency, microstructure, fabrication temperature, material composition, and utilization, dental ceramic materials are categorized. Given the speed at which the medical industry is developing, zirconia-based ceramic matrix composites (CMCs) may provide a compelling substitute for Ti-based implants. Applications of dental zirconia and alumina-based ceramics have improved during the last 10 years [73]. Ceria-stabilized tetragonal zirconia (Ce-TZP) has emerged as an intriguing alternative to the widely used yttria-stabilized zirconia (Y-TZP). However, it is necessary to regulate its microstructure to enhance the strength of Ce-TZP ceramics. Researchers employed CaO to co-dope Ce-TZP ceramics. Additionally, CaO-doping facilitated the creation of Ce-TZP ceramics that were as translucent as various commercially available 3Y-TZP ceramics, thereby expanding the potential for using Ce-TZP in dental restorations [74].

Additionally, the utilization of polymeric composite materials and polymers in dental implants has experienced a significant surge as a result of their enhanced benefits. The researchers are motivated to identify a substitute for conventional dental implants because dental implant material has been restricted to the continuous use of metal/composites, which has certain limitations. Polymer materials can be considered a futuristic substitute for conventional materials due to the incorporation of optimistic properties, such as a lower weight than metals, through surface and bulk alterations. Biocompatibility and bioactivity exhibit substantial enhancements with the additional incorporation of nano-fillers and reinforcements [75]. Polyetheretherketone (PEEK) is a thermoplastic polymer that is highly effective and can be employed as a dental implant abutment material. It can reduce stress shielding and has an elastic modulus comparable to bone. PEEK is a radiolucent material that can be bonded to ceramics or veneered with composite materials to enhance the radiographic imaging of PITs. PEEK is a material that is frequently employed in

orthopedic and spinal procedures. Its mechanical and biological properties make it an ideal choice for dental implant abutments [76].

### Metallic nanoparticle's antibacterial properties

Antibiotic overuse has increased bacterial resistance and, consequently, declined the efficacy of the few antibiotics still in circulation. On the contrary, AuNPs exhibit considerable potential as antibacterials owing to their substantial specific surface area, facile functional group modification, and wide-ranging antibacterial activity. By adjusting reaction conditions, it is possible to modify particle size, solubility, and surface modification, all of which are intimately associated with their antibacterial properties [77]. A potentially effective strategy for surmounting microbial resistance to antibiotics involves the implementation of metal NPs and their oxides [78, 79]. Furthermore, studies on nanomaterials have produced data on a potential correlation between a nanomaterial's morphological properties and the degree of toxicity it delivers [26, 80]. However, using harsh chemicals and a lot of energy is necessary for the typical production of NPs [81–83].

Furthermore, the precise correlation between the morphology and toxicity of nanomaterials remains poorly understood. Bacteria are hazardous and potentially fatal agents that can cause and spread infectious diseases [84]. It has been shown that metallic NPs have exceptional antibacterial properties that make them valuable as self-modified therapeutic agents both in vitro and in vivo. They have potential therapeutic uses via various antibacterial mechanisms because of their broad spectrum of antibacterial effectiveness [85, 86]. NPs not only impede the progression of bacterial resistance but also expand the range of antibacterial activity by circumventing the direct binding of bacterial cells to specific receptors, exhibiting encouraging efficacy against Gram-positive and Gram-negative microorganisms [87]. Their characteristics, including minimal toxicity, the ability to traverse the blood–brain barrier, and a reduced propensity to induce resistance in microbes compared to antibiotics, render them a prospective therapeutic alternative against *S. aureus*. The efficacy of metal-based NPs as an antibacterial agent targeting *S. aureus* has been demonstrated in numerous research investigations [88].

Implant insertion triggers type I and type IV complex antigen/antibody responses, which result in allergic reactions. On Titania implants, however, the adherence of microorganisms has a long-term impact on the implants and significantly affects the healing process of teeth. Inside the mouth cavity, plaque may develop as a result of roughness or chemical breakdown on implants. Adhesion angle measurements show no discernible variation in surface modification after Ti plates were submerged in the bacterial solution for about one hour to quantify the number of bacteria on the plates. Compared to polished Ti, the quantity of adhesive bacteria is much reduced on stable Titania (Ti/zirconia NPs). Therefore, to promote results, physical modification (coating with silicon/Ti NPs) dramatically reduces microbial adherence. Implants made of Ti that have been physically altered cause the bone to respond, forming inorganic nanoporous materials widely employed to create drug-releasing implants. Surface modification modifies the linking and dispersion of $TiO_2$ within a resin matrix, as well as the hardness and strength of dental resin-based composites [89].

Dental glue may also include AgNPs to enhance antibacterial qualities. This is because the released $Ag_+$ may inactivate essential bacterial enzymes, preventing the DNA from replicating and ultimately resulting in bacterial cell death. However, adding AgNPs to dental adhesives presents several difficulties. Firstly, these NPs' propensity for easy oxidation or photoreduction in ambient circumstances may cause them to rapidly aggregate and lose a large portion of their antibacterial activity. Second, the hydrophobic dental monomer exhibits less solubility of AgNPs when added directly, and their antibacterial properties are short-lived. Furthermore, adding AgNPs to dental materials may result in tooth-colored materials changing cosmetically. To address the issues mentioned above, a sensible Ag delivery system must be created [90].

For instance, EMT zeolites were created and exposed to Ag ion exchange in a separate investigation. *Streptococcus mutans* (*S. mutans*), *Streptococcus gordonii*, and *S. sanguinis* were chosen to produce single-species biofilms and serve as typical strains of cariogenic infections. As a result, the adhesives containing Ag + exchanged zeolites demonstrated their potential use for anti-biofilm and anti-caries clinical applications by their exceptional antibacterial qualities, making them "bioactive" adhesive materials [90]. The findings of a study that identified the physiological pathways underlying the antibacterial response of Gram-negative bacteria *Escherichia coli* (*E. coli*) to AgNPs using gene deletion mutants suggested that the physicochemical properties of the NPs could significantly affect both the mechanism and the magnitude of delivered toxicity [91].

Zn oxide NPs (ZnO-NPs) have been shown to have vigorous antibacterial activity against both Gram-positive and Gram-negative bacteria in several investigations. Regarding *E. coli* and *S. aureus*, the antibacterial action depends on the size of the applied NPs [92]. The impact of different methods of ZnO-NPs synthesis and the primary categories of modifications applied to NPs-ZnO to enhance its antibacterial efficacy are also examined [93]. NPs have the potential to be very important in the management of many medical conditions because of their unique physiochemical traits and remarkable biocompatibility [94].

Furthermore, as a potential antibacterial treatment approach to address the above-noted drawbacks, antimicrobial photodynamic therapy (aPDT) was studied. As a treatment for a wide range of localized infections, photodynamic inactivation (PDT), also known as antimicrobial or antibacterial PDT, was suggested (PDI). By creating deadly ROS, particularly singlet oxygen ($^1O_2$), aPDT used the right excitation light and photosensitizers (PSs) and oxygen to enable a non-specific assault on microbes. The singlet PS was unstable and could instantly release energy and change back into the triplet form. The energy produced was taken up by the oxygen in the tissue to create ROS, which oxidized strongly and were very reactive, causing the bacteria's lipids to oxidize quickly. As a result, the delicate membrane lipids were destroyed, which ultimately caused the bacteria to die. Semiconducting materials ZnO and $TiO_2$ have unique optical, biocompatible, and biodegradable qualities. The nanosurface layer showed promise in infection prevention despite the lack of data about nanomaterials-based aPDT for treating PI. Ag plating, anodization, and sintering processes were used to form surface nanocoatings on implants made of $TiO_2$, hydroxyapatite (HA), and Ag. By reducing the biofilm on the surface of implants by 97.5%, the dual-layered Ag-nHA nanocoating prevented bacterial development in the surrounding medium. For Ti alloy implants, this innovative

nanocoating provided faster bone healing, osseointegration, and a decreased risk of infection [95, 96].

Many researchers have suggested using aPDT to fight biofilms and periodontal diseases, yet there are still several issues. To guarantee low toxicity, for example, PS parameters, the method of surface modification and PS dosages, and the irradiation intensity should be rigorously studied. These factors impact the kind and kinetics of bio-distribution and toxicity at the cellular and tissue level. Furthermore, it is essential to look at the effective PS delivery, organ distribution, accumulation, retention, metabolism, and clearance qualities at the organ level. To protect the beneficial microflora in the oral environment, PS must increase the pathogens' selectivity. To prevent oxidative damage to the host cells, the irradiation intensity must be rigorously and regularly verified before clinical use. Furthermore, it is essential to conduct in vivo investigations using animal models to validate the viability of therapeutic uses. To successfully use these findings in clinical settings, further research is required [97].

Single-metal NPs, or metallic nanomaterials, are often more stable and take longer to dissolve. On the other hand, when added to a biological environment, metal oxide and metal alloy-based nanomaterials tend to show less stability and are more prone to dissolution and ion release, which causes the generation of ROS and oxidative stress in cells. The recurring worries highlight how crucial it is to handle metallic NPs carefully because of how unpredictable their effects might be. Since many compounds are safe in nanoform, it is evident that several nanomaterials that were previously thought to be compatible may be dangerous in their nanoforms, even if research on the magnitude and mechanism of toxicity are conflicting. A database listing the health risks associated with various NPs and a comprehensive analysis are necessary to determine the pharmacokinetic characteristics of various NP types. This data may open up new avenues for NP assessment, both in vivo and in vitro. The processes of NPs' transmission, accumulation, long- and long-term safety and toxicity, interactions with cells, receptors, emotional signaling pathways, and global phagocytosis activity should all be investigated in studies. Comprehending the relationship between these "new building materials" and biological systems can safeguard these materials in several medical domains, including diagnosis and therapy (Fig. 3) [98].

## Metal nanoparticles utilized in implant coating

Currently, the medical industry employs a diverse array of implant materials. In orthopedics, traumatology, oncology, and reconstructive surgery, alloys of Co–Cr, Ta, Nb, Zr, Mg, and Fe, carbon nanostructured implants, metals and alloys (e.g., Ti, stainless steel), and polymers (including polymer meshes and their composites) are extensively employed. Additionally, ceramics (bioinert, bioglass, and bioresorbable) are used. This is due to their exceptional mechanical and physical properties, as well as their resistance to corrosion and other advantageous characteristics. Additionally, they exhibit remarkable biological compatibility (Fig. 4) [100, 101].

### Silver NPs in dental implant

To prevent infections, Ag has long been used in therapeutic settings as an antibacterial agent. As such, it has a leading position in surface modification of medical implants. The

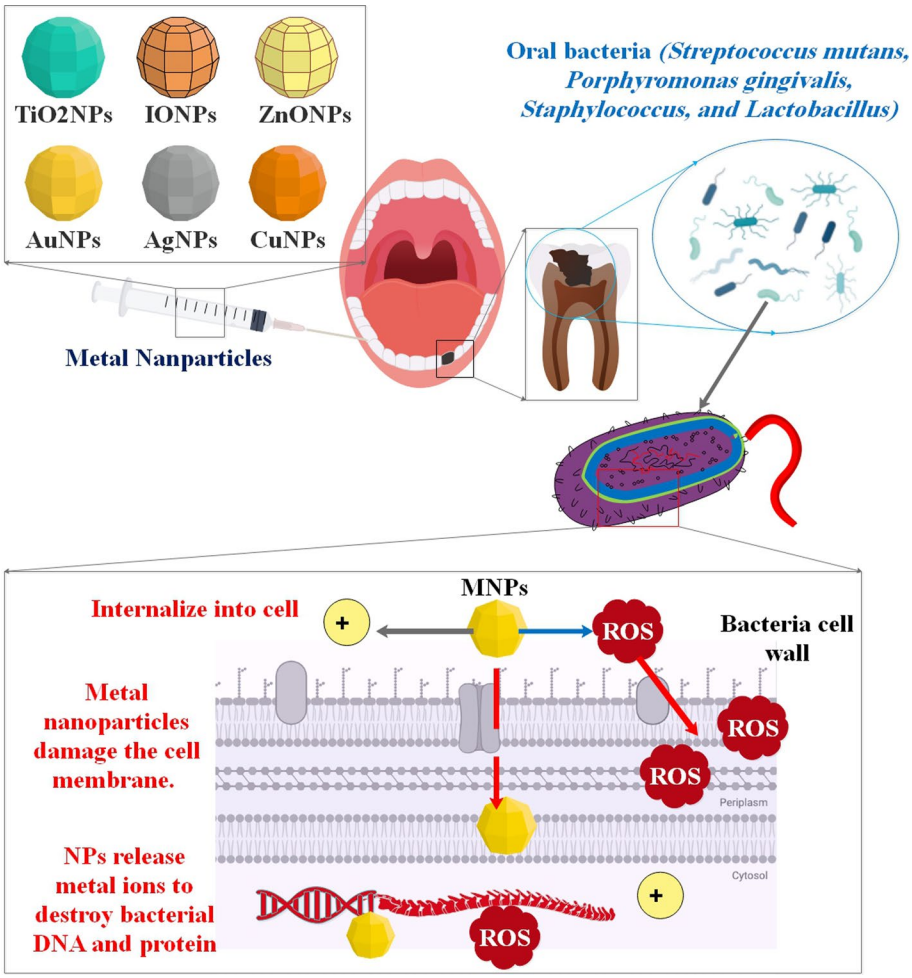



**Fig. 3** Schematic illustrating metal NPs' antibacterial action mechanism. Because of their diverse physiochemical characteristics, NPs have multifaceted bactericidal capabilities. The ionic metals that are liberated from MNPs exhibit a range of antibacterial activities. They may be very hazardous to bacteria by interacting with their phospholipid layers in bacterial cells or disrupting the functioning of different intracellular macromolecules, including enzymes and DNA. One of the primary mechanisms for the antibacterial effect of NPs is the dynamics of the cell-surface interface, and the surface topography and nanostructure of NPs have a significant impact on their antibacterial activity. The nanostructures of MNPs also play a crucial role in inducing antibacterial effectiveness. Additionally, the nanotoxicity of NPs is often attributed to their ability to induce oxidative stress via the introduction of reactive oxygen species (ROS), which also enables NPs to be fatal to bacterial cells [99]

doping of original surfaces with ions and the coatings made of coordination compounds, NPs, metallic Ag, and Ag salts are only two of the many various forms of Ag that are being considered [102, 103]. The primary application for this variety was in the fabrication of metal implants, with Ti serving as the primary model. In contrast, the modification of ceramics primarily involved ion doping and the incorporation of NPs into composite coatings. Research has focused on using Ag to modify the surface of polymeric implants, including PEEK. This research has involved the development of nanostructured Ag coatings and the immobilization of Ag cations. Based on these principles, AgNPs exhibit greater efficacy in comparison to metallic Ag coatings and Ag compounds [104, 105].

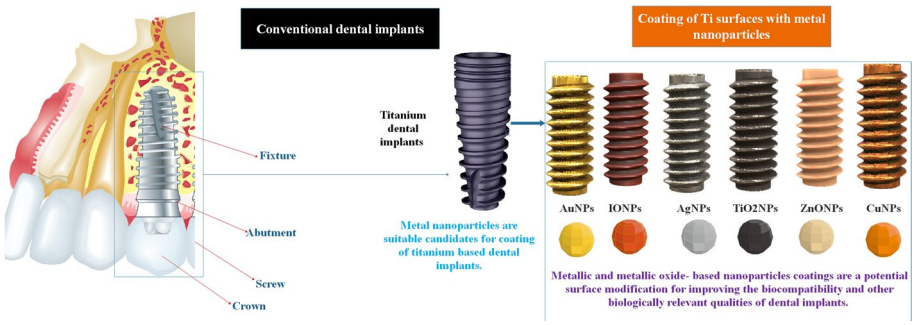



**Fig. 4** The use of metal nanoparticles (NPs) as an implant covering to stop PIDs is shown in this illustration. Implant fixation may be enhanced by coating titanium surfaces with NPs, which can improve soft tissue integration and osteogenesis. In addition, osteoconductive NPs create a chemical connection with the bone to help implants be biologically fixed [99]

In addition, the increasing interest in $Ag^{+}$ stems from its antimicrobial activity and nontoxicity to human cells. Studies (both in vitro and in vivo) have demonstrated that Ag materials can potentially impede bacterial adhesion to dental implants. It has been shown that Ag-containing implants are highly biocompatible, exhibiting neither genotoxicity nor cytotoxicity. Additionally, Ag-containing implants demonstrated no systemic or local adverse effects [106]. In several medical disciplines, elemental Ag has been utilized as an antimicrobial agent, and AgNPs encapsulated in various film coatings have been used to impart antimicrobial activity to the surfaces of Ti implants. AgNPs are called biocompatible coatings because dental implants typically require negligible amounts. Hence, the biocompatibility of the surface and the enhancement of the antibacterial capability of the implant are achieved through the incorporation of a suitable quantity of Ag [107]. The bactericidal efficacy of metallic Au surfaces is generally regarded as unverified [108].

Specific research studies were conducted to investigate the effects of AgNPs incorporation into the surface coating of dental alloys on cytotoxicity and antibacterial properties. The antimicrobial efficacy of dental alloys containing AgNPs at concentrations of 10, 4, and 2 μmol/L was evaluated against *Streptococcus aureus* and *Staphylococcus aureus* (*S. aureus*). Cytotoxic values were significantly elevated in all dental alloys comprising 0% AgNPs, which served as the control groups. When AgNPs were incorporated, cytotoxicity values were diminished. Regarding antibacterial efficacy, there was no statistically significant disparity observed between dental alloys incorporating AgNPs and the corresponding control groups. The findings indicated that pure Ti and Co–chromium alloys exhibited cytotoxic effects on MC3T3-E1 and BMSC. However, the cytotoxicity could be mitigated by the addition of AgNPs. It was determined that the concentrations of AgNPs utilized in this investigation exhibited no antibacterial activity against *S. aureus* or *Streptococcus aureus* [109].

Additive manufacturing (AM), or 3D printing of bone defect models, is gaining a lot of popularity in the biomedical profession because it may help create individualized, dimensionally exact implants. Ti–6Al–4V (Ti64) alloys are becoming increasingly preferred in creating these implants because of their modest stress shielding effect and high biocompatibility. However, their weak osseointegration potentials and absence of antibacterial characteristics often cause implant loosening and microbial infections,

leading to PIDs. Experiments conducted on *S. aureus* and *E. coli*, together with in vitro cell assays using MG-63 cell lines, indicated that the surface-modified samples produced by the recommended method were highly biocompatible and had sufficient antibacterial qualities. The generated surface-modified samples also showed a significant increase in corrosion resistance over the original 3D-printed Ti64 alloys. Increased corrosion resistance was shown via electrochemical impedance spectroscopy (EIS). The results demonstrate the potential of surface-modified 3D-printed Ti64 alloys for use in applications involving rigid tissue implants [110].

To balance the implant's cytocompatibility and antibacterial activity, a structurally homogeneous dopamine–Ag (DA/Ag) nanocomposite was fabricated on the implant surface for this investigation. The findings indicate that DA/Ag nanocomposites synthesized in an acidic environment (pH 4) exhibit a uniform composition and a greater concentration of $Ag^{+}$ ions on the Ti surface. Conversely, in neutral (pH 7) and alkaline (pH 10) conditions, a distinct core–shell (PDA) configuration is formed. Furthermore, subjecting porous Ti to heat treatment improved the durability of the PDA–AgNPs nanocomposite coatings. By the results of the hypodermic implantation, osteogenesis, cytotoxicity, and antibacterial tests, the homogeneous PDA–AgNPs nanocomposite coating promoted optimal soft tissue healing and bone formation around the implants, striking a balance between cytocompatibility and antibacterial activity. Antibiotic-loaded surfaces with favorable cytocompatibility and excellent antibacterial activity can be easily synthesized using the method described in this study. This development is anticipated to enhance the therapeutic effectiveness of Ag composite-coated dental implants [111].

The novel studies employed a green synthesis method and coffee powder to produce AgNPs. The implants were coated with Ag-PVP nanocomposites at varying concentrations using the deep coating method; the antibacterial properties of these samples were then analyzed. The results obtained indicate the presence of an extensive zone of inhibition when Ag-PVP coating is present. Furthermore, investigations and analyses have been conducted on the repeatability of the zone of inhibition test, toxicology analysis, and pull-off adhesion of samples. The MTT results indicate that 118.6 μg/mL is the optimal concentration of Ag-PVP nanocomposite to be used without causing cellular toxicity. The zone of inhibition is readily observable for both strains of bacteria at this concentration. Five days later, when the antibacterial test was repeated, it was determined that the zone of inhibition of the implants was permanent. In summary, this research paper introduces a straightforward, functional, replicable, and extensive technique for coating medical equipment and implants, thereby impeding the growth of infections in the implant vicinity [112].

#### Gold NPs in dental implant

Two different types of Au have been shown to have antimicrobial properties. One is nanoporous gold (NPG), which may destroy *E. coli* and *S. epidermidis* thanks to its nanometer-scale open pores [113]. A contact between the NPG's surface and the bacterial cell wall, as well as an interaction between the cell wall and the cell membrane, make up the mechanism of action of NPG. The second kind is AuNPs. It is well known that conjugate preparation or surface functionalization may enhance the antibacterial capabilities of AuNPs [77]. It has been demonstrated that conjugates of AuNPs with

antibiotics and antimicrobial peptides possess superior antibacterial activity compared to the constituent elements alone [114]. Functionalized AuNPs are regarded as bacterial antibiofilm agents in the same manner as AgNPs [115]. Researchers raise concerns regarding the potential toxicity and long-term environmental and human safety implications of AuNPs [116]. It was noted that AuNPs might be more biocompatible than AgNPs due to the absence of ROS production in their mechanism of action. It is important to note that ultra-small particles (1–2 nm) are more toxic due to the size effect, which increases the likelihood of irreversible binding to biopolymers, in addition to ROS. However, numerous in vitro experiments involving cell cultures failed to detect any discernible toxicity associated with AuNPs ranging in diameter from 3 to 100 nm [105]. It is ideal for implant surfaces to facilitate the adherence of target tissue cells while simultaneously impeding pathogen adhesion. To restrict biofilm formation, one primary method for reducing bacterial infiltration is to increase and diminish the antibacterial capability and compatibility of implant surfaces, respectively [107].

AuNPs are highly appealing for application as osteogenic agents owing to their potential to induce osteoblast differentiation. To promote bone regeneration, an osseointegrated Ti implant surface clad with AuNPs was utilized in a study. Through chemical treatment with (3-Mercaptopropyl) trimethoxysilane (MPTMS), researchers generated a Ti surface that had been silanized. Subsequently, researchers immobilized the Ti-AuNPs layer onto these surfaces using Au–S bonding. The in vitro findings demonstrated that applying Ti–AuNPs to human adipose-derived stem cells (ADSCs) significantly promotes osteogenic differentiation by upregulating the mRNA expression of genes specific to osteogenic differentiation. In addition, the in vivo findings demonstrated that Ti–AuNPs significantly affected the formation of the osseous interface. Investigators determined that Ti–AuNPs can function as osseointegration-inducing dental implants to promote the formation of an osseous interface and sustain nascent bone formation via these in vitro and in vivo experiments [117].

To prepare AuNPs for usage in implant dentistry, new research aims to evaluate their osteoinductive capacity using Salacia chinensis (SC). Moreover, these NPs were declared non-toxic after evaluations of their cytocompatibility and blood compatibility with erythrocytes and periodontal fibroblasts, respectively. The enhanced percentage of cell viability in MG-63 cell lines exposed to AuNPs, in contrast to the control group, validated the osteoinductive potential of AuNPs. This suggests that stable, ecologically benign, and biocompatible AuNPs may be a powerful bone inductive agent when used in dental implant treatment [118].

The most significant barrier to dental implant treatment in individuals with diabetes is still poor implant osseointegration. When the researchers first noticed that the BMSCs of diabetic rats had a very high abundance of miR204. When forced expression of miR204 was present, the osteogenic ability of BMSCs was dramatically reduced, whereas the osteogenic capacity was significantly increased when miR204 was inhibited. Moreover, the miR204 inhibitor was conjugated with AuNP-antagomiR204 and then diluted in a poly(lactic-*co*-glycolic acid) (PLGA) solution. The surface of the Ti implant was encapsulated using a PLGA solution containing AuNP-antagomiR204. Cellular tests revealed that the encapsulated AuNP-antagomiR204

was freed from the PLGA sheet and consumed by adhering BMSCs. The osseointegration-promoting properties of the AuNP-antagomiR204 released from the PLGA sheet were further verified in vivo animal experiments. MiR204 misexpression was shown to be the cause of poor osseointegration in diabetes mellitus; PLGA sheets enabled the release of AuNP-antagomiR204, which suggests a potentially helpful method for functionalizing the surface of Ti implants to improve osseointegration [119].

Wang et al.'s research aimed to assess the analgesic and osteoinductive qualities of AuNPs made from phytochemicals derived from *Anogeissus latifolia* (*A. latifolia*). It was discovered that green AuNPs exhibited remarkable stability in several blood components, such as human serum albumin (2%), bovine serum albumin (2%), cysteine (0.2 M), and histidine (0.2 M). Furthermore, when the biofabricated AuNPs were tested for cytocompatibility and blood compatibility using erythrocytes and periodontal fibroblasts, respectively, it was discovered that they were not dangerous. The osteoinductive potential of AuNPs was confirmed when MG-63 cell lines were exposed to them, as shown by the much-increased proportion of viable cells compared to the control group. Analgesic activity experiments revealed that the aqueous leaf extract of *A. latifolia* and the AuNPs that were produced demonstrated a substantial antinociceptive effect. Wang et al.'s results indicate that stable, biocompatible AuNPs may be used as bone-inducing agents in dental tissue implantation procedures and as efficient analgesics for pain management in the nursing profession (Fig. 5) [120].

#### Titanium NPs in dental implant

The in vitro and in vivo investigations about antibacterial coatings on Ti-based implants were examined by Zhao et al., who concluded that advancements have been achieved in this area [121].

Nevertheless, due to the interaction between corrosive media and metals, these substances degrade once they are incorporated into the human body. Adjacent to the implants, inevitable byproducts of the corrosion reactions are detrimental to the health of the vital organs. Nickel (Ni) ions discharged during the corrosion process of NiTi alloy implants represent an instance of such byproducts [122]. Higher corrosion resistance and, hence, lesser toxicity from liberated metallic ions are two of the most crucial characteristics of a material's viability for bio-applications [123]. The presence of any disparity in the chemical composition between the bone structure and the metallic implants leads to complications in the bonding between the bone and the implant, resulting in future concerns for the patient [124].

The antimicrobial properties of Ag ions have been well recognized, and Ag ions are both non-allergenic and non-toxic to mammalian tissue. Nevertheless, metallic Ag lacks the strength to function as a load-bearing metal implant. However, Ti lacks antimicrobial properties. Hence, the use of Ag-coated Ti implants might potentially serve as an effective measure in the prevention of deep body infections associated with implants [125].

Although TI implants are often utilized in clinical settings, one of the most frequent and dangerous side effects is post-operative infection [126]. An implant surface with durable antibacterial properties is extensively sought to reduce implant infection [127].

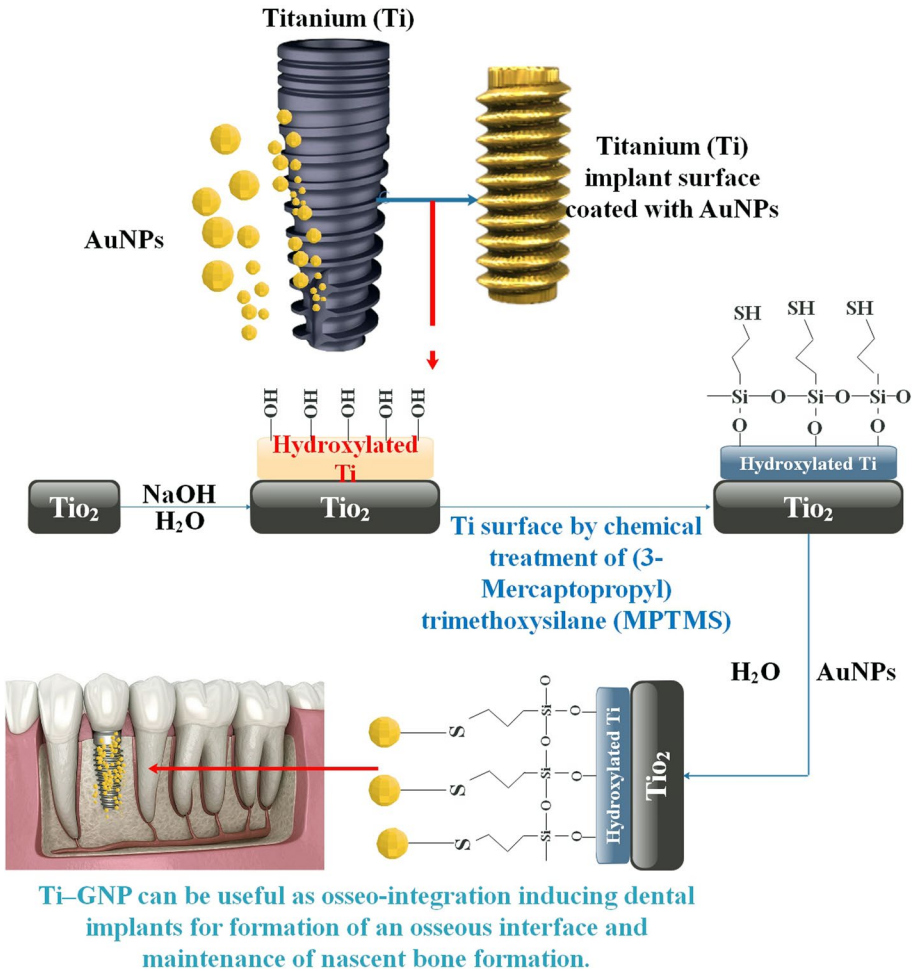



**Fig. 5** Via the formation of Au–S bonds, the AuNPs were conjugated on the surface of silanized Ti implants. The administration of Ti–AuNPs to ADSCs greatly stimulates osteogenic differentiation by upregulating the mRNA expression of genes relevant to osteogenic differentiation, as evidenced by the in vitro results. Furthermore, the in vivo results showed that Ti-AuNPs had a significant impact on the osseous interface's development. Through these in vitro and in vivo investigations, researchers discovered that Ti–AuNPs may serve as osseointegration-inducing dental implants to encourage the creation of an osseous contact and support nascent bone growth. [117]

Anodized Ti nanotubes ($TiO_2$-NTs) are considered efficient reservoirs for loading or releasing powerful antibiotics, whose systemic administration is linked to various severe adverse effects. This is because of their high trapping efficiency. To create a prolonged release profile, ciprofloxacin, a highly effective antibiotic, was coated with various chitosan layers after being loaded into $TiO_2$-NTs with a high encapsulation efficiency of 93%. Research on in vitro release showed that longer lasting release was associated with a larger chitosan layer count. Minimum inhibitory concentrations (MICs) of 1 μg/mL were found for both *Peptostreptococcus* and *Fusobacterium endodontic* species when the formulation's antibacterial activity was evaluated against them [128]. Dental implant therapies have a greater failure risk in patients with diabetes mellitus (DM). The osteogenetic potential and cell adhesion of several modified Ti surfaces were reduced by high glucose circumstances. On several modified Ti surfaces, high glucose circumstances increased

intracellular ROS levels and apoptotic rates; *N*-acetylcysteine (NAC) mitigated these effects. By reversing the overproduction of ROS in vitro, the $TiO_2$ nanotubes (TNT) surface mitigated the osteogenetic inhibition caused by high-glucose states, in contrast to the sandblasted and acid-etched (SLA) surface. The optimal osteogenetic potential of TNT surface in DM rats was further validated in the in vivo experiment by micro-CT scan analysis [129]. Dental implant therapies have a greater failure risk in patients with diabetes mellitus (DM). The osteogenetic potential and cell adhesion of several modified Ti surfaces were reduced by high glucose circumstances. On several modified Ti surfaces, high glucose circumstances increased intracellular ROS levels and apoptotic rates; *N*-acetylcysteine (NAC) mitigated these effects. By reversing the overproduction of ROS in vitro, the $TiO_2$ nanotubes (TNT) surface mitigated the osteogenetic inhibition caused by high-glucose states, in contrast to the sandblasted and acid-etched (SLA) surface. The optimal osteogenetic potential of TNT surface in DM rats was further validated in the in vivo experiment by micro-CT scan analysis [130]. Uhm et al. looked at the possibility of using an Ag coating on the surface of anodic $TiO_2$ nanotubes to stop infections in dental implants. Researchers deposited AgNPs onto a $TiO_2$ surface using a magnetron sputtering technique. Compared to untreated control surfaces, the amount of *S. aureus* found on an AgNPs-loaded $TiO_2$ nanotube surface was much lower, according to in vitro antibacterial research. Except for the group that received treatment at the maximum input power density of 5 $W/cm^2$, which was evaluated by the researchers for the magnetron sputtering method, no cytotoxicity was seen. The results demonstrated that magnetron sputtering may produce Ti NTs surfaces coated with antibacterial AgNPs [131].

Through its effects on the Wnt, mitogen-activated protein kinase (MAPK), and forkhead box protein $O_1$ ($FoxO_1$) signaling pathways, TNT decreased oxidative stress and increased osteoblastic activity. However, since a robust negative association was discovered between elevated superoxide ($O_2^{\cdot -}$) and reduced SIR3 protein level, $TiO_2$NPs cause oxidative stress, inhibit osteogenesis, and weaken the antioxidant defense system. Furthermore, Ti implant alloy activates the NOX pathway, which increases ROS production and causes osteoblast cells to become cytotoxic. Numerous pathways associated with oxidative stress are stimulated by $TiO_2$NPs. The use of Ti implants coated with $TiO_2$ nanotubes to lessen oxidative stress and encourage osteogenesis during bone remodeling is supported by scientific research. To verify the cellular and molecular cross-talk in bone remodeling discussed in this study, large sample sizes and carefully monitored clinical studies are needed [132].

#### Zinc-based NPs in dental implant

Particularly, dental implantology is developing a growing interest in Zn materials. ZnO exhibits considerable variation in form and dimension. Hence, employing diverse objectives is advantageous. Determining the magnitude of ZnO-NPs is thus a simple process. Antibacterial activity has been observed against both Gram-positive and Gram-negative microorganisms. In addition, its activity on textiles and oral surfaces is commendable. Zn's antibacterial properties are recognized for their potential to promote healing and infection prevention following implant surgery. Additionally, Zn can stimulate bone development, which is essential for the longevity of dental implants. Zn-based NPs may also encapsulate dental implants to enhance their tensile strength and abrasion

resistance. Zn-based NPs are permissible for intravascular application due to their low toxicity and biocompatibility. The relatively simple synthesis process enables the production of substantial quantities at a justifiable expense [133].

Although ZnO nanorods with surface engineering show impressive antibacterial properties, their extreme cytotoxicity severely limits their potential for biological applications. Inspired by the in vivo breakdown process of Zn, ZnO nanorods are converted into the thermodynamically more stable Zn phosphate ($Zn_3(PO_4)_2$) by a simple hydrothermal treatment in a hydrogen phosphate solution. One can precisely modify the surface morphology, generation of ROS, and release of $Zn^{2+}$ to circumvent the cytotoxic effects of ZnO nanorods without compromising their antibacterial capacity by modulating the conversion ratio. Moreover, reprogramming the metabolic configuration of human BMSC, an optimized quantity of $Zn^{2+}$ liberated from the $ZnO/Zn_3(PO_4)_2$ hybrid coating promotes osteogenic differentiation and extracellular matrix mineralization. Using a rabbit femur infection model associated with implants suggests that the hybrid $ZnO/Zn_3(PO_4)_2$ coating can facilitate osseointegration even when pathogenic bacteria are present. The surface modification technique described herein imparts exceptional pro-osteogenic and antibacterial characteristics to Ti-based implants, thereby establishing substantial clinical promise in dentistry and orthopedics [134] (Table 1).

## Metal nanoparticle in peri-implant mucositis

Examining the effects of particles at the nano- and microscales on the formation of the conditions required for the pathological inflammatory process inside tissues was the aim of researchers. By co-culturing human monocytic leukemia cells (the THP-1 cell line) with nanoscale metal particles (NSMP) that were removed from dental implant surfaces, it was possible to assess the survival of immunocompetent cells. Although it was previously believed that the Ti alloy was "bioinert," researchers were able to ascertain the possibility of contact between immunocompetent cells and the alloy as well as the effect of that interaction on licensed medical products via the use of flow cytometry. The present clinical case and the results of histological analysis of soft tissue biopsy specimens served as the foundation for multidisciplinary studies. Researchers found that for the constituents of fibrous capsules to form microparticles during the osseointegration of dental implants, there has to be a functional load. X-ray and electron microscopy were used to establish that the composition of the dental implants and the discovered nano- and microparticles matched. DLS confirmed that the supernatants removed from the dental implant surfaces of both manufacturers' systems included NPs. It was confirmed by the research that NSMP has a role in the pathological and physiological processes of inflammation. Experiments have shown the autoimmune component of the pathogenesis of chronic immunopathological inflammation in tissues (PIM and PI). By switching to an in vitro model, it was possible to examine the effect of the "bioinert" $TiO_2$ compound NPs on human immune system cells in an experiment. As a result, it was shown that there exists a critical dose of NPs that, in the presence of persistent inflammation, leads to their coagulation into micron-sized particles. This concept suggests that more multidisciplinary research is required to enhance therapeutic, diagnostic, and preventive algorithms for patient care during implant treatment [135].

**Table 1** Applying metallic NPs in peri-implant diseases, such as peri-implantitis

| Metallic nanoparticles | Applications | Functions | Refs. |
|---|---|---|---|
| ZnO nanorods | ZnO nanorods are used to coat titanium (Ti)-based implants to prevent PIDs. Facilitate osseointegration | The hybrid ZnO/$Zn_3(PO_4)_2$ coating can facilitate osseointegration even when pathogenic bacteria are present. The surface modification technique described herein imparts exceptional pro-osteogenic and antibacterial characteristics to Ti-based implants, thereby establishing substantial clinical promise in dentistry and orthopedics | [134] |
| AgNPs | Nanoparticles (NPs) are used to coat dental implants to prevent PIDs. Increased antibacterial properties | The antimicrobial efficacy of dental alloys containing AgNPs at concentrations of 10, 4, and 2 µmol/L was evaluated against *Streptococcus aureus* and *S. aureus*. Cytotoxic values were significantly elevated in all dental alloys comprising 0% AgNPs, which served as the control groups. When AgNPs were incorporated, cytotoxicity values were diminished | [109] |
| CA@Ag/SF | CA@Ag/SF is used to coat Ti-based implants to prevent PIDs. Facilitate osseointegration | CA@Ag/SF-coated Ti implants dramatically increased bone regeneration and caused fast, but secure, osseointegration upon in vivo implantation in rat femoral-condyle lesions, suggesting tremendous clinical application potential | [167] |
| Dopamine–silver (DA/Ag) | PDA–AgNPs nanocomposite coating promoted optimal soft tissue healing and bone formation around the implants | By the results of the hypodermic implantation, osteogenesis, cytotoxicity, and antibacterial tests, the homogeneous PDA–AgNPs nanocomposite coating promoted optimal soft tissue healing and bone formation around the implants, striking a balance between cytocompatibility and antibacterial activity | [111] |
| Ag-PVP nanocomposites | NPs are used to coat dental implants to prevent PIDs. Increased antibacterial properties | The implants were coated with Ag-PVP nanocomposites at varying concentrations using the deep coating method. The results obtained indicate the presence of an enormous zone of inhibition when Ag-PVP coating is present. Five days later, when the antibacterial test was repeated, it was determined that the zone of inhibition of the implants was permanent | [112] |
| Ti-AuNPs | Ti-AuNPs are used to coat Ti-based implants to prevent PIDs. Facilitate osseointegration | The in vitro findings demonstrated that applying Ti–AuNPs to ADSCs significantly promotes osteogenic differentiation by upregulating the mRNA expression of genes specific to osteogenic differentiation. Ti–AuNPs can function as osseointegration-inducing dental implants to encourage the formation of an osseous interface and sustain nascent bone formation via these in vitro and in vivo experiments | [117] |

**Table 1** (continued)

| Metallic nanoparticles | Applications | Functions | Refs. |
|---|---|---|---|
| AuNPs | AuNPs have the potential to function as a potent bone inductive agent in the context of dental implant therapy in PIDs | Assess the osteoinductive capability of AuNPs mediated by SC in preparation for their use in implant dentistry. It can be deduced that stable, environmentally friendly, and biocompatible AuNPs have the potential to function as a potent bone inductive agent in the context of dental implant therapy | [118] |
| AuNP-antagomiR204 | AuNP-antagomiR204 as coating of Ti-based implants to prevent PIDs. Facilitate osseointegration | Deficient osseointegation in diabetes mellitus was determined to be the result of miR204 misexpression; PLGA sheets facilitated the release of AuNP-antagomiR204, which represents a potentially practical approach for functionalizing the surface of Ti implants to enhance osseointegration | [119] |
| AgNPs | As an antibacterial agent for the treatment of PI | AgNPs inhibit the development of biofilms by oral bacterial flora, including mixed-species *S. aureus*. Triple-irradiated NPs exhibited the most pronounced antimicrobial properties. By modifying dental implants in this manner, PI could be prevented | [141] |
| AgNP-modified Ti surface | NPs as coating of dental implant for treatment PI. It increased antibacterial properties | The findings showed that by adjusting the expression levels of genes linked to biofilm formation (fnbA and fnbB for *S. epidermidis*, and icaA and icaR for *S. aureus*), an AgNP-modified Ti surface may suppress bacterial adhesion and biofilm development | [142] |
| Ag–ZnO NPs | Ag–ZnO NPs as coating of dental implant for treatment PI. It increased antibacterial properties | A decrease in wettability and an increase in surface irregularity were the outcomes of this coating. Significantly diminished bacterial biofilm formation was observed in abutments that were altered. This promotes enhanced adaptation of the soft tissue and the development of a robust soft tissue seal surrounding subsequent superstructures implanted in implants | [143] |
| TNT-AL-AgNPs | TNT-AL-AgNPs as coating of Ti-based implant for treatment PI. Facilitate osseointegration and increase antibacterial functions | The TNT-AL-AgNPs implant was biocompatible with osteoblasts and had osteoinductive characteristics. In vitro, this release demonstrated antibacterial solid qualities. Antimicrobial-releasing implants that release TNT-AL-AgNPs in response to low pH might be used as a model for PI management using this innovative design of low pH-triggered AgNPs | [144] |
| Ti surfaces coated with AgNP | As a therapeutic and anti-inflammatory agent in PI | The incorporation of antibacterial properties onto the implant surface and the mitigation of PI inflammatory processes may be accomplished through the formation of an AgNP layer | [145] |

**Table 1** (continued)

| Metallic nanoparticles | Applications | Functions | Refs. |
|---|---|---|---|
| AgNPs | Increased antibacterial properties in PI | The anti-biofilm activity of all concentrations of AgNPS that were tested was most pronounced when applied to MDR *P. aeruginosa*. The present research outcomes underscore the significance of AgNPS in impeding the growth of *P. aeruginosa* and expose a possible utilization of AgNPS to eliminate *P. aeruginosa* biofilms | [146] |
| AuNPs-TNTs | NPs as coating of dental implant for treatment PI. It increased antibacterial properties | For the potential application of an AuNP-decorated TNT substrate in enhancing the antibacterial properties of dental implant surfaces (PI), researchers have concluded their research. Combining ultrasound with $TiO_2$-doped metal ions, the study proposes a method for developing a nanoplatform with effective anti-bacterial properties | [148] |
| Au-TNT | This NP plays a role in bone regeneration around the dental implant and is an anti-inflammatory and antibacterial agent in treating PI | Au-TNT, on the other hand, had outstanding antibacterial activity in vivo, showing a 3-log CFU reduction in comparison to the control group. Research also demonstrated that Au-TNT encouraged bone regeneration and decreased inflammatory factor levels. Offers a sonodynamic-catalytic nano platform for effective removal of biofilm and treatment of PI infections | [149] |
| Ti NPs | NPs as coating of dental implant for treatment PI. It increased antibacterial properties | The results indicate that Ti particles may stimulate the production of high levels of ROS by recruiting an abnormal number of neutrophils capable of producing high levels of metalloproteinase | [156] |
| Magnetic NPs | Increased antibacterial properties | That local administration of vancomycin into the femoral canal, in conjunction with hyperthermia induced by magnetic NPs, improved bacterial eradication in a biofilm-based colony. This involves utilizing magnetic NP-induced hyperthermia to disrupt the protective effect of bacterial biofilms and to optimize the therapeutic effect of systemic antibiotics on the PI region | [168] |
| nZnO/MTC-Ti | nZnO/MTC-Ti as coating of Ti-based implants to treatment PI. Facilitate osseointegration and increase antibacterial properties | It was discovered that the nZnO/MTC-Ti implants exhibited superior in vivo capabilities for promoting bone regeneration, antibiosis, and osseointegration. The remarkable efficacy of nZnO/MTC-Ti implants in promoting osseointegration and preventing bacterial infection was suggested by these results, indicating a tremendous opportunity for addressing immediate/early loading hazards and PI of dental implants | [159] |

**Table 1** (continued)

| Metallic nanoparticles | Applications | Functions | Refs. |
|---|---|---|---|
| ZnO-NPs | Increase antibacterial properties in PI | Biogenic ZnO-NPs demonstrated a significant inhibitory effect against organisms that induce peri-implantitis (PI), namely *E. coli* and *S. aureus*. Biogenic ZnO-NPs exhibit a significant inhibitory capacity against bacteria that induce PI | [160] |
| Nano-$CeO_2$ | Nano-$CeO_2$ as coating of Ti-based implants to treatment PI | The potential of $CeO_2$-modified Ti surfaces to augment the antimicrobial capabilities of dental implants is exceptionally bright. An innovative nano-octahedron $CeO_2$ coating applied to Ti exhibited significant therapeutic promise in mitigating and eradicating PI | [162] |

Human gingival fibroblasts (HGFs), the primary cells of the PI soft tissues, were transplanted on AgNP-doped Ti–6Al–4V surfaces to assess the biocompatibility of the modified surfaces. The findings of this study suggest that at doses of 100 ppm, 200 ppm, and 300 ppm, Ti–6Al–4V surfaces coated with 8 nm and 30 nm AgNPs do not exhibit appreciable cytotoxicity against HGFs. Researchers demonstrated that after 72 h, the HGF proliferation rate started to rise again after its initial stop. When paired with findings from another research carried out by the same team, the antibacterial activity against common periodontal pathogens in this study suggests that AgNP-doped Ti–6Al–4V surfaces might be helpful in implant abutments as a means of reducing PID [136]. Researchers should focus on treating PIM to monitor PI since metal NPs may be able to prevent and cure it.

## Metal nanoparticles as antibacterial agents in peri-implantitis treatments

The accumulation of anaerobic microbes around the dentist significantly contributes to PI inflammation, possibly resulting in implant loss if left untreated [137]. More and more metal NPs are used for unique purposes, such as antibacterial agents [138]. Among the PI diseases that impact the adjacent structures of endosseous dental implants are PI mucositis and PI [139]. The extensive distribution of PI bone loss presents challenges in effectively managing biological complications that have the potential to compromise the sustained efficacy of osseointegrated implant reconstructions [140]. PI-supporting tissues have been found to contain metal and Ti particles. Extensive research has been conducted in orthopedics to investigate metal particle release as a potential etiologic factor. It has been observed that metal particle release induces aseptic retraction around arthroplasties and is linked to implant failures [29]. In the following section, we have examined the application of various types of metal NPs in treating PI.

### AgNPs in peri-implantitis treatments

The antibacterial activity of resized AgNPs, produced by re-irradiating an aqueous colloidal solution of Ag with a Green or Infrared laser one or three times, was compared to that of unmodified Ti discs in one study. Considering the antibacterial properties demonstrated by AgNPs, the researchers' objective is to examine their impact on

multispecies biofilms that contribute to the formation of PI. For this objective, colloidal suspensions of AgNPs were generated via laser ablation in deionized water utilizing two distinct lasers. AgNPs inhibit the development of biofilms by oral bacterial flora, including mixed-species *S. aureus*. Triple-irradiated NPs exhibited the most pronounced antimicrobial properties. By modifying dental implants in this manner, PI could be prevented [141].

Based on a bacteria-cell co-culture study, the objective of this research was to examine the antibacterial efficacy of Ti surfaces functionalized with nano-Ag against epidemic *Staphylococcus aureus* by analyzing the regulation of biofilm-related genes. To accomplish this objective, two epidemic *Staphylococcus* strains representative of the pathogen were utilized: *S. aureus* (USA 300) and *S. epidermidis* (RP62A). The results demonstrated that an AgNP-modified Ti surface could inhibit bacterial adhesion and biofilm formation by modulating the expression levels of biofilm-related genes (icaA and icaR for *S. aureus*; fnbA and fnbB for *S. epidermidis*. Additionally, a novel study on the co-culture of bacteria and fibroblasts demonstrated that adding AgNPs to such a surface facilitates the survival, adhesion, and dissemination of mammalian cells more effectively than *S. aureus* and *S. epidermidis*. As a result, it was established that the modified surface exhibited a potent anti-infective effect against both planktonic and sessile bacteria via the synergistic interaction between AgNPs and ion release. Moreover, it creates a path towards more effectively meeting the clinical requirements [142].

The present article outlines an innovative coating composed of AgNPs and ZnO. To modify healing abutments for use as drug delivery systems in oral implantology, this coating was applied. The inhibitory effect of the substance on biofilm formation was evaluated against *S. mutans*, *S. oralis*, *S. aureus*, and *E. coli*. A nanostructured coating was formed by adequately depositing ZnO 0.1% AgNPs onto the abutments; this coating resulted in an increase in surface roughness and a decrease in wettability. Abutments that were modified reduced bacterial biofilm formation by a significant margin. As a result of their rounded, inadequately dispersed, and NP-coated cells, the experimental abutments were not conducive to bacterial settlement and replication as determined by SEM research. Experimental healing abutments coated in an Ag–ZnO-NPs formulation were the focus of one study. The purpose of the abutments was to establish a localized antibacterial milieu that would deter early colonizing species, thus promoting enhanced adaptation of the soft tissue and the development of a robust soft tissue barrier surrounding subsequent superstructures embedded in the implant [143].

A study found that the pH level around the PI surface can drop to as low as 5.5 during bacterial infection. The variation in pH can function as a sensor to regulate the discharge of antimicrobial drugs from the implant's surface. The purpose of this research was to develop a PI infection control device using titania nanotube arrays (TNT) that release AgNPs in response to pH variation. Compared to pH 7.4, the discharge of AgNPs from the TNT-AL-AgNPs implant was enhanced at pH 5.5. In contrast to AgNPs released at pH 7.4, those released at pH 5.5 exhibited a significant increase in antimicrobial activity against gram-positive and gram-negative microorganisms. Implantation of TNT-AL-AgNPs promoted osteoblast differentiation and proliferation in vitro but had no discernible effect on osteoblast morphology. AgNPs were successfully incorporated into TNT via an acetal linker, thereby preserving the surface properties of TNT. As a result,

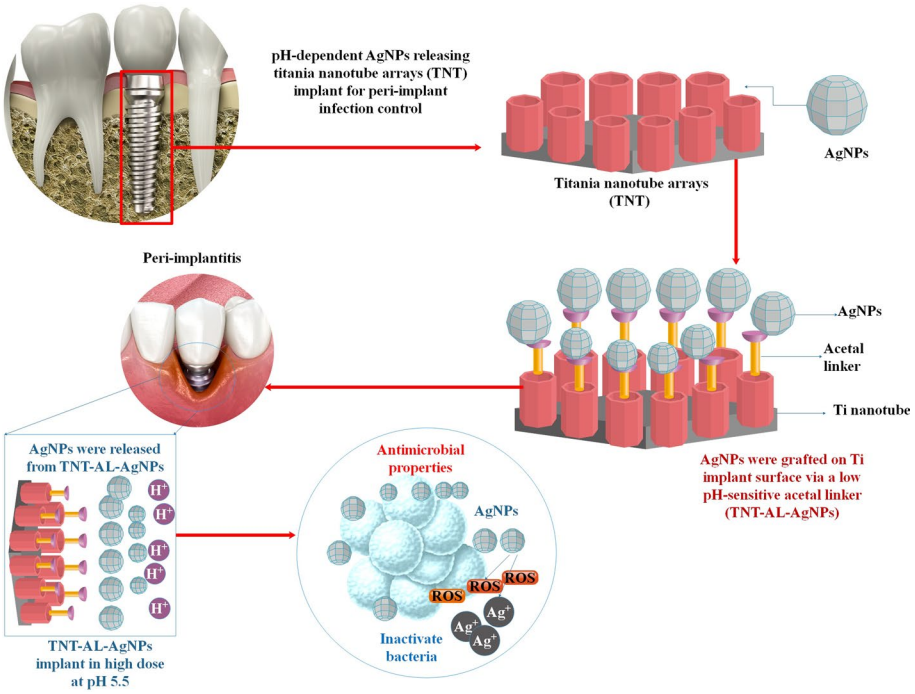



**Fig. 6** Create a titania nanotube array (TNT) implant that releases AgNPs in response to pH changes to manage peri-implant infections. Using a low pH-sensitive acetal linker, AgNPs were effectively attached to the TNT surface without changing its properties. AgNP release was rapidly increased at pH 5.5, similar to the pH of bacterial infection, as opposed to physiological pH 7.4. AgNPs produced at pH 5.5 exhibited antibacterial activity that was greater than that of pH 7.4. TNT-AL-AgNPs did not impede osteoblast adhesion, morphology, or differentiation. They were also biocompatible. To treat peri-implant infection, TNT-AL-AgNPs may be an infection-triggered antimicrobial that releases a unique implant model [144]

this novel design of low pH-triggered AgNPs that release TNT-AL-AgNPs could serve as a model for PI infection control using antimicrobial-releasing implants triggered by infection [144].

A study aimed to develop and assess the antibacterial properties of Ti surfaces coated with AgNPs, which, when applied to the surface of dental implants, could potentially inhibit such processes. AgNPs presence was demonstrated to be present on the treated surfaces. The particles had a mean diameter of 58 nm, deviating by 25 nm, and followed a Gaussian distribution; the infill factor was 25%. Antibacterial analysis revealed that the samples coated with NPs exhibited a statistically significant antibacterial effect of 64.6%. Additionally, tests demonstrated that the NPs are affixed to the Ti surface securely and are non-cytotoxic. The incorporation of antibacterial properties onto the implant surface and the mitigation of PI inflammatory processes may be accomplished through the formation of an AgNP layer. This study has shown that AgNPs can induce pathology in mammalian cells; therefore, it is crucial to fix the particles securely to prevent their release into the bloodstream (Fig. 6) [145].

A study aimed to separate multidrug-resistant *P. aeruginosa* from dental implants and use AgNPs to regulate the bacteria's development and biofilm. To isolate *P. aeruginosa*, thirty specimens from PI patients were obtained. Sterile paper points (diameters 30–45 mm) were used to extract bacterial samples from the PI pocket that was infected.

From thirty clinical specimens, three *P. aeruginosa* were successfully isolated. The majority of the prescribed antibiotics did not work on *P. aeruginoas* isolates. All of the separated microorganisms were inhibited by AgNPs. The notable anti-biofilm activity against multi-drug resistant (MDR) *P. aeruginosa* was shown by all tested doses of AgNPs. Current research demonstrates how AgNPs inhibit *P. aeruginosa* development and suggests a possible use for AgNPs in removing *P. aeruginosa* biofilms [146].

In an additional study, a twin cathode glow discharge plasma system was employed to reactively sputter-deposit surgical grade commercially pure Ti in conjunction with the multi-element (TiZrTaNbMo)N high entropy nitride (HEN) at varied Ag concentrations. The antibacterial efficacy of the HEN-Ag nanocomposite coatings against isolates of *E. coli*, *S. aureus*, and *Candida albicans* (*C. albicans*) was tested based on the bacterial inhibitory zones and bacterial death efficiency. The results of these investigations suggest that the Ag-free HEN coating was composed of a face-centered-cubic (FCC) nitride phase. This phase exhibited favorable mechanical characteristics, corrosion resistance, and osteogenic activity; however, no antibacterial properties were detected. On the other hand, the $HEN_{0.9}Ag_{0.1}$ coating, which consists of AgNPs (approximately 10 nm in diameter embedded in amorphous/nanocrystalline high-entropy nitride), exhibits commendable mechanical and anti-corrosion properties, as well as superior cell compatibility and antibacterial capabilities. These attributes suggest that the $HEN_{0.9}Ag_{0.1}$ coating can furnish dental implants with exceptional protective efficiency. Despite the $HEN_{0.8}Ag_{0.2}$ nanocomposite coating demonstrating enhanced antibacterial effectiveness, it was observed that it might be susceptible to in vitro cytotoxicity [147].

#### AuNPs in peri-implantitis treatments

An ultrasound-enhanced antibacterial implant surface was fabricated by researchers using AuNPs-modified $TiO_2$ nanotubes (AuNPs-TNTs) in a study. When utilized as a synthetic tooth surface, coatings composed of AuNPs-TNTs demonstrated remarkable biocompatibility. Significantly, when subjected to ultrasound treatment, AuNPs-TNTs produced more reactive oxygen radicals than the bare Ti surface. *P. gingivalis* was utilized as the model bacteria for a proof-of-concept application; the AuNPs-TNTs, in their proposed form, demonstrated a substantial enhancement in antibacterial activity when subjected to a straightforward ultrasound treatment. This antibacterial film presents a novel approach to designing the surface of an artificial implant coating that aims to address the issue of dental implant failure caused by bacterial infections. Combining ultrasound with $TiO_2$-doped metal ions, the study proposes a method for developing a nanoplatform with effective anti-bacterial properties [148].

A potential new therapeutic option for biofilm infections has been identified: ultrasound-activated antibacterial sonodynamic therapy (aSDT). In this study, an activatable nano platform (Au-TNT) created on the implant's surface is suggested for aSDT. When exposed to ultrasonic radiation, Au-TNT could quickly produce $O_2$, which would improve aSDT's anti-biofilm effectiveness by reducing the hypoxic microenvironment of biofilm. Furthermore, it can generate singlet oxygen ($^1O_2$) and hydroxyl radicals, which have a powerful antibacterial effect on pathogenic biofilms of different species based on biofilm thickness, biofilm metabolism, cell membrane rupture, and bacterial survival rate. Conversely, Au-TNT had exceptional antibacterial efficacy in vivo, with a 3-log

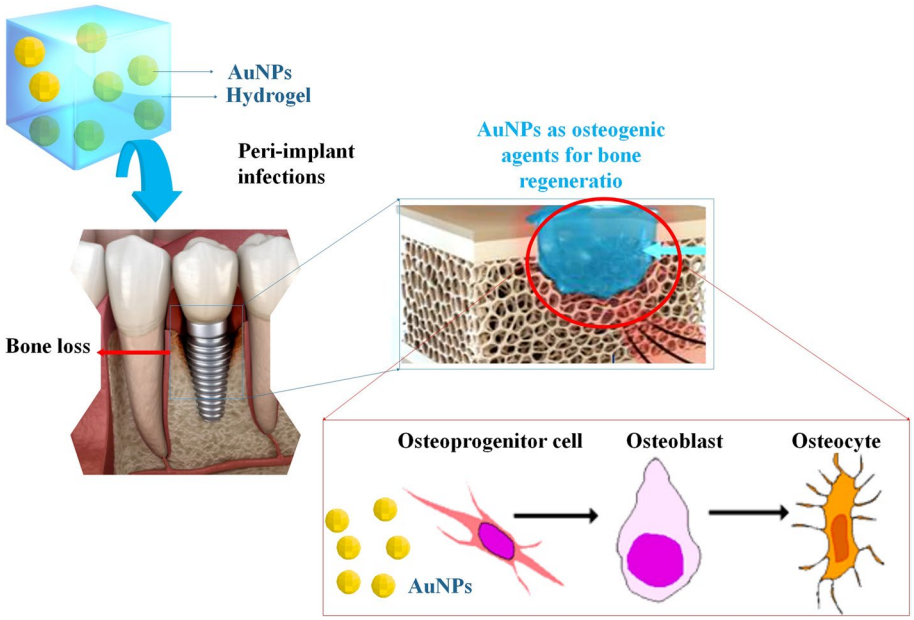



**Fig. 7** AuNPs exhibit unique properties to be used in dentistry and can be a novel application in dental caries, bone regeneration, periodontology, implantology, and tissue engineering. AuNPs are added to various biomaterials to boost their benefits because of their antifungal and antibacterial qualities. Because of their excellent surface specificity and biocompatibility, AuNPs may be utilized as osteogenic agents to promote bone growth in PI. AuNPs can stimulate osteogenic properties and expedite cellular proliferation and activity [151]

CFU decrease relative to the control group. Surprisingly, research also demonstrated that Au-TNT encouraged bone regeneration and decreased inflammatory factor levels. This work, therefore, offers a sonodynamic-catalytic nanoplatform for the effective removal of biofilm and treatment of PI infections [149].

The superelasticity of NiTi alloy renders it a clever material that facilitates more straightforward integration with bone structures and helps to minimize stiffness. However, the bioactivity and antibacterial activity of NiTi alloy restrict its use in dentistry. In another study, Ni–Ti–O nanotubes, which may be bioactive and photocatalytic, were synthesized and applied to the surface of NiTi alloy. More precisely, they used AuNPs to coat Ni–Ti–O nanotubes to benefit from the photocatalytic action that occurs under visible light at 470 nm, which amplifies the antibacterial activity. The remarkable antibacterial activity that Au-coated Ni–Ti-O nanotubes displayed when exposed to visible light at 470 nm, as shown by the enzymatic activity and antibacterial colony-forming unit tests, was also caused by the photocatalytic effect. Therefore, the expression of antibacterial properties in dental applications seems promising when paired with Au-coated Ni–Ti–O nanotubes and photo functionalization based on visible light (Fig. 7) [150].

#### CuNPs in peri-implantitis treatments

An in vitro study was found to quantify the antibacterial efficacy of a Cu-deposited Ti surface on the PI-associated strain *P. gingivalis* (DSM 20709), using the surface as a model for dental implants. Researchers demonstrated that Cu was deposited onto Ti discs via a combined deposition-anodization procedure utilizing spark-assisted

anodization. Variation in process time permits the deposition of various concentrations of Cu on the surface using this technique. In addition to examining the adhesion of *P. gingivalis* to the discs over 2, 4, and 6 h, conventional culturing was utilized to determine the antibacterial impact of Cu released in solution. On Cu-deposited discs, bacterial cell viability is severely inhibited; after 6 h, CFU decreases by three log units relative to the control. In summary, the presence of Cu-functionalized Ti substantially diminishes the viability of adhered bacteria and the number of viable bacteria in the vicinity of the Ti. Cu thus forms a "safe zone" encircling implants, providing protection against surface-emitted Cu and facilitating enhanced implant healing [152].

Inflammation caused by dental plaque buildup, or PI, may lead to the loss of bone that supports dental implants, which can cause the implants to fail. In a study under anaerobic circumstances, the antibacterial activity of six metal and metal oxide NPs, together with two of their composites, were tested against bacterial pathogens linked to PI. The MIC and minimum bactericidal concentration (MBC) against *P. intermedia*, *P. gingivalis*, *F. nucleatum*, and *A. actinomycetemcomitans* were used to evaluate the activities of Ag + CuO composite and Ag + ZnO composite, as well as CuO, ZnO, $TiO_2$, $WO_3$, and AgNPs. To investigate the dynamics of ZnO NPs' antibacterial activity, time-kill tests were used. The range of MIC and MBC values were, respectively, < 100 μg/mL to 2500 μg/mL and < 100 μg/mL to > 2500 μg/mL. In decreasing sequence, Ag > Ag + CuO > $Cu_2O$ > CuO > Ag + ZnO > ZnO > $TiO_2$ > $WO_3$ was the activity of the NPs evaluated. ZnO time-kill experiments showed a substantial reduction in growth of all examined species in four hours, with 100% growth for *P. gingivalis* occurring in two hours and 100% growth for *F. nucleatum* and *P. intermedia* in 3 h. Antimicrobial NP-coated Ti surfaces of orthopedic and dental implants should improve implant success rates [153].

#### TiNPs in peri-implantitis treatments

In these years, there has been an increase in interest in understanding how Ti particles and ions react in creating a foreign body reaction. PI marginal bone loss resulting from PI has been hypothesized to be caused by an alteration in the foreign body equilibrium between the dental implant and the host immune system [154].

To induce an aseptic foreign body reaction, soft tissues surrounding the coronal point of implants implanted bilaterally in the maxillary first molar region were injected with 20 mg Ti particles in one study. Macrophages were additionally diminished in the experimental group through the local administration of liposomal clodronate (Ti + LipClod). As controls, Ti-injected rodents were administered phosphate-buffered saline (Ti + PBS) or an inert liposome containing Ti (Ti + Lip). When contrasting the Ti + LipClod group with the control groups, the latter exhibited a substantial reduction in both bone loss and macrophage density in the vicinity of the implant. PIT was infiltrated with more macrophages, predominantly M1 phenotype, in both control groups. Conversely, the Ti + LipClod group exhibited a decrease in macrophage density, with M1 macrophages comprising marginally more than M2 macrophages. Subsequently, there was a substantial upregulation in the messenger RNA expression levels of TNF-α, IL-1β, IL-6, and receptor activator of nuclear factor-κB ligand (RANKL) in both control groups when compared to the Ti + LipClod group. In light of these findings, the authors hypothesized that Ti particles negatively impact PIT by stimulating the local secretion of inflammatory

cytokines by macrophages, precisely the M1 phenotype. Therefore, the influence of Ti particles on PI bone loss can be attributed to macrophage polarization, indicating that these particles induce a host immune response marked by macrophage activation in response to a foreign body [155].

The purpose of a study conducted by researchers is to ascertain the impact of Ti NPs discharged from the implants on osteoresorption and chronic inflammation in the surrounding tissue. The dysregulated MSC population was suggested by the presence of adipose-like tissue and increased ZFP467 expression, together with changes in vascular shape. According to the findings, Ti particles may promote the generation of elevated ROS by drawing in an unusually high number of neutrophils that are metalloproteinase-producing cells. This leads to the induction of collagen fiber deterioration. These occurrences might affect the commitment of MSCs, resulting in an imbalance in bone regeneration. Researchers' analysis of PI-affected tissues concluded that the presence of Ti NPs was correlated with ROS production [156].

Researchers describe in this study an N-halamine polymeric coating on the surface of Ti that possesses biocompatibility, stability, and long-lasting renewable antibacterial activity. The coating is potently biocidal against both the principal pathogenic bacteria of PI infection and complex bacteria isolated from PI patients, according to research. Furthermore, its antibacterial effectiveness can endure for an extended duration (12–16 weeks) both in vitro and in animal models, as well as in the human oral cavity. This characteristic typically encompasses the entire process of osseointegrated interface formation. Moreover, it is possible to restore its antibacterial properties through simple rechlorination after ingestion, thereby emphasizing the significant potential of a renewable antibacterial coating in dental implants. These results suggest a promising application prospect for the prevention and treatment of PI infection [157].

The objective of another study is to develop porous $TiO_2$ coatings on Ti using a combination of magnetron sputtering and dealloying processes to incorporate Cu. Furthermore, photothermal therapy is utilized to augment the prophylactic efficacy of Cu ions against bacterial infections. The dealloying process effectively eliminated the majority of the Cu element from the magnetron-sputtered Cu-containing films, resulting in the formation of porous $TiO_2$ coatings on Ti. Photothermal conversion efficacy was substantially enhanced by forming porous nanostructures when exposed to NIR-II light. In both in vitro and in vivo experiments, the combined effect of hyperthermia and Cu ions enhanced antibacterial activity; the antibacterial efficiency against *S. mutans* can reach 99%. Additionally, the porous $TiO_2$ coatings demonstrated remarkable biocompatibility. By dealloying changes in the Ti surface structure, it may be possible to develop a novel method for augmenting the antimicrobial characteristics of Ti implants [158].

#### Other metal NPs in peri-implantitis

ZnO NPs exhibit enhanced antibacterial capabilities; nevertheless, they are susceptible to rapid $Zn^{2+}$ release, resulting in cytotoxicity. By employing the evaporation-induced self-assembly method (EISA) and one-step spin coating, ZnO NP-loaded mesoporous $TiO_2$ coatings (nZnO/MTC-Ti) were inventively developed as a potential dental implant modification in this study. Mesoporous $TiO_2$ coatings (MTCs) controlled the deposition

and synthesis of ZnO NPs within the nanoscale pores. In addition to optimizing the charge distribution on the surface, the long-term steady-state release of $Zn^{2+}$ was controlled by the synergistic effects of MTC and ZnO NPs on nZnO/MTC-Ti. It was discovered that the nZnO/MTC-Ti implants exhibited superior in vivo capabilities for promoting bone regeneration, antibiosis, and osseointegration. The remarkable efficacy of nZnO/MTC-Ti implants in promoting osseointegration and preventing bacterial infection was suggested by these results, indicating a tremendous opportunity for addressing immediate/early loading hazards and PI of dental implants [159].

Biogenic ZnONPs have been identified as inhibitors of pathogens that induce PI. In an investigation, *Andrographis paniculata* leaf aqueous extract (APLAE) was utilized to synthesize ZnONPs, optimized, characterized, and tested in vitro against bacteria that induce PI. Biogenic ZnO NPs demonstrated a significant inhibitory effect against organisms that induce PI, namely *E. coli* and *S. aureus*. A study deduces, from the experimental findings, that biogenic ZnO NPs exhibit a significant inhibitory capacity against bacteria that induce PI [160].

An investigation assessed the efficacy of glucose-1-phosphate (Glc-1P) biofunctionalized Zn peroxide ($ZnO_2$) NPs with varying sizes (4–5 nm) and synthesis ratios (1–10:1). The NPs targeted the anaerobes *F. nucleatum*, *P. gingivalis*, and *P. intermedia*, in addition to the yeast *C. albicans*, *A. actinomycetemcomitans*, *Enterococcus faecalis*, *S. aureus*, and *L. paracasei*. Gram-negative anaerobes and *A. actinomycetemcomitans* were inhibited by the $ZnO_2$/Glc-1P NPs at a pH-dependent MIC of 25 μg/mL and MBC of 50 μg/ml. In contrast, the tested gram-positive species and *C. albicans* were not impeded. The intracellular release of oxygen and the subsequent attachment of NP chains to the bacterial outer membrane. The invasion was observed exclusively in elongated, dividing cells when NPs containing stabilizers other than glucose were present, potentially due to the more porous cell wall in the parting layer. Using glucose-1-phosphate to decorate $ZnO_2$ is a Trojan horse strategy to enable their assimilation by oxygen-sensitive Gram-negative bacterial cells [161].

Nanostructured ceria, known as nano-Ceric oxide ($CeO_2$), exhibits antibacterial and anti-inflammatory properties. The researchers in this study devised an innovative approach to modify the surface of implants by applying various configurations of nano-$CeO_2$ onto Ti surfaces to augment the surfaces' antibacterial and anti-inflammatory characteristics. Early-stage bacterial attachment of *S. sanguinis* was greater on nanorod $CeO_2$-modified Ti than on another $CeO_2$-modified Ti, according to the results. In conclusion, the antibacterial activity of all three varieties of nano-octahedron $CeO_2$-modified Ti was equivalent, whereas its anti-inflammatory effect was most pronounced. Hence, the potential of $CeO_2$-modified Ti surfaces to augment the antimicrobial capabilities of dental implants is exceptionally bright. An innovative nano-octahedron $CeO_2$ coating applied to Ti exhibited significant therapeutic promise in mitigating and eradicating PI [162].

#### Metal base nanozymes in peri-implantitis

Nanozymes are nanomaterials that replicate the properties of enzymes, such as metals (Au, Ag, Pt, Pd, Ir, Au@Pt), metal compounds ($Fe_3O_4$, $CeO_2$, $MnO_2$, CuS, MnSe), non-metals (g-$C_3N_4$, GO), and SWNTs. Nanozymes possess characteristics of natural

enzymes, such as the capacity to catalyze substrate oxidation and conform to the same kinetic, concentration, and pH patterns. Additionally, nanozymes can control the quantities of reactive oxygen and nitrogen species (RONS) in cells [163]. As they demonstrate enzyme-like activity with multifunctional nanomaterials, nanozymes are gaining prominence in nanocatalytic medicine. Antibacterial agents of significant potency are nanozymes due to their exceptional biocompatibility and broad-spectrum antibacterial activity [164]. Nanozymes have been transformed into helpful antibacterial agents via biocatalytic processes. The use of nanozymes in the treatment of oral disorders, such as dental caries, dental pulp diseases, oral ulcers, PI, oral cancer monitoring, oral bacteria and ions, and soft and hard tissue regeneration, has not, however, been well-reviewed in the literature [165].

Researchers have reported on Cu-doped carbon dots (Cu-CDs) with improved catalytic (catalase-like, peroxidase-like) activity in the oral environment. These dots efficiently prevent bacteria (*S. mutans*) from adhering at first and then breaking up biofilms. Interestingly, the adjacent oral tissues are not negatively impacted by the production of ROS and $O_2$. Mainly, Cu-CDs show a strong affinity for peptidoglycans (PGN) and lipopolysaccharides (LPS), giving them remarkable antibacterial capabilities against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria. As a result, these nanocrystals promote faster wound healing by preventing purulent infection. Additionally, the results of the Cu-CDs/$H_2O_2$ system are superior to those of other methods, such as CDs and clinically used $H_2O_2$, particularly when considering the system's minimal dentin and enamel deterioration [163].

Researchers have created a PI treatment plan that is both effective and safe. Using the kinetic energy of microsized oxygen bubbles produced by the catalytic reaction between $H_2O_2$ and $MnO_2$ nanozyme sheet-doped silica diatom microparticles (Diatom Microbubbler, DM), this technique includes decontaminating implant-bound biofilms. Unlike traditional antiseptics like chlorhexidine or 3% $H_2O_2$, when used independently, quickly moving microsized DM particles can enter small gaps between implant fasteners and apply the proper force to remove biofilms without harming the surrounding mucosa or implant surfaces. As a result, the DM cleaning procedure promotes the successful reosseo-integration of the implant surface damaged by PI (Table 1) [166].

## Advantages and disadvantages of metal nanoparticles

PI is now a primary cause of implant loss and a significant issue for 28–56% of patients. Thus, sustaining the patient's quality of life and health depends on efficient PI prevention and control. Surgery, local irrigation, and antimicrobial therapy are often used to treat failing implants [169]. Antibiotics are used as an adjunct to mechanical treatment to suppress or eliminate infectious agents, with studies exploring their use alongside surgical interventions for PI. However, systemic antibiotics have not been effective in treating PI. The remarkable antibacterial effects were seen in NPs that were re-irradiated three times. This dental implant modification might stop PI from developing [170]. The non-specific bacterial toxicity mechanisms exhibited by metal-based NPs—namely, their failure to bind to a particular receptor within the bacterial cell—not only impede the development of bacterial resistance but also expand the range of antibacterial activity [171].

Furthermore, the principal metal nano-antibacterial agents include Ag, Au, Cu, iron, $TiO_2$, and ZnO, among others. Metal oxide NPs (e.g., $Ag_2O$, FeO, CuO, ZnO, MgO, $TiO_2$-CaO) are regarded as potentially effective antibacterial agents [172]. AuNPs are used in several medication delivery and diagnostic applications. In addition, different metal NPs like AgNPs are used in various medicinal applications, including separation science and innovative drug delivery systems [173]. It is common knowledge that Ag possesses antimicrobial and inflammatory properties. This characteristic is utilized selectively to accelerate the healing process and is used commercially in wound dressings, various pharmaceutical dosage formulations, and medical implant coatings. Additional metal NPs, such as Platinum (Pt) NPs, have been assessed for their potential health benefits. They have been effectively implemented in biomedical contexts, either in their pure form or alloyed with other metal NPs. Metal NPs are increasingly being utilized in biomedicine and related fields on a global scale [174, 175].

However, metal NPs that contain metal as a primary component may be toxic. Extended use of poisonous substances for therapeutic purposes is an ineffective strategy. Numerous biological mechanisms, including cell viability and proliferation, could be negatively impacted by these NPs. Immunotoxicity may result from exposure to these NPs; adverse effects on the immune system may manifest via autophagy, inflammation, oxidative stress, and apoptosis. Additional vital organs that may be harmed by prolonged exposure to metallic NPs include the brain, liver, and kidney [175]. Nevertheless, the distinctive physicochemical characteristics of metal-based NPs not only bestow auspicious biological effects but also present unforeseen harmful risks to the human body. To apply metal-based NPs to humans in a safer manner, a comprehensive comprehension of NP toxicity is required [176]. On the contrary, nanomaterials composed of metal oxides and metal alloys demonstrate a diminished level of stability. They are more prone to dissolution and ion release upon exposure to a biological environment. This results in the generation of ROS and oxidative stress within cells. Due to the high mobility of NPs in a variety of biological tissues, the investigation of their adverse effects is a crucial concern that must be satisfactorily resolved before their biomedical application. Assessing the short-term and long-term toxicity of metal and metal oxide NPs or their nano-formulations is crucial for ensuring the safety of the global biosphere; neglecting this could lead to severe consequences [98].

The infiltration of PIT and PI bacterial plaque by Ti degradation products in the form of microparticles or ions may induce an inflammatory response accompanied by bone resorption. This finding may have implications for the pathogenesis of PI [177]. Research has indicated that the introduction of Ti particles or ions during implant insertion, early and late stages of healing, as well as treatments administered during PI, may potentially contribute to PI via various mechanisms. These mechanisms include cellular response, DNA methylation, foreign body reaction, and modifying the oral microbiome by promoting dysbiosis. However, additional research is required to clarify the intricate interplay between these mechanisms and Ti particles/ions in the development and advancement of PI [178]. Ti particles have the potential to stimulate the generation of elevated levels of ROS and attract an abnormally large population of neutrophils capable of producing high concentrations of metalloproteinase. The degradation of collagen

fibers is induced as a result. These occurrences might affect MSC commitment by causing an imbalance in bone regeneration [156].

As an antimicrobial agent, ZnO in the form of NPs has also demonstrated promise; however, research on this NP's antimicrobial activity is limited. However, previous studies have documented that this NP exhibits sensitivity towards *E. coli*, *S. aureus*, and various other Gram-positive species, thereby indicating its potential as a broad-spectrum antimicrobial agent. In their investigation, Nair et al. employed ZnO particles varying in dimension from 1.2 μm to 40 nm. They demonstrated that, similar to nano-Ag, the antibacterial efficacy of ZnO escalates as the particle size decreases. According to the findings of Brayner et al., concentrations of 7–13 nm ZnO NPs exceeding $1.3 \times 10^{-3}$ M exhibited potent antimicrobial activity. The authors hypothesized that lower concentrations would not impact bacterial viability due to the bacteria's ability to metabolize $Zn^{2+}$ as an oligo element [153]. The utilization of ZnO in time-kill assays revealed a substantial reduction in the growth of every species examined within four hours. Specifically, the growth of *P. gingivalis* reached 100 percent within two hours, while *F. nucleatum* and *P. intermedia* reached 100 percent within 3 h. Applying antimicrobial NPs to the surfaces of dental and orthopedic implants Ti ought to result in a heightened success rate of the implants [153].

Researchers aim to evaluate the antibacterial activity against single and multispecies bacterial models and the cytotoxic effects of Zn oxide and Cu NPs (ZnO-NPs/Cu-NPs) on HGF cell cultures. Across all strains, the ZnO-NPs and Cu-NPs MICs ranged from 78.3 μg/mL and 3906 μg/mL to 125 μg/mL and 625 μg/mL, respectively. In a multispecies model, the administration of 125 μg/mL of each NP demonstrating bactericidal action was linked to an observed decrease in the total biomass volume (μ3). When exposed to nanostructures containing Cu-NPs, significant differences were found in the quantities of viable and nonviable biomass, in contrast to ZnO-NPs. While both NPs caused dose-dependent cytotoxicity in mitochondria, ZnO-NPs produced more intracellular ROS and released more LDH. At 50 μg/mL, Cu-NPs caused the formation of cleaved caspase-3, which at low dosages and early on in the process started the apoptotic pathway. After 24 h, ZnO-NPs are often biocompatible at concentrations of 78–100 μg/mL, but Cu-NPs are still incompatible at concentrations lower than 50 μg/mL. Antibacterial activity in a monospecies paradigm is strain-dependent, while 10 min after exposure in a multispecies model necessitated lower doses [179].

Despite the potential of NPs to address this issue by their multi-target mechanism of action, further investigation is warranted. Before the routine medical application of NP, formulation, characterization, and testing must be standardized. Due to the diversity of NP protocols described in the scientific literature, it is not easy to corroborate the findings of current studies in support of an antibiotic substitute. Additionally, few studies investigate the impact of NP on human cells. Alongside medical applications, cytotoxicity and immune response must be investigated to balance the concentration required for the desired activity and the depreciation of cytotoxicity and immune response. NP concentrations between 5 and 10 g/mL have been identified as toxic to eukaryotic organisms. A situation in which the concentration of efficacious antimicrobials exceeds the level of cytotoxicity may present issues for its practical application. In conclusion, for maximum validation, future research should consider standardized procedures in NPs

fabrication; this should include an assessment of cytotoxicity and an inflammatory response. Furthermore, to combat the growing prevalence of multidrug-resistant bacterial strains, it is best to conduct tests on clinical isolates instead of the conventional strains obtained from microbial collections [180].

The emergence and increasing popularity of nano-engineered Ti dental implants can be attributed to the ability to manipulate implant properties, achieve superior integration with tissue, and provide localized therapy. Anodization is considered superior to other novel and clinically applied nano-engineering strategies. This is due to its ability to produce controlled biocompatible titania nanostructures in a scalable and cost-effective manner, which enables the customization of implant topography, chemistry, bioactivity, and therapy. The successful implementation of this approach in a complex dental implant environment, which also requires the integration of soft tissues, will establish a precedent for the broader implant market, encompassing orthopedic implants, joint replacements, and craniofacial implants [33].

The toxicity and intranuclear cell absorption of $ZrO_2$ and $TiO_2$ particles, as well as the adherence of different anaerobic bacteria on $ZrO_2$ and $TiO_2$ implants, were compared. When compared to $ZrO_2$-implants, the adhesiveness of every species of bacteria that was studied was noticeably greater on Ti-implants. $TiO_2$-particles or Ti-particles covered in a $TiO_2$-layer should be the particles expelled from Ti-implants. The size (NP or MP) and oxidation state of discharged Ti-particles determine their toxicity. NPs in particular were more genotoxic and cytotoxic than similar microparticles. At greater exposure concentrations than lower concentrations, $TiO_2$- and $ZrO_2$-NPs have demonstrated a substantial increase in the intranuclear cell uptake ratio, which may raise the risk of DNA damage. In contrast to Ti-implants, $ZrO_2$-implants have less bacterial adhesion. Consequently, $ZrO_2$-implants may help to lessen biological problems (as PI) [181].

The majority of the studies that were examined showed that dental implant surfaces treated with AgNPs had a longer lasting antibacterial effect and decreased cytotoxicity. The release mechanism of the AgNPs from the Ti surfaces is strongly related to the cytotoxicity and antibacterial action; a delayed release promotes cell survival and proliferation. There isn't much clinical research using AgNPs currently available. Thus, it is impossible to quantify the clinical advantages. Concerns have also been raised about potential mucosal discoloration and biocompatibility. But in addition to the systemic impacts, further, in vivo and clinical research is needed to address those problems effectively. Given the complexity of PI, every treatment—including AgNPs—must undergo clinical validation before its efficacy is assessed. One of the things restricting is the absence of such confirmation. By delivering a more secure and consistent release of AgNPs, future research should concentrate on the unfavorable responses of the PIT. Since no clinical testing of such AgNP surfaces has been done, this might result in further clinical translation [182].

Lastly, an unanticipatedly high release of organic molecules—such as antibiotics and analgesics—loaded into the nanotubes may cause cytotoxicity. Depending on the released dose, acute toxicity might result from this burst release (ascribed to the high diffusion gradient of the drug-releasing implant upon implantation) and manifest as the emergence of specific symptoms according to the intrinsic toxicity of the medication. Therefore, it is necessary to optimize and regulate the medication profile release. For

NP-eluting dental implants to be successful, cytotoxicity and NP treatment must be balanced. It is possible to regulate the toxicity and localization of NPs by modification significantly. To reduce harmful effects, for example, NPs may be coated with thick polymer shells or silica layers, or their production can be carried out using "green" harmless substances. The toxicity of NPs is greatly influenced by their size, shape, crystal structure, and surface charge. These factors may be managed to provide therapeutic effects that are desired without causing cytotoxicity [33]. Consequently, many preclinical investigations are needed to explore immune system interactions and unexpected impacts. Second, it is critical to improve the accuracy of formulations based on functional NPs. Consequently, when NPs attach to their target, their pharmacological activity must be preserved. Given our limited knowledge of the many biological pathways relating to NPs and their potential effects on the human body, the importance of nanostructure designs and manufacturing procedures within this context is indisputable. It underscores the need for clinical effectiveness studies. Other essential characteristics distinguishing dental implementations from other ailments include the ability to provide scale-up production, control over crucial design elements, and final pricing. The capacity of orthopedic and dental implants to demonstrate osseointegration with the host bone tissue is a crucial feature in obtaining the benefit of long-term mechanical performance. To provide commercial implants the ability to initiate a biological response and expedite the bone regeneration process, topographic and/or physicochemical surface modification was generated. Specifically, surface alterations impact the main interfacial processes between the implant and surrounding cells, connective tissue, and blood. Following implantation, the device makes first contact with blood generated by bone injury, which results in the creation of a blood clot rich in fibronectin. This blood clot acts as a scaffold for the cells of the new tissue. Next, a mineralized collagenous interfacial matrix is released on the implant surface by the collected osteogenic cells in the blood clot, which starts the formation of new bone [183].

## Conclusion

PI mucositis may be reversed early by treating and eliminating the underlying cause. PI is characterized by marginal bone loss and PI mucosal inflammation. The local administration of antibiotics alone or in combination with nonsurgical or surgical therapy for PI showed positive results despite the lack of data. It is still debatable whether systemically given antibiotics should be used in conjunction with nonsurgical or surgical procedures. However, for the last several years, medication resistance has also increased in patients with gum disease, and the present trend of human bacteria becoming increasingly resistant to antibiotics. The unique conditions in the gum region and how biofilm builds make antibiotics less effective against these microorganisms. We need innovative approaches to address gum problems. Metallic NPs are relevant to treating PI because they prevent the growth of several bacteria. Therefore, the novel metal NPs provided a unique viewpoint on the development of effective antibacterial and anti-inflammatory scaffolds for the treatment of PI. The discharge of metal particles has been the subject of extensive research in orthopedics as a possible etiologic factor. It is recognized that this phenomenon leads to aseptic erosion around arthroplasties and is correlated with implant failures. Emerging knowledge in dental medicine regarding the release of metal/Ti particles

implies that biomaterials present at the interfaces between the abutment and bone might potentially affect the pathogenesis of PI bone loss. Various research has shown the potential of metal NPs such as Au, Ag, Cu, and Zn as an antibacterial coating for Ti dental implant bases. Additionally, metal NPs may be used in conjunction with other therapeutic approaches or instead of antibiotics for PI with further research. However, their use in the clinic is minimal. These NPs must undergo extensive testing to check for adverse effects to guarantee their safe use. The availability of primary materials, the cost of their processing, their post-use sustainability and recyclability, and other factors must all be taken into account when putting the circular economy idea into practice.

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**Author contributions**
M.H.H.: writing—review and editing, writing—original draft, visualization, validation, software, resources, methodology, investigation, formal analysis, data correction, conceptualization, grammar checking, writing–original draft, figure designing. A.M.: writing–review and editing, data correction, software, writing—original draft, investigation, figure designing. M.H.A.: writing–review and editing, data correction, writing–original draft, investigation. R.A.K.: writing–review and editing, methodology, writing–original draft, table editing. A.J.Z.: writing–review and editing, data curation, writing–original draft. A.S.M.: writing–review and editing, data curation, writing–original draft. Z.H. A.: writing–review and editing, writing–original draft, resources, methodology, project administration. Z.P., P.A.: writing–review and editing, writing–original draft, visualization, validation of files sent by other authors, supervision, methodology, formal analysis, conceptualization, project administration. All authors read and approved the final manuscript.

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