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Titanium Dioxide Nanoparticles in Dentistry: Multifaceted Applications and Innovations

Radwan Ali[1,*] and **Abdulkareem Hussain Alwan**[2]

[1] *College of Dentistry, Ilam University, Ilam, Iran.*
[2] *Department of Periodontics, Department of Dentistry, Al-Rafidain University College, Baghdad 10011, Iraq.*
[*] **Corresponding author name:** *Radwan Ali*, **Email:** `r.gatea@ilam.ac.ir`

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ABSTRACT

At present, titanium dioxide nanoparticles (TiO_2 NPs) find effective application in human consumables, pharmaceuticals, beauty products, cutting-edge healthcare, and dental care due to their non-toxic, non-allergenic, and biocompatible properties when in direct proximity to the human body. These NPs exhibit exceptional versatility in terms of their satisfactory chemical steadiness, cost-effectiveness, potent oxidation characteristics, elevated refractive index, and improved visual appeal. These NPs are produced using traditional techniques (both physical and chemical) as well as modern biological methods (biological, eco-friendly, and derived from biological sources), each carrying its own set of strengths and weaknesses in this current era. The importance of TiO_2 NPs in the medical field encompasses applications in drug delivery, cancer treatment, orthopedic implants, biosensors, instruments, and devices. In dentistry, they play a crucial role as biomaterials in items like toothpaste, oral antibacterial solutions, teeth whitening products, and adhesives. Furthermore, TiO_2 NPs hold a significant position in various dental specialties. They are utilized in orthodontics for wires and brackets, in endodontics for sealers and obturating materials, in maxillofacial surgeries for implants and bone plates, in prosthodontics for veneers, crowns, bridges, and acrylic resin dentures, and in restorative dentistry for glass ionomer cement (GIC) and composites.

Keywords: Dental zirconia, Fixed dental prosthesis, Implant abutments.

1 Introduction

The emergence of nanotechnology has resulted in a significant increase in the utilization of nanoparticles (NPs) in various fields such as biomaterials, antibacterial agents, drug delivery systems, electronics, sunscreens, and cosmetics [1]. Nanomaterials have been described as substances of either natural, synthetic, or accidental origin, composed of particles grouped together or existing freely, where at least 50% of the particles have one or more dimensions falling within the 1–100 nm range. Furthermore, for a substance to be classified as a nanoparticle, one of its three dimensions must fall within the range of 1–100 nm. Oxide NPs exhibit distinctive chemical and physical characteristics as a result of their constrained size and the higher density of surface sites at their corners. The physicochemical attributes of fine particles (FPs) differ from those of NPs with a similar composition. The solubility of TiO_2 FPs is limited, and they exhibit low levels of toxicity [2]. TiO_2 NPs demonstrate superior catalytic performance in comparison to FPs, resulting in their increased usage in both consumer and industrial goods. The characteristics of TiO_2 NPs may present a potential concern for human health and contribute to the unique biological effects associated with these NPs. TiO_2 NPs are widely recognized and versatile oxides. They are produced in larger quantities owing to their satisfactory chemical stability, affordability, potent oxidation capabilities, elevated refractive index, and robust oxidation properties [3]. TiO_2 NPs are utilized in the optical industry as semiconductors, mainly because they possess the crucial characteristic of a wide band gap . Additionally, their distinct ionic and

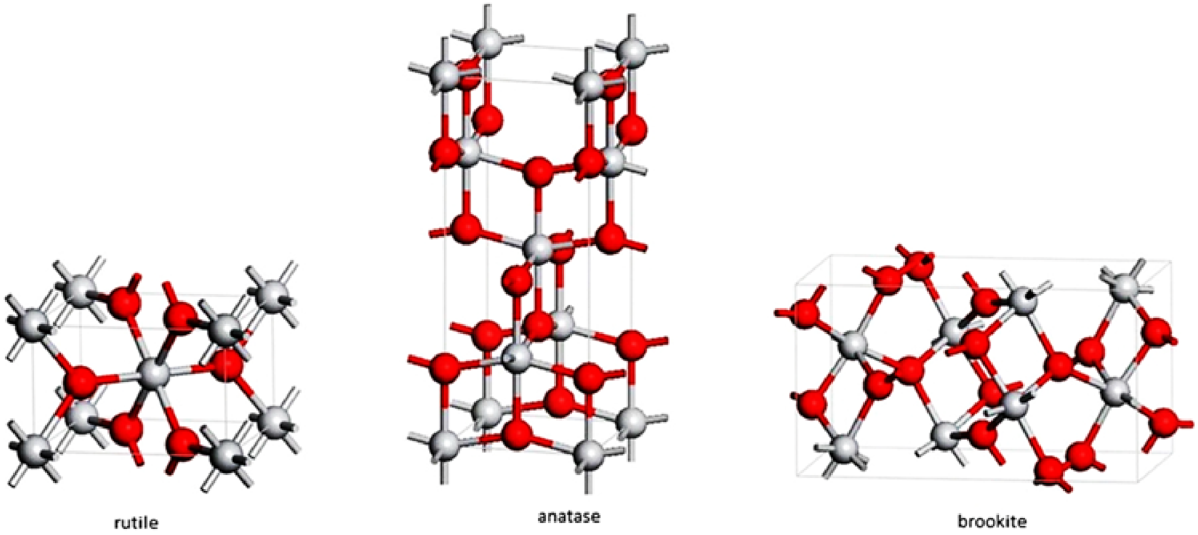

Fig. 1. Tetragonal structures of crystalline forms of rutile, anatase and brookite TiO_2 NPs [4].

electrical properties have made them valuable in electronic devices and sensor applications. Since these NPs are in the form of a water-insoluble white powder, they can be employed in the paint industry as pigments [5].

Naturally, there are three polymorphic variations of TiO_2 NPs: rutile, brookite, and anatase, each possessing distinct crystalline structures (Fig.1). These forms have found extensive use in the gemstone industry. TiO_2 NPs have been utilized as photocatalysts for breaking down waterborne pollutants, as additives in food, and as agents with antibacterial and antimicrobial properties [6]. TiO_2 NPs have the potential to eliminate fungi, viruses, bacteria, and cancer cells. TiO_2 NPs have been employed in cancer treatment through both sonodynamic and photodynamic therapy (PDT) methods [7]. These NPs possess the capacity to transform light energy into heat during photothermal therapy. This is facilitated by their high water affinity, robust chemical and thermal stability within living organisms, minimal toxicity, effective light absorption, and efficient thermal conductivity. The nanoscale structure of TiO_2 has found application in delivering a range of anticancer drugs, including temozolomide, cisplatin, doxorubicin, and daunorubicin [8]. In the past, NPs coated with polyethylene glycol have been employed in photothermal therapy for treating melanoma. TiO_2 NPs have been incorporated into dental applications to improve the mechanical characteristics of biomaterials while preserving their biocompatibility [9].

Past research has employed TiO_2 NPs to enhance the adhesive strength and antimicrobial attributes of composites [10]. TiO_2 NPs have additionally been applied to enhance the duration for which cements remain workable, their setting time, push-out bond strength, and compressive strength. By introducing titania NPs, the mechanical characteristics of the resins have been fine-tuned [11]. Furthermore, dental polymers have been infused with silver-doped titania NPs to yield strong bactericidal effects [12].

2 TiO_2 NPs

These NPs are frequently referred to as TiO_2 or titania since they are metal oxides. Titania is accessible in the form of a fine, white powder and/or a thin film. There are four natural crystal forms of titanium oxide: TiO_2 (B), brookite, anatase, and rutile [13]. The blend of anatase and rutile crystal phases in TiO_2 NPs, commonly found, demonstrates greater inertness and stability when compared to the anatase crystal phase, which exhibits higher chemical reactivity. The chemical reactivity of the anatase crystal phase form might be advantageous in effectively targeting and eliminating cancer cells. The TiO_2 NPs are renowned for their widely recognized appealing attributes, encompassing magnetic, optical, thermal, physicochemical, electrical, rheological, mechanical, and biological properties. Due to their cost-effectiveness, insolubility, and high refractive index ($n = 2.4$), these NPs find extensive applicability in various fields even under standard conditions. Their exceptional whiteness further augments their value across diverse industries. Furthermore, due to their diminutive size, TiO_2 NPs find extensive application in a wide range of products including anti-odor textiles, water disinfectants, dietary supplements, cosmetics, indoor sprays, household appliances, paper, plastics, food packaging materials, sunscreens, electronic devices, pharmaceuticals, fibers, baked goods, sensors, glazes, and food coloring agents [14].

2.1 *Methods for Producing TiO_2 NPs*

The production of NPs is accomplished through two primary approaches known as conventional (top-down) and biocompatible (bottom-up) methods. In the conventional (top-down) techniques, synthesis relies on physical and chemical methods, while the biocompatible (bottom-up) methods extensively utilize biological, green, and biological derivative approaches [15].

The top-down approach encompasses processes that fragment bulk materials into NPs using physical methods like thermal decomposition, sputtering, laser ablation, nanolithography, and milling. On the other hand, chemical techniques in this category involve co-precipitation, laser pyrolysis, the sol-gel process, spray pyrolysis, chemical vapor deposition, the aerosol process, reverse micelle, atomic/molecular condensation, the microemulsion process, and the hydrothermal method . The synthesis procedure significantly influences the transition phase, which involves changing from an amorphous state to either anatase, rutile, or brookite [16]. Yet, this approach introduces imperfections in the surface structure and form of the resulting material. This becomes a primary constraint since the surface chemistry and physical attributes of the NPs heavily rely on both the surface structure and morphology [17]. The chemical method is the preferred choice for producing TiO_2 NPs because of its straightforward manufacturing process and its ability to precisely regulate the size and morphology of the NPs. However, its application is restricted by its costly manufacturing process, potential harm to the environment, high energy requirements, and a lack of sustainability. Additionally, the need for elevated temperature and pressure hinders large-scale production, limiting its use in various fields [18]. Furthermore, the electrophoretic production of TiO_2 NPs is both convenient and efficient, but it necessitates the use of hazardous non-aqueous solvents, as noted by Boccaccini et al. in earlier investigations [19]. These non-aqueous solvents lead to detrimental consequences, such as contamination of aquatic and land environments, environmental degradation, and harm to wildlife and their habitats. Moreover, when these non-aqueous solvents evaporate into the surrounding air, they can pose health risks due to their toxicity [19]. The microwave-assisted method for producing TiO_2 NPs is widely embraced for its time efficiency and its ability to uniformly and rapidly heat the reaction mixture to the desired temperature, which is a notable advantage. While cost-effective, it can be relatively costly due to the higher heating power required. While cost-effective, it can be relatively costly due to the higher heating power required. Since this method demands a substantial amount of energy, it is not conducive for producing TiO_2 NPs in significant quantities [20].

The sol-gel method for producing TiO_2 NPs has been thoroughly explored to create NPs with greater crystallinity. This involves the formation of a sol, followed by gelation and solvent extraction. This approach comes with a high cost due to the use of pricey raw materials, which can result in the formation of cracks and a reduction in volume for the newly formed TiO_2 NPs during the drying stage [21].

The solvothermal technique involves subjecting the mixture to elevated pressure and temperature over an extended period (pressure $<$ 1 atm and temperature $>$ boiling point of water). This procedure demands a significant amount of time and involves substantial upkeep expenses for autoclaves, as the equipment used is rather costly. Furthermore, the introduction of extra surfactants in this procedure not only complicates the reaction but also results in an overabundance of impurities [22].

Presently, hydrothermal synthesis methods have gained widespread use because of their simplicity in producing TiO_2 NPs, which can be applied on a large scale, such as in the case of TiO_2 nanotubes. The hydrothermal process tends to be costly as it necessitates higher levels of energy, surfactants, pressure, and temperature. Furthermore, this is a lengthy procedure, resulting in a lower yield of TiO_2 NPs [22]. Reports indicate that alterations in temperature within the range of 100 to 200 $\circ$C do not provide precise control over the size, shape, and crystallinity of the nanotubes. As a result, the structure and other characteristics of the resulting NPs undergo alterations, such as the transformation from nanotubes to nanofibers [23]. Chemical synthesis involves the use of elevated temperatures, high pressure, as well as costly and potentially hazardous chemicals, which can have detrimental effects in specific medical applications [24].

2.1.1 Traditional (Top-Down) fabrication

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2.1.2 *Biosynthesis (Bottom-Up)*

The bottom-up approach entails biological creation utilizing microorganisms (including bacteria, algae, fungi, and parasites), green synthesis utilizing various parts of plants (such as roots, leaves, shrubs, herbs, and seeds), and biological synthesis using derivatives (like eggshell, albumin, lignin, etc.). In this method, smaller-sized atoms or molecules undergo reduction or oxidation processes to produce NPs. These atoms or molecules naturally come together, without the need for toxic chemicals or solvents, to create NPs. The resulting NPs exhibit minimal imperfections and defects in their surface structure, topography, and physicochemical attributes, including size, shape, crystalline phase, functional groups, structure, and texture. Primarily, TiO_2 NPs generated through biological and green methods are highly compatible with biological systems and safe, as they do not produce toxic byproducts [26].

Likewise, recent studies demonstrate the effective contribution of microorganisms in the biological synthesis process due to its simplicity and time efficiency. NPs of TiO_2 generated through various microorganisms yield high quantities that exhibit stability, sustainability, cost-effectiveness, as well as being safe and compatible with biological systems. This is attributed to the utilization of natural enzymes and proteins inherent in microorganisms, which serve as both capping and reducing agents. Therefore, in biological synthesis, a diverse range of life forms and organisms is employed, spanning from basic prokaryotic bacterial cells to intricate eukaryotic cells like angiosperms [27]. Various green synthesis techniques incorporate biological compounds like polyoxometalates, polysaccharides, Tollens reagent, and phytochemicals (including phenols, terpenoids, flavonoids, and cofactors) found in plants. These compounds serve as both capping and stabilizing agents, working to enhance and fortify the stability of the freshly formed TiO_2 NPs. Biological compounds like albumin, eggshell, gelatin, lignin cellulose, starch, arginine, peptides, polyamine, lysozyme, pomelo peel, and protamine have been employed in the synthesis of biocompatible, biosafe, and cost-effective TiO_2 NPs. The direct synthesis approach is the most biocompatible technique for producing TiO_2 NPs, as it does not require the use of additional externally introduced templates, capping agents, reducing agents, etc. Therefore, the natural biological extracts and their derivatives employed in the synthesis process can form a robust capping layer, contributing to the biocompatibility and stability of these NPs [28]. Furthermore, this approach enables the cost-effective and high-yield mass production of TiO_2 NPs. These NPs are dependable and safe for use, as the method does not involve high temperatures, high pressure, excessive energy, or toxic chemicals [29].

The biocompatible synthesis technology represents a modern and advanced approach compared to conventional methods. The traditional techniques for synthesizing TiO_2 NPs are expensive and have negative impacts on both human health and the environment [30]. The distinctions between biocompatible and conventional TiO_2 NPs are outlined in [31].

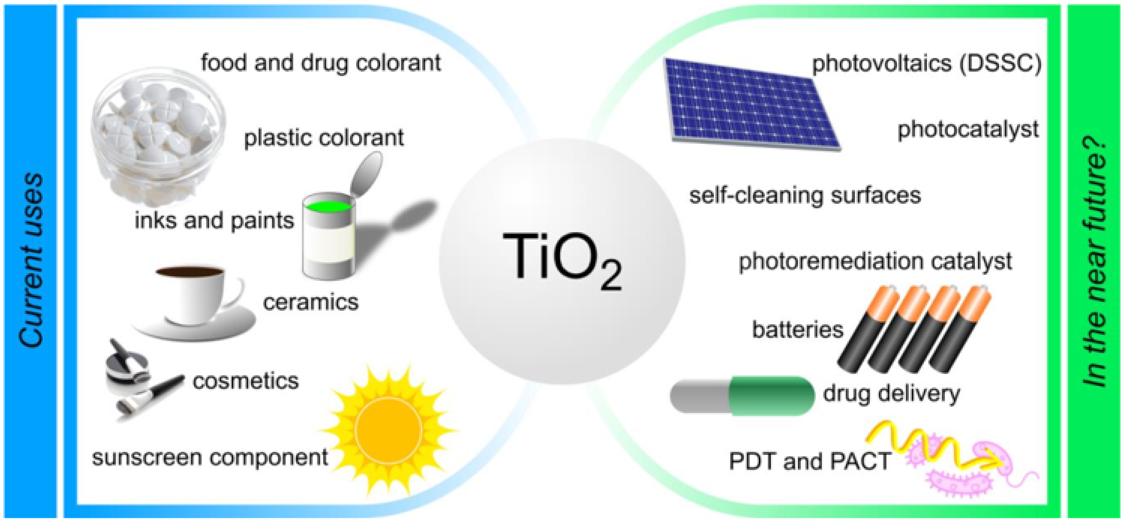

Fig. 2. Existing applications and potential future use of TiO_2; PACT – antimicrobial photodynamic therapy; PDT – photodynamic therapy; DSSC – dye-sensitized solar cell [32].

2.1.3 *Traditional and biological production*

Several factors play a role in regulating the synthesis of TiO_2 NPs, rendering them suitable for applications in medical and dental fields. These key factors that contribute significantly encompass the overall duration, environmental parameters, temperature, synthesis procedures, pH of the solution, extract concentration, and the choice of raw materials, as illustrated. Temperature is a crucial factor that governs the synthesis of TiO_2 NPs through three different approaches. Physical methods demand the highest temperatures (>350 °C), whereas chemical methods necessitate temperature levels below 350 °C. Conversely, TiO_2 NPs are synthesized through microbial means at temperatures below 100 ◦C, while plants utilize ambient temperature or lower. Therefore, the characteristics of the TiO_2 NPs are influenced by the temperature of the reaction medium [33].

The pressure applied to the reaction medium significantly affects the size and shape of biological and green TiO_2 NPs. Studies have shown that the rate of metal ion reduction in biological and green TiO_2 NPs is accelerated under ambient pressure, attributed to the use of natural biological agents . The overall incubation time in the reaction medium significantly affects both the type and quality of TiO_2 NPs produced through biological and green synthesis methods. Moreover, factors such as exposure to light, the synthesis procedure, and storage conditions play a substantial role in determining the characteristics of TiO_2 NPs synthesized through these methods. Over time, particle aggregation may occur, leading to either the growth or reduction in size of the particles, ultimately affecting their effectiveness and shelf life [33].

Modifying the shape and size of TiO_2 NPs has allowed for control over their melting point, subsequently influencing their properties. This implies that as the size of TiO_2 NPs falls within the nanometer scale range, their melting point is lowered. It is relatively straightforward to induce a shape transformation in TiO_2 NPs that exhibit various configurations but possess similar energy levels. These adaptable characteristics also have an impact on their various chemical properties [33]. The attributes of TiO_2 NPs are significantly affected by the surrounding environment. Individual TiO_2 NPs undergo a transformation into core-shell TiO_2 NPs either through interaction with substances or absorption by materials in the nearby environment. This transformation occurs through either corrosion or oxidation processes within the environment. The biological TiO_2 NPs exhibit greater thickness and size as a result of the coating that forms around them [38]. This coating may contribute to their potent characteristics. In a research study, zinc sulfide NPs swiftly altered their crystalline structure when transitioning from a wet to a dry environment. In a different investigation, the chemical properties of cerium-nitrate NPs underwent alterations when peroxide was introduced into their suspension medium [33].

3 TiO_2 NPs in Dental Applications

In the past, graphene and other NPs were extensively used due to their versatile features, which encompass excellent biocompatibility, physicochemical attributes, and antimicrobial effectiveness. Moreover, it exhibited high conductivity along with a substantial surface area. It demonstrated resistance to wear and friction and could serve as a stabilizing substrate for the NPs [34]. Moreover, graphene was a preferred material for a range of dental uses including bone grafting, tissue engineering, regeneration of pulp and periodontium, dental cements and adhesives, resins, teeth whitening agents, dental implants, collagen membranes, and oral saliva biomarkers. Employing graphene in dentistry led to improved favorable results, however, its production for industrial applications posed significant challenges in terms of time and complexity [35]. This marked the first step towards introducing other biocompatible and economically viable nanomaterials in the future of nano dentistry. Out of these, a TiO_2 nanoparticle was ranked among the top five most prevalent, readily accessible, and suitable NPs for industrial applications. There has been a continuous increase in the global production of TiO_2 NPs, leading to greater availability for various industries. At present, TiO_2 NPs exhibit high biocompatibility, coupled with minimal toxicity and low allergenic potential, rendering them exceptionally well-suited for applications in the medical fields (Fig.2). TiO_2 NPs are versatile and flexible due to their remarkable properties, including enhanced strength, light weight, brightness, UV resistance, high density, cost efficiency, pure white color, and high resistance to corrosion. They also exhibit long-lasting chemical stability and durability [36]. Furthermore, these NPs exhibit elevated mechanical strength, excellent electrical conductivity, reduced thermal diffusivity, chemical stability, resistance to corrosion and wear, and limited thermal conductivity. In their pure state, these NPs are malleable and can be readily molded into various shapes and types, rendering them resistant to fatigue.

The favorable mechanical and physicochemical attributes of TiO_2 NPs, including size, shape, surface features, structure, texture, crystallinity, and phase state, can be readily achieved, rendering them superior to other metal oxide NPs. As stated in previous studies, the biocompatibility of these TiO_2 NPs is further attributed to their low ion release and stability. When inadvertently exposed to air, these NPs have the ability to form a protective TiO_2 layer on their surface. This prevents the metal inside the NPs from dissolving and undergoing alterations. The chemically inactive TiO_2 layer is pivotal for ensuring the biosafety and compatibility of these NPs within the human body [37]. Due to these diverse attributes, the application of TiO_2 NPs in the dental and medical sectors has witnessed a swift surge. Based on earlier studies, significant amounts of pure titanium, approximately 99.5%, with a small proportion of interstitial elements like carbon, oxygen, and nitrogen (around 0.5%), have been deemed secure, biocompatible, and devoid of allergenic properties for use in both dental and medical contexts. The findings of this study suggest that substantially higher quantities of titanium oxide would be necessary to elicit any allergic or toxic reactions in humans [38].

3.1 TiO_2 NPs in Orthodontics

Lately, TiO_2 NPs have been integrated into dental composite resin adhesives, enhancing their mechanical resilience and adding antimicrobial characteristics, particularly beneficial for bonding applications in orthodontics. Various concentrations of TiO_2 NPs in standard composite resin demonstrated strong antibacterial effectiveness against S. sanguinis and S. mutans, with the highest shear bond strength to enamel observed at a 5% weight concentration [39]. TiO_2 NPs find application in orthodontic wires because of their enhanced stability, durability, biocompatibility, and lack of allergenic potential. TiO_2 NPs were also employed in surface treatments of orthodontic wires. Researchers observed that orthodontic wires lacking a surface coating of TiO_2 NPs exhibited increased bacterial adhesion (specifically S. mutans) in the oral cavity compared to orthodontic wires with a TiO_2 NPs surface coating [40]. Another study concluded that ceramic orthodontic brackets, when coated with TiO_2 NPs on their surface, exhibited the highest antimicrobial effectiveness against pathogenic bacteria (S. mutans and C. albicans) [41]. This highlights the significant contribution of TiO_2 NPs in the field of orthodontics [42].

3.2 TiO_2 NPs in dental implants

Dental implants are frequently composed of titanium owing to its robust mechanical and chemical characteristics. Dental implants incorporating TiO_2 NPs exhibit improved osteogenic and antibacterial properties. However, there remains a slight risk of periimplantitis, which can be mitigated by surface modification of the TiO_2 implant with additional materials. TiO_2 NPs are highly versatile and can be seamlessly integrated with various other elements without generating any harmful effects. Coating TiO_2 implants with zinc not only rendered them novel and cytocompatible but also heightened their antibacterial capabilities against S. mutans and Porphyromonas gingivalis [43].

Furthermore, enhancing the TiO_2 implant with multiple layers of TiO_2 NPs improved its adhesion and strength within the bone. The TiO_2 implants subjected to heat treatment also demonstrated robust viability of osteoblasts and exhibited antibacterial effectiveness against Porphyromonas gingivalis [44]. The TiO_2 implant treated hydrothermally demonstrated non-cytotoxicity towards mammalian cell lines and promoted increased calcium deposition from osteoblasts, along with displaying antimicrobial activity against methicillin-resistant Staphylococcus aureus [45]. Therefore, it is crucial to hinder bacterial adhesion on implant surfaces, aiming to extend their lifespan, stability, and resilience by averting infections . Another noteworthy feature of TiO_2 NPs is their robust compatibility with blood, enabling straightforward surface modifications when utilized in conjunction with compatible implants [46]. The regeneration of nerves through Schwann cells towards dental implants is facilitated by the ceramic coating of HA nanocomposites onto the TiO_2 NPs [47]. Presently, innovative dental implants incorporating multiple layers of TiO_2 NPs are being introduced for use [48]. Because of the enhanced cell adhesion, proliferation, migration, differentiation, and superior wettability of surfaces incorporating TiO_2 NPs, these particles have emerged as a promising method for producing robust scaffolds for implants. In a prior investigation, titanium surfaces were utilized for the growth of TiO_2 NPs in the form of nanotubes. These nanotubes were integrated with ZnO NPs, which had a diameter ranging from 20 to 50 nm, and they were firmly attached to the walls of the TiO_2 nanotubes. Implants primarily based on TiO_2 NPs exhibited potent antibacterial effects against S. mutans and Porphyromonas gingivalis, achieved through a gradual and steady release of zinc ions [49]. In a separate study, TiO_2 NPs were employed to create TiO_2 nanorod arrays (TNFRs) for the surface modification of implants. The Ti substrate modified with TiO_2 nano-arrays encouraged the attachment, growth, and differentiation of human periodontal ligament stem cells towards bone-forming cells. Furthermore, TiO_2 nanorod arrays (TNRs) demonstrated enhanced antifungal and antibacterial characteristics [50]. The implants based on TiO_2 NPs and coated with hydroxyapatite nanocomposites were also effective in facilitating robust osseointegration with bone tissue [51].

3.3 *TiO_2 NPs in oral disinfectants and mouthwashes*

Dental caries, also known as tooth decay, is a prevalent oral disease characterized by the erosion of enamel and dentin surfaces of teeth caused by acid-producing bacteria. As a result, this initially results in the formation of white spots, which can ultimately lead to the loss of the tooth. The worldwide issue of tooth decay can be effectively prevented by using modern oral disinfectants containing metal oxide NPs, in contrast to conventional options like chlorhexidine [52]. Earlier studies have demonstrated the strong antimicrobial effectiveness of oral disinfectants containing TiO_2 NPs against Streptococcus mutants, the pathogenic species responsible for tooth decay or dental caries [53]. Furthermore, these oral disinfectants and mouthwashes incorporating TiO_2 NPs play a role in averting the development of white spots on the surfaces of teeth following orthodontic treatment [42].

3.4 *TiO_2 NPs in dental restoration materials*

The effectiveness of dental restorative materials relies heavily on their biological durability and chemical, mechanical, and physical characteristics. TiO_2 NPs have demonstrated highly efficient antimicrobial properties in various applications such as bases, composites, sealants, cements, adhesives, and lining materials. In a prior study, Garcia-Contreras et al. [26] demonstrated that the incorporation of TiO_2 NPs in glass ionomer cement introduces a new and durable restorative material in dentistry. This material exhibits stability, longevity, and the ability to resist strong chewing forces, thanks to its antimicrobial properties. The introduction of TiO_2 NPs into traditional composite restorations led to the development of advanced nanocomposites. These exhibit compatibility with living cells and demonstrate antimicrobial effectiveness against *E. coli* and S. aureus, common culprits in the development of tooth decay or dental caries [54]. Furthermore, the incorporation of Ag into TiO_2 NPs has been employed as a restorative material because of its potent antimicrobial properties against *S. aureus* [55]. Incorporating varying concentrations of TiO_2 NPs into GIC restorative materials significantly affects their mechanical and physicochemical characteristics. In a research endeavor, GIC restorative material was enriched with TiO_2 NPs averaging a particle size of approximately 21 nm, aiming to scrutinize its mechanical and physicochemical attributes. When TiO_2 NPs were introduced, the titanium oxide NP-infused GIC exhibited a notable augmentation in flexural strength, hardness strength, compressive strength, enamel shear bond strength, and dentin shear bond strength compared to the conventional GIC restorative material [56]. In a separate investigation, introducing a blend of 2 wt% TiO_2 NPs and 1 wt% of CnC into the standard GIC restorative material resulted in an 18.9% increase in compressive strength and an impressive 151% surge in tooth enamel shear bond strength compared to the conventional GIC restorative material [57]. TiO_2, ZnO, and Ag NPs were integrated into the standard GIC at a concentration of 10% wt and subjected to assessments for their mechanical and physicochemical characteristics. The TiO_2 NPs employed in this investigation possessed a porous structure, rendering them more robust compared to ZnO NPs and Ag NPs. The TiO_2 NPs and ZnO NPs exhibited notably greater compressive strength, whereas the compressive strength of the Ag NPs was on par with the control group using conventional GIC restorative material [58]. Incorporating 3% (w/w) TiO_2 NPs into the GIC restorative material enhanced both its mechanical strength and antibacterial attributes, without compromising the material's fluoride release capacity. This highlights a distinct advantage of TiO_2 NP-induced GIC [59]. In various prior studies conducted by Elaska et al. and J. Sun et al., the introduction of TiO_2 NPs led to a notable enhancement in both mechanical strength and antibacterial properties, albeit limited to a concentration of up to 3% [60].

In a recent study conducted by A. Mansoor et al. [26], it was affirmed that the incorporation of 3 and 5 wt% TiO_2 NPs into the standard GIC led to a noteworthy augmentation in both flexural strength and compressive strength in comparison to the traditional GIC.

3.5 *TiO_2 NPs in teeth whitening products*

A TiO_2 nanoparticle has demonstrated enhanced cosmetic effects in teeth whitening in the field of dentistry. In a research study, TiO_2 NPs were introduced into a 3.5% hydrogen peroxide (H2O2) teeth whitening agent, leading to improved enamel aesthetics and color when compared to the conventional 3.5% H2O2 whitening agent lacking TiO_2 NPs [61]. Nitrogen-doped TiO_2 NPs have demonstrated both antimicrobial properties and enhanced teeth whitening effects, while also reducing sensitivity [62]. Moreover, a blend of TiO_2/Ag NPs was employed in H2O2 as a teeth whitening agent and subsequently evaluated for its in vivo cytotoxicity. The blend of TiO_2/Ag NPs exhibited reduced cytotoxicity in comparison to the whitening agent containing only H2O2 [63].

In a prior investigation, a gel containing a combination of TiO_2 NPs and hydrogen peroxide (H2O2) was utilized to enhance the teeth whitening effectiveness of H2O2. Consequently, by incorporating TiO_2 NPs, the H2O2 concentration could be lowered to 6% without any discernible disparity in the whitening outcome compared to 35% H2O2. Moreover, tooth sensitivity was diminished when the H2O2 concentration was reduced to 6% along with the application of TiO_2 NPs [64].

3.6 *TiO_2 NPs in acrylic resins*

Poly-methyl-methacrylate (PMMA) stands out as the top choice for denture base resin, employed in the fabrication of dental prosthetics like complete and partial dentures. PMMA is preferred due to its compatibility with the body, safety, pleasing appearance, lightweight nature, and cost-effectiveness in dental prosthetics. The dental prostheses made from PMMA may experience a decrease in their physical, chemical, and mechanical attributes, leading to potential issues like voids, irregularities, pores, and cracks . Such imperfections diminish the mechanical characteristics [65] and elevate the proliferation of microorganisms on these prostheses. Candida albicans is the most harmful microorganism that adheres to these dental prostheses. If left unmanaged, it can lead to serious infections in the oral cavity [66]. The attributes of PMMA can be enhanced through the integration of nanotechnology [67].

TiO_2 NPs are also incorporated into PMMA acrylic resins to enhance their mechanical strength and hardness. Additionally, the incorporation of these NPs demonstrated improved photopolymerization and biocompatibility with minimal levels of cytotoxicity, mutagenicity, and genotoxicity [68]. The adhesive properties of TiO_2 NPs in PMMA of acrylic resins have been significantly improved for dental prosthesis. This has been achieved through the formation of a robust bond between the carbonyl group of PMMA and the hydroxyl group of TiO_2 NPs. This has led to enhanced physical, chemical, and mechanical properties of these prostheses [69]. Furthermore, it lessens the likelihood of pathogenic microorganisms, particularly Candida albicans, from thriving and multiplying. This is due to the augmented antimicrobial potency achieved by incorporating TiO_2 NPs [70]. TiO_2 NPs are viewed as the most favorable choice for incorporation into PMMA due to their comparatively lower explored toxicity on living cells compared to other types of NPs [71].

TiO_2 NPs exhibit a broad spectrum of activity against various microorganisms, encompassing both Gram-negative and Gram-positive bacteria as well as fungi. Previously, elevating the proportion of TiO_2 NPs in PMMA resulted in a notable enhancement of PMMA's antimicrobial properties, leading to a substantial reduction in bacterial adhesion [68]. The combination of TiO_2 and silicon dioxide nanofillers in PMMA exhibited enhanced antibacterial properties when exposed to UV light, leading to the degradation of microorganisms with extended exposure. This research affirmed that the incorporation of TiO_2 NPs with other elements, metals, and alloys for dental applications is both compatible and safe [72].

3.7 *TiO_2 NPs in toothpaste formulations*

Titanium Dioxide NPs are included in oral toothpaste formulations at concentrations ranging from 1% to 10% by weight, aiming to prevent sensitivity and tooth decay. They use these NPs in oral toothpaste formulations with an average particle size falling between 100 and 300 nm. These particles readily dissolve in enamel, dentin, and cementum, effectively preventing the development of tooth decay and sensitivity [73].

The robust connection between organic compounds in dental tissues (enamel) and TiO_2 NPs enables a controlled release of fluoride from oral dentifrices, which becomes embedded in the tooth's structure. Over time, the tooth's matrix experiences reduced solubility and a gradual decrease in fluoride release [74]. Moreover, earlier studies provide evidence that heightened adherence of TiO_2 NPs to dental tissues, specifically enamel, leads to a reduction in the size of hydroxyapatite crystals in enamel. This results in enhanced hue, value, and chroma, which preserves the natural color of human tooth enamel [75].

3.8 *TiO_2 NPs in dental bonding agents*

Dental bonding agents are minimally invasive restorative materials commonly utilized in dentistry. Dentin adhesives are the most frequently employed bonding agents in dentistry. Over time, the connection between the dentin adhesive and the dentin surface weakens and becomes less secure [76]. This happens because of the collagen-rich, water-absorbing characteristics of dentin and the breakdown of the robust covalent bond between them due to hydrolytic degradation. Ultimately, the adhesive bond to the dentin surface completely breaks down. The addition of TiO_2 NPs in adhesives has been explored to study their adherence to human teeth [77]. In a recent study where TiO_2 NPs were integrated into dental adhesives, it was determined that they exhibited improved biocompatibility along with reduced solubility and water absorption in comparison to traditional adhesives utilized in dentistry. Therefore, it is strongly advised to incorporate these NPs in the present adhesive dentistry practices

. A different study explained that the inclusion of TiO_2 NPs in self-adhesive cements resulted in a higher degree of conversion (DC) compared to traditional varieties [78]. TiO_2 NPs, when employed as fillers, have the potential to enhance the mechanical and physicochemical characteristics of adhesives. Therefore, TiO_2 NPs exhibit significant potential as strengthening additives in dental adhesives, offering a range of benefits [79].

In the past, researchers combined TiO_2 NPs with a light-curable orthodontic composite paste to create resin composite adhesives enriched with TiO_2 NPs. These adhesives effectively minimized enamel demineralization and added antibacterial features to dental adhesive systems. The shear bond strength and adhesive remnant index of the nanocomposites containing TiO_2 NPs closely matched those of the control composite [75]. In a separate study, nanocarbons that included TiO_2 NPs were combined to create a biomineralized adhesive material used in dentistry. The newly developed nano-adhesive, which includes TiO_2, demonstrated photocatalytic properties that disrupted bacterial acidity. Furthermore, it showed a beneficial influence on tooth re-mineralization in simulated body fluids [80].

3.9 TiO_2 NPs in dental prosthesis (Veneers, Crowns, and Bridges)

Enhancing both the strength and visual appeal of teeth involves substituting the outer enamel layers with synthetic materials like sapphire, diamond, and ceramics, chosen for their excellent biocompatibility and aesthetic qualities. The susceptibility of these materials to breakage due to their brittleness is mitigated by the incorporation of NPs, thereby enhancing their mechanical attributes [81].

Presently, titanium dioxide NPs (TiO_2 NPs) are integrated into ceramics to elevate both the visual appeal and mechanical strength of crowns and bridges. The inclusion of TiO_2 NPs in ceramics not only improved their visual appeal but also their mechanical attributes compared to conventional ceramics lacking TiO_2 NPs. This was achievable thanks to its pure white appearance, resistance to fatigue, light weight, low elastic modulus, biocompatibility, corrosion resistance, and strength [82].

Titanium is a naturally occurring, abundant, and pure element known for its low toxicity and absence of allergic reactions, distinguishing it from other metals and elements utilized in dental prosthetics like cobalt, beryllium, nickel, iron, steel, stainless steel, chromium, and so forth. Therefore, TiO_2 NPs are regarded as biologically safe, compatible with living tissues, readily accessible, and cost-effective nanomaterials suitable for incorporation in dental prosthetics like veneers, crowns, and bridges utilized in the oral cavity [83].

3.10 TiO_2 NPs in Scaffolds/Bone grafting for maxillofacial applications

Naturally, bone is a material on a nano-scale, with dimensions smaller than 100 nm. The materials employed for bone grafts in the maxillofacial regions, encompassing the face, oral cavity, head, neck, ear, and nose, typically consist of composites primarily composed of organic compounds (predominantly collagen) reinforced with inorganic elements. The nano-crystallites exhibit an open microstructure, with nanopores distributed among the crystallites. The structure of this material will be finalized by filling the pores on the micrometer scale. Through this process, a textured surface area is generated at the interface between the biomaterial and the cell, which is crucial for promoting rapid cell proliferation. Bone graft materials should possess specific characteristics, including the ability to induce bone formation, easy processability, non-sintering properties, synthetic composition, high porosity, nanostructured form, and the capacity to undergo degradation through osteoclast activity [84].

TiO_2 NPs find application in bone grafting due to the heightened strength, biocompatibility, low elasticity modulus, corrosion resistance, and remarkably lightweight nature of titanium in graft compositions, surpassing other metals and elements. These attributes collectively render titanium an excellent biomaterial, particularly for its incorporation into the human body in the shape of metal prostheses. Furthermore, titanium is the preferred material for crafting internal metal plates, wires, and meshes, including fracture fixations, cranioplasty plates, cranioplasty meshes, cranioplasty wires, and coronary artery stents [85]. Moreover, titanium scaffolds and meshes, along with prostheses, are widely recognized for their use in procedures involving nose, eye, maxilla, mandible, ear reconstruction, and ossicular replacements [86].

3.11 TiO_2 NPs in endodontics

Titanium and its metal oxide alloy, also referred to as titanium oxide, are employed in the fabrication of maxillary and mandibular obturators, as well as in the production of files, spreaders, carvers, and reamers [86]. Dental tools crafted from a blend of nickel and titanium are highly favored for endodontic procedures due to their flexibility, which renders them resistant to fractures. Examples include files, spreaders, carvers, and more [87].

4 TiO_2 NPs: A Highly Compatible Material for Medical and Dental Uses

The perfect oral biomaterial should demonstrate excellent thermal, optical, electrical, biological, mechanical, physical, and chemical characteristics, coupled with exceptional biocompatibility. The TiO_2 NPs encompass nearly all the attributes of an optimal oral biomaterial. Hence, they are employed as antimicrobial agents, in dental restorative materials, dental prosthetics, to diminish bacterial adherence to tooth surfaces, offering defense against dental caries, acting as bleaching agents, contributing to dental implants, and playing a role in orthodontics. These TiO_2 NPs demonstrated lasting benefits for dental implants. Surface modifications offer numerous advantages, including reduced bacterial attachment, increased hardness, biocompatibility, minimal toxicity, chemical stability, low density, notable adsorption capacity, cost-effectiveness, potent antimicrobial properties, and enhanced mechanical characteristics. They also demonstrated exceptional functionality, enduring stability, robustness against fatigue, high mechanical strength, low thermal diffusion, exceptional lightness, resistance to corrosion and wear, elevated electrical conductivity, and low thermal conductivity. This serves to bolster their stability, sustainability, and overall longevity. Due to their significantly augmented mechanical strength, hardness, lightweight nature, and pale coloration, they have emerged as the most versatile, cutting-edge, and flexible nanomaterials. TiO_2 NPs exhibit a wide range of antimicrobial properties, including antibacterial, anti bactericidal, antiparasitic, and antifungal activity, targeting various pathogenic microorganisms such as Gram-negative bacteria, Gram-positive bacteria, parasites, and fungi. TiO_2 NPs are considered safe, and they have received approval from the FDA for use in human food, pharmaceuticals, cosmetics, and materials that come into contact with food [88]. Earlier studies [89] investigating biosafety and biocompatibility found no cytotoxic effects within various concentration ranges (1–20) mg/cm2 following oral administration. Even at the highest dosage of 1000 mg/kg BW/day, no signs of toxicity or allergic reactions were observed upon exposure to TiO_2. Numerous studies have indicated that the ingestion of varying doses of TiO_2 NPs per kilogram of body weight did not result in significant uptake of TiO_2 from the gastrointestinal tract into the bloodstream or various internal organs. It was also observed that absorption from the gastrointestinal tract into the blood, urine, and other organs was minimal.

5 Conclusions and futures prospects

TiO_2 NPs are considered safe for use in advanced medical and dental applications due to their compatibility with biological systems, lack of adverse effects, and absence of allergic reactions with human tissues. To date, attributes such as size, shape, phase structure, surface morphology, coating, and surface texture have been recognized as key factors influencing their biocompatibility. Recent investigations into TiO_2 NPs emphasize that the synthesis method plays a crucial role in determining their biocompatibility, further supporting their suitability for medical and dental uses. This is attributed to the controllability of the synthesis process, which involves factors such as temperature, pressure, pH, melting point, environment, and stability of the solution medium employed in the production of these NPs. Furthermore, these TiO_2 NPs are both cost-effective and readily accessible, which is the primary factor driving their utilization. Hence, upcoming research should integrate the optimal synthesis method to generate TiO_2 NPs that are both biologically safe and compatible, as well as environmentally friendly. These can then be employed in cutting-edge nanomedicine and nano dentistry.

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