Heliyon 11 (2025) e42169

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Current trends and research advances on the application of TiO_2 nanoparticles in dentistry: How far are we from clinical translation?

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ARTICLE INFO

Keywords:
Inorganic nanoparticles
Titanium dioxide
Composite
Antibacterial properties
Mechanical properties
Glossiness

ABSTRACT

The great potential of nanotechnology-based knowledge during the past decade has shown great potential to elevate human living standards and enhance healthcare conditions through diagnosing, preventing, and treating different diseases. Among abundant nanoparticles (NPs), inorganic NPs feature distinctive biological and physicochemical properties compared to their conventional counterparts which do not endow. TiO_2 NPs possess excellent properties including low-cast, antibacterial properties, biocompatibility, and physicochemical stability. The present review highlights and discusses the current trends in applying TiO_2 NPs in dentistry ranging from TiO_2-based nanocomposite in endodontics, orthodontics, and biofilm prevention. Moreover, the potential of TiO_2 NPs in developing new photodynamic therapy and the next generation of oral care products is outlined. In the end, the clinical translation of TiO_2-based dental materials is brought to the forefront which is impetus and of great importance to developing inorganic NP-based dental materials.

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https://doi.org/10.1016/j.heliyon.2025.e42169
Received 16 July 2024; Received in revised form 15 January 2025; Accepted 21 January 2025
Available online 22 January 2025

1. Introduction

Tooth loss is a common problem in the geriatric population which can influence food swallowing, appearance, and quality of life. The fixed or removable dental prosthesis can be utilized for the rehabilitation of partial or complete tooth loss which can enhance the aesthetic and functional performance. Furthermore, microbial communities known as biofilms can house various fungal and bacterial species that cause challenging dental diseases such as dental caries and periodontal diseases. For instance, enamel dissolution occurs due to the accumulation of acidogenic biofilm on the tooth's surface through a process called demineralization, which if not timely manner, can develop dental caries [1]. The control of this biofilm formation inside the oral cavity is challenging.

The captivating research area of nanotechnology and its various applications have attracted the attention of the scientific community. The history of nanotechnology can be traced back to 1959 when Richard Feynman proposed a lecture and spoke about the manipulation of atoms and molecules for the creation of smaller particles and this laid the foundation for modern nanotechnology [2]. Ten years later, the terminology of nanotechnology was coined and vigorous progress was ushered in the 1990s [3]. The term nano is derived from the Greek word Dwarf. The International Organization for Standardization (ISO) has defined nanoscale as a size ranging from 1 to 100 nm [4].

The exploitation of nanotechnology in medicine refers to nanomedicine seeking innovation in the healthcare of patients [5]. They can be categorized based on their dimension as zero-dimensional, one-dimensional, two-dimensional, and three-dimensional. Among them, zero-dimensional is commonly utilized in dentistry [6,7]. The nanoparticles differ from their macroscale counterparts in terms of physicochemical properties and biological behaviour mainly due to their submicron size and high surface area to volume ratio [8]. Therefore, they enjoy many benefits including improved efficiency, increased selectivity, and reduced toxicity [9]. Among diverse nanoparticulate formulations applied in nanomedicine, inorganic nanoparticles such as metal oxides (TiO_2, CuO, ZnO) hold great promise by virtue of their nanostructures, and unique physicochemical properties [10]. As can be seen in Fig. 1, the investigation of the NPs with antibacterial properties in dental applications is rapidly increasing.

Previous authors published review articles discussing the potential of nanomaterials in dentistry [6,11–13]. Jandt et al. gave an overview of the principle of nanomaterials and stated that the antibacterial properties of nanomaterials are the ones with high clinical impact and the presence of nanomaterials has a great influence on the biomineralization process and in turn, hard tissue regeneration [6]. Bapat et al. have revealed that the healing of lost dental tissue can be facilitated in the presence of NPs which is attributable to their high reactivity, increased protein-surface interactions and antibacterial properties [11]. Priyadarsini et al. have reviewed the utilisation of different NPs in dentistry and revealed that antibacterial NPs can be used in the polishing of enamel surfaces to prevent dental caries. Also, they can be used in drug-releasing dental implants to prevent and cure oral disorders [12]. Hossain et al. have focused on how therapeutic NPs can be used in dental implants and showed that NPs can be bound to the surface of dental implants leading to a better integration of dental implants and bypassing the side effects post-implantation [13]. The significance of this paper is portrayed in addressing how photocatalytic TiO_2 NPs play a role in enhancing mechanical properties, remineralization, whitening (aesthetics), biofilm inhibition, and biocompatibility of orthodontic and endodontic dental materials (Fig. 2). In response to this, the authors sought to provide an updated review of the current progress on the application of TiO_2 NPs in orthodontics and endodontics and their relevant clinical evaluations. Furthermore, the prospect of their translation into clinical practice is accentuated. The authors hope that the collated data in this review can aid established researchers and dental practitioners in having a grasp of the current status of using TiO_2 NPs and their effectiveness in dental applications and contribute to this field in the coming days to ameliorate the quality of life in patients with dental complications.

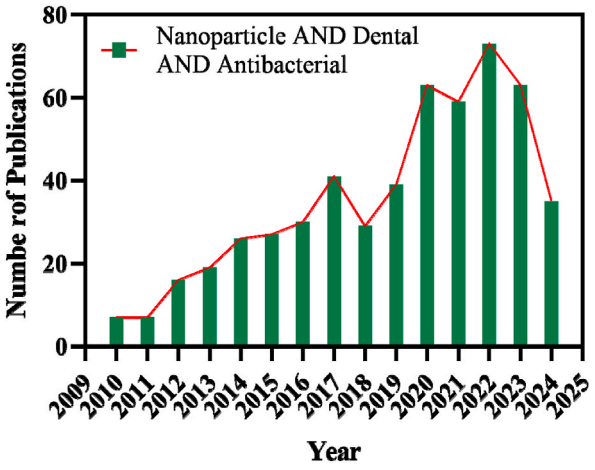

Fig. 1. The number of publications of antibacterial NP-based materials for dental applications, based on the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) a web-based information service.

2. Literature strategy

The PubMed database (www.ncbi.nlm.nih.gov/pubmed) was comprehensively searched to gather the previously published papers from 2010 to 2024 for related papers on the application of TiO_2 NPs in dentistry. The authors used the terms "Nanoparticle AND Dental", and "Nanoparticle AND Antibacterial" or a combination thereof in the search. The following criteria were considered for this review paper: (1) English written papers; (2) original research articles and review papers; (3) TiO_2 NPs; (4) antibacterial properties. A total number of 220 articles were retrieved. These published papers were further closely analysed to determine their eligibility for inclusion in this review. After the elimination of duplicate references, 127 papers were selected for this review paper.

3. NPs in dentistry

Teeth in the oral cavity have different parts including dentine, enamel, cementum, pulp as well as periodontal ligament. The main functions of the teeth are cutting and crushing foods for easy swallowing and digestion [14]. Furthermore, it plays a role in improving the self-confidence and quality of life in individuals. Therefore, disease-based tooth loss can negatively affect eating patterns and speaking [15]. Thus, attempts have been made to protect teeth in dentistry. The teeth can be protected by different compounds in dentistry inclusive of amalgam, glass ionomer (GIC), composites, and teeth bleaching products [12]. Composites, amalgam, and GIC cement have been used to seal the dental cavity. Although these compounds are applied in dentistry, however, they have certain drawbacks. Dental amalgams are unesthetic and comprised of mercury and extensive removal of healthy teeth which declines their application [16]. Due to the aforementioned concerns related to dental amalgam, resin matrix composite has been recognized as the most clinically applied material for repairing dental caries due to its biocompatibility and operability. Nevertheless, the failure of dental restorations is exacerbated by the composite resin because of its shorter service life and low antibacterial properties [17,18]. The GIC is commonly used in filling dental cavities due to their adhesion ability and translucency. The formation of chemical bonding with enamel and dentin is the advantage of GIC. Nonetheless, it possesses some disadvantages inclusive of insufficient mechanical properties, high solubility at the setting stage, and inferior aesthetics [19]. A summary of the drawbacks of conventional materials used in dentistry is tabulated in Table 1. Given these disadvantages, NPs are introduced in dentistry [20]. In the case of dentistry, NPs aim to mimic the natural soft and hard tissue architecture by adapting dental biomaterials to effectively restore lost tissue and provide antibacterial properties [21]. The use of NPs in dentistry is mainly categorized into (I) antibacterial and (II) reinforcement. The NPs are chemically and biologically active and show good antibacterial properties due to their size and active surface area. Therefore, they can be used as a coating [22].

The NPs can be added to restorative materials and adhesive systems to improve their mechanical and physical properties. It was found that the restorative materials fail because of secondary caries, fracture, and microleakage resulting from biofilm accumulation. Adding NPs to resin composite and GIC and acrylic materials proved to reduce polymerization, and shrinkage, improve mechanical properties, and give better optical properties [23]. TiO_2 NPs with a size of fewer than 100 nm have distinct surface chemistry and morphologies. Their biocompatibility, biosafety, biostability, photocatalytic activities, cost-effectiveness, and antibacterial properties have made them stand out among metal oxide-based NPs for cutting-edge dental applications [24]. Their biocompatibility is mainly determined by their dimensions, shapes, phases, topographies, and methods of synthesis. Different methods of synthesis of TiO_2 NPs are beyond the scope of this review. Thus, for a deeper understanding of the method of synthesis for TiO_2 NPs, the readers are encouraged to consult reviews and chapter books published elsewhere [1,25,26].

4. Antibacterial role of TiO_2 NPs

The TiO_2 NPs intrinsically possess antibacterial activity due to the production of cytotoxic oxygen radicals [38,39]. The toxicity of TiO_2 NPs to bacterial strains is through the attachment of TiO_2 NPs to the cells by electrostatic force due to their larger surface area. This leads to the disintegration of the bacterial cell wall, lipid peroxidation of the cell membrane, and flow out of the cytoplasm [40]. Therefore, they can be beneficial in dental applications as antibacterial additives. For instance, Giti et al. have investigated the effects of TiO_2 NPs on the antibacterial performance of acrylic resin polymethyl methacrylate (PMMA) denture base resin [41]. Their findings

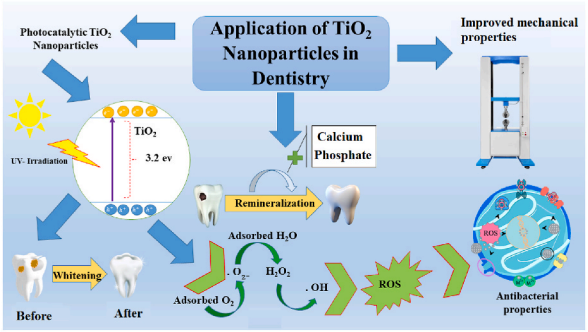

Fig. 2. The role of photocatalytic TiO_2 NPs in dentistry including antibacterial and mechanical properties, tooth whitening, and remineralization.

Table 1
A summary of drawbacks of conventional materials used in dentistry.

Dental material	Drawbacks	Reference
Amalgam	Reduced aesthetic, mercury toxic effect	[27–29]
GIC	Poor mechanical properties, initial setting reaction, moisture sensitivity, insufficient fluoride release, inferior aesthetic	[19,30–33]
Composite resin	Higher rate of secondary caries, marginal microleakage, restricted mechanical strength, polymerization shrinkage	[34–37]

showed that the addition of 7.5 % TiO_2 NPs increased the antibacterial activity against *C.albicans*. Moreover, Ragheb et al. have studied the antibacterial performance of TiO_2 NPs incorporated in a clinical trial (completely edentulous patients) and found a remarkable reduction in the colonization of *C.albicans* after one month [42]. In the research conducted by Zhang et al., the TiO_2/PDA composite revealed antibacterial activity against *S.auerus* which was ascribed to the presence of TiO_2 and the production of ROS (Fig. 3a–c) [43]. Esteban et al., have incorporated the N-doped TiO_2 NPs into the Optibond Solo Plus commercial dental resin and found that they strongly inhibited the activity of *S.mutans* cariogenic biofilm in dark conditions compared to unaltered dental resin [44]. The antibacterial properties were attributable to the presence of N-doped TiO_2 NPs itself which was not dependent on the light irradiation. This section highlights that TiO_2 NPs as additives can provide antibacterial activity in their own right. Nevertheless, it should be noted that the addition of antibacterial TiO_2 NPs should not affect the mechanical properties and colour stability of dental material.

Another mechanism for the antibacterial activity of TiO_2 NPs is photocatalytic activity. When TiO_2 NPs are exposed to blue light and UV light (particularly at wavelengths below 385 nm) in the presence of water and oxygen, they are oxidised more eagerly upon exposure to UV light leading to the production of ROS (hydrogen peroxide, superoxide anions, and hydroxide) and in turn, oxidative stress [25,43,45,46]. The generated ROS are highly reactive and possess high oxidizing potential which makes them perilous to microorganisms [26,47]. The photocatalytic activity of TiO_2 was found to induce a higher level of ROS compared to dark conditions and thereby higher antibacterial properties [48]. As can be expected, UV light is necessary for the induction of redox reactions at the surface of particles. This is associated with their narrow band gap and rapid combination of electron (e^-) and holes (h^+) in pure TiO_2 [49]. The wide band gap with energy of 3.2 eV in TiO_2 NPs limits their photo-absorption to the UV light spectrum and the formed ROS has limited quantum yields. The utmost antibacterial effect of TiO_2 NPs is obtained at lower wavelengths based on their photochemistry. This further indicates that the sensitivity of TiO_2 NPs is required to be shifted to visible light to maximize their antibacterial potentials. To achieve this, different strategies have been used such as the modification of TiO_2 NPs with *Syzygium aromaticum* compound which showed a slight red shift compared to pure TiO_2 NP [50], doping non-metallic elements such as nitrogen (N) into the TiO_2 NPs which enhance the quantum yields, further increasing their absorption spectrum [51], and the upconversion of TiO_2 using light transducer and exposure to near-infrared light (NIR) [52]. To this end, the method of evaluating the antibacterial properties of TiO_2 NPs in dental materials needs to be taken into account. In recent years, various methods have been employed by researchers including minimum concentration, cell count, disk diffusion, well diffusion, and live/dead assay [53]. Among them, the cell counting method which is done by the Agar plate is advantageous due to its accuracy, and simplicity. In this microbiological method, the bacteria are cultured on the Agar plate and the cell counting is reported in the colony-forming unit (CFU), logs, or the percentage of growth inhibition. In the present review paper, the CFU is utilized to compare the antibacterial properties of TiO_2-based dental materials and appliances. The readers are encouraged to consult with a review paper published elsewhere for more details on the methods of evaluating antibacterial properties [54].

4.1. Antibacterial orthodontic materials

Orthodontics is a speciality in which teeth are programmed to be in a pre-determined direction by the application of a controlled force upon teeth [55]. The brackets are the essential tools in fixed orthodontic treatment and the enamel around the brackets may be demineralized due to the potential accumulation of microbial biofilm [56]. This subsequently increases the risk of caries, and gingival inflammation [57]. In the following section, the effects of TiO_2 NPs on the antibacterial performance of orthodontic materials are discussed. The bacterial cells have the potential to accumulate around the retainer in the fixed bonded retainer which is made up of a

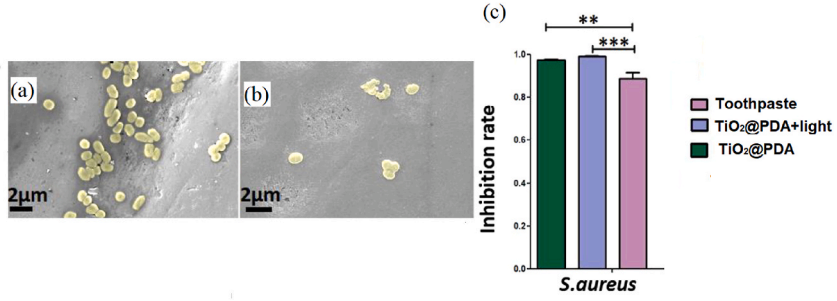

Fig. 3. A comparison of antibacterial activity (a) on-sell toothpaste, (b) TiO_2/PDA composite without irradiation and (c) inhibition rate of different treatments against *S.auerus*. Reprinted with permission Copyright (2018) American Chemical Society [43].

piece of wire and the composite resin bonded to the tooth. To tackle this, Kotta et al., have incorporated 1 wt% TiO_2 NPs into the conventional composite and their results significantly inhibited biofilm formation and showed a decrease in colony counts of *S.mutans* [58]. In another study, Sodagar et al. have added 1 wt%, 5 wt% and 10 wt% TiO_2 NPs into the Transbond XT and their findings showed a meaningful decrease in the colony of *S.mutans* within 3 days [59]. Behnaz et al., have added 2 wt% TiO_2 NPs into the Transbond X orthodontic adhesive and found a preventive effect on the WSL formation after 1 month of evaluation [60]. GIC cement is widely used in orthodontic treatment to bond brackets and bands. To enhance the antibacterial performance of orthodontic cement, 10 wt% of TiO_2 NPs were added to the GIC cement, and the antibacterial activity against *S.mutans* was significantly improved [61]. In a study, the effect of TiO_2 NP coating on the white spot formation of stainless-steel orthodontic wire was clinically evaluated. Their results have demonstrated that the coating of orthodontic wires with TiO_2 NPs significantly decreased the colonization of *S.mutans* after 4 weeks of insertion in orthodontic patients and this decrease was more effective in the mandible (lower arch) than maxilla (upper arch) [62]. This was ascribed to the flow of saliva at that site and the surface hydrophilicity of TiO_2-coated wires. Ghasemi et al. also coated stainless brackets with TiO_2 NPs and revealed a significant reduction in colony counts compared to the uncoated counterpart [63]. Cao et al., have coated N-doped $TiO_{2-x}N_y$ thin film on a stainless steel edgewise bracket and exhibited strong prevention of *S.mutans* adherence [64]. In an attempt by Zhang et al. the metal bracket was coated with nano-Ag/TiO_2 NPs and effective antibacterial effects against *S. mutans* with good biocompatibility were found [65]. To this end, PMMA was coated with the atomic layer deposition technique (ALD) and the findings revealed a significant decrease in the attachment of *C.albicans* on TiO_2-coated PMMA compared to PMMA [66].

Orthodontic resin comprising orthodontic adhesive and primer acts as a binder between the bracket and tooth enamel. The WSL or enamel demineralization can be developed in the areas adjacent to the orthodontic bracket acid biofilm [67]. To tackle this, Sodagar et al., added 10 % TiO_2 NPs to the orthodontic resin composite and showed a significant reduction in the number of *S.mutans* compared to the unmodified resin composite [68]. Another study conducted by Putri et al. has revealed contradictory results in which the addition of TiO_2 NPs to orthodontic adhesive resin did not significantly affect the numbers of *S.mutans* colonies around the bracket compared to brackets bonded with orthodontic adhesive resin [69]. This could be because the concentration and size of the TiO_2 NPs affect their antibacterial performance meaning that the higher the concentration of NPs and the smaller the size of TiO_2 NPs, the higher the antibacterial activity. A summary of the TiO_2-incorporated orthodontic appliances and auxiliaries *in vitro* is tabulated in Table 2. As can be observed from the data in Table 2 the incorporation of TiO_2 NPs led to a lower CFU which is an indication of the higher antibacterial properties [44]. This section showed that the incorporation of TiO_2 NPs enhances the antibacterial properties.

5. Effect of TiO_2 on mechanical properties

5.1. Endodontic dental materials

A healthy dentition plays an important role in the well-being of individuals in all age groups. Edentulism is known as a major universal concern [74] and could be a permanently debilitating disorder [75]. To tackle this disorder, the use of dentures is in high demand due to the increase in the aged population. Acrylic resin is widely used as denture base material [76]. Polymethylmethacrylate (PMMA) is one of the important members of acrylic resin which is commonly used denture base resin and has been in use since the inception of denture base resin [77,78]. This is ascribed to favourable properties over metallic dentures including biocompatibility, aesthetics, stability in the oral cavity, and low cost. Nonetheless, it is liable to breakage under dynamic masticatory load and handling practices due to poor flexural and impact strength [36]. This is an important issue as dentures should remain intact during falling and chewing [71]. The properties of denture base resin can be ameliorated by adding reinforcing agents such as fillers. With progress in nano-dentistry, nano-scaled fillers have been increasingly used to reinforce dental resin [79]. In this regard, the effect of TiO_2 NPs addition to the denture base resin as an additive or used as a coating is discussed in the following section.

5.1.1. PMMA

PMMA-based resin has been widely utilized in dentistry as removable base plates, denture bases, as well as functional appliances mainly due to their biocompatibility and aesthetics [80]. However, their key weakness is the restricted mechanical strength comprising low flexural strength [36]. Consequently, PMMA denture base materials often fail during eating or falling [81]. To tackle this, the use of inorganic TiO_2 NPs as additives can alter the mechanical performance of PMMA [82]. Fahad et al., have fabricated TiO_2/PMMA nanocomposite for potential dental application and their findings revealed that the addition of 1 wt% and 3 wt% TiO_2 NPs ameliorated

Table 2
A summary of TiO_2-incorporated orthodontic appliances and axillaries found in the literature.

Orthodontic appliances	CFU/mm^2 -control	CFU/mm^2-modified	NP (wt.%)	Bacterial cells	References
Orthodontic bracket	401.21 ± 13.72	37.82 ± 5.15 [a]	NA	*S.mutans*	[70]
Orthodontic bracket	12588.3 ± 66.2	658.3 ± 66.2[a] 406.8 ± 66.2 [a]	NA	*S.mutans*	[63]
Orthodontic composite	69.1 ± 14.5	8.2 ± 3.95 [a]	1	*S.mutans*	[71]
Orthodontic adhesive	889.76 ± 115.14	435.33 ± 41[a] 133 ± 23.25[a] 14 ± 3.60 [a]	1 5, and 10	*S.mutans*	[68]
Orthodontic adhesive	889.67 ± 115.14	14 ± 3.60	10	*S.mutans*	[69]
Orthodontic adhesive	44.2	5.2	1,3	*S.mutans*	[72]
Orthodontic adhesive	5.73 ± 0.10 4.10 ± 0.42 5.17 ± 0.57	2.51 ± 0.65[a] 1.51 ± 0.46[a] 1.18 ± 0.70 [a]	1	*S.mutans*	[73]
Fixed retainer composite	899.3 ± 134.1	454.6 ± 176.5[a]	1	*S.mutans*	[58]

[a] indicates a significant difference (p value < 0.05).

the flexural strength of PMMA resin. This was ascribed to the formation of a strong connection between the material and the reinforcing phase. However, increasing the TiO_2 content to 5 wt% decreased the flexural strength [83]. The study conducted by Jehan et al. has shown that the addition of 2.5 wt% TiO_2 NPs into the PMMA led to a significantly higher flexural strength compared to that of pure conventional PMMA [84]. This was due to the reduction in the adherence of biomolecules and an increase in surface hydrophilicity. In the study published by Jehan et al., the addition of TiO_2 NPs into the PMMA resin significantly enhanced the flexural strength in both distilled water and artificial saliva [85]. Khalil et al. have demonstrated that the addition of TiO_2 NPs into PMMA led to a significant increase in flexural strength. This is associated with the enhanced bonding between the matrix and filler [86]. In a study conducted by Abdelraouf et al., the addition of 5 wt% TiO_2 NPs into the PMMA led to an increase in the flexural strength after the inclusion of TiO_2 NPs [87]. In contrast, Pai et al., have shown that the addition of TiO_2 NPs gradually decreased the flexural strength of PMM by increasing the content of TiO_2 NPs [88]. Azmy et al. observed that the addition of 3 wt% TiO_2 NPs increased the flexural strength of PMMA while further increasing the content of TiO_2 NPs to 7 wt% decreased the flexural strength [89]. This may be due to the formation of clusters which act as areas of stress concentration which weaken the flexural strength. Similar results were observed for the addition of 5 wt% and 7 wt% TiO_2 NPs into the conventional resin due to the agglomeration of TiO_2 NPs and the creation of stress-concentrating centres which compromise the flexural strength [90]. In research conducted by Bangera et al., the addition of 1 wt % and 3 wt% TiO_2 NPs increased the flexural strength while further increasing the TiO_2 content to 5 wt% decreased the flexural strength compared to pure PMMA [91]. In another report, Akay et al. have incorporated 1 wt% 3 wt% and 5 wt% TiO_2 NPs to acrylic resin and their results revealed that 3 wt% TiO_2 NP showed a significantly higher flexural strength while other concentrations decreased the flexural strength [92]. AlQahtani et al., have used layering as a new approach to add TiO_2 NPs to PMMA and their finding showed a significant decrease in flexural strength in 1 wt% one-layer approach by increasing the content of TiO_2 NPs [93]. Raj et al. have shown that the addition of 3 wt% did not show a remarkable decrease in flexural strength when compared to conventional resin [90]. Alhotan et al. have modified PMMA resin by adding 1.5 wt%, 3 wt%, 5 wt% and 7 wt% TiO_2 NPs and their findings showed a gradual decrease in flexural strength by increasing TiO_2 content and the values of flexural strength were not significantly different from pure PMMA [94]. Nazirkar et al., have added 0.5 wt% and 1 wt% TiO_2 NPs into the acrylic resin and reported a significant decrease in the flexural strength [95]. In the same token, Sodagar et al. added 0.5 wt% and 1 wt% TiO_2 NPs and found a decrease in the flexural strength of PMMA [96]. Rashahmadi et al. have found an increase in the flexural strength of PMMA with the addition of 0.5 wt% compared to pure PMMA. While the addition of 1 wt% and 2 wt% TiO_2 showed nearly identical flexural strength to pure PMMA [97]. In another study, Karci et al. studied the effect of 1 wt%, 3 wt% and 5 wt% TiO_2 on the mechanical performance of PMMA and revealed that the addition of 1 wt% significantly enhanced the flexural strength of PMMA in both heat- and auto-polymerized acrylic resin. This was attributed to the more homogenous dispersion of NPs in the PMMA matrix [98]. As can be observed from the data in Table 3, the results of flexural strength are disparate which can be ascribed to several parameters inclusive of the size of TiO_2 NPs, water temperature, and the type of acrylic resin. For example, Alraziqi et al., have shown that increasing water temperature decreases the flexural strength due to the acceleration of water permeability into the acrylic resin [99]. According to the literature above, on the one hand, the following reasons could explain the enhancement of flexural strength in the PMMA resin composite: (I) improved bonding between the matrix and filler [83,86], (II) increase in surface hydrophilicity [84]. On the other hand, the flexural strength of PMMA resin composite is compromised when the content of TiO_2 NPs exceeds a certain limit of 5 wt% [90,92] 7 wt% [89,90]. This was possibly due to the formation of clusters which act as areas of stress concentration resulting from aggregation and agglomeration of

Table 3
A summary of flexural strength of TiO_2-incorporated PMMA dental resin composite.

Acrylic resin	Dimension (nm)	Flexural strength (MP)-modified	Flexural strength (MPa)-control	Reference
Cold-cure	30–50	193.49 ± 5.27 [a]	178.18 ± 4.95	[84]
Cold-cure	30–50	189.34 ± 5.5.96 [a]	176.11 ± 10.04	[84]
Cold-cure	30–50	141.06 ± 6.41 [a]	98.43 ± 2.26	[85]
Cold-cure	30–50	140.80 ± 9.08 [a]	97.97 ± 4.10	[85]
Cold-cure	15	52.26 ± 5.48 [a]	24.94 ± 5.37	[86]
Cold- cure	<25 nm	137.6 ± 3.2 [a]	75.4 ± 2.1	[87]
Heat-cure	25	94.4 ± 5.38 [a]	138.56 ± 4.84	[88]
Heat-cure	26	83.4 ± 3.2[a] 62.2 ± 2.5	59.4 ± 5.5	[89]
Heat cure	–	280.96 ± 28.21 202.74 ± 24.93[a]	298.95 ± 20.24	[90]
Heat-cure	10–25	102.98 ± 18.21 91.28 ± 23.96	97.17 ± 5.07	[91]
Heat-cure	28	214.92 ± 10.29[a] 143.56 ± 13.05 [a]	184.04 ± 10.92	[92]
Heat-cure	26	42.4 ± 3.7 [a]	88.6 ± 6.2	[93]
Heat-cure	26	90.1 ± 7.1	88.6 ± 6.2	[93]
Heat-cure	26	88.18 ± 5.4	88.6 ± 6.2	[93]
Heat-cure	20–30	91.5 ± 8.3 88.1 ± 11.5	89.2 ± 6.3	[94]
Heat-cure	7	76.38 ± 11.03	90.65 ± 9.67	[95]
Cold-cure	21	34.6 ± 3.17	43.5 ± 3.44	[96]
Heat-cure	20	4.17 ± 3.9 3.98 ± 7.3	4.02	[97]
Heat polymerized	13	116.46 ± 3.9[a] 104.6 ± 7.3 [a]	110.2 ± 6.4	[98]
Auto-polymerized	13	110.76 ± 5.6 95.09 ± 4.5	100.21 ± 9.4	[98]
Microwave polymerized	13	110.08 ± 7.2101.66 ± 7.8 [a]	106 ± 8.3	[98]
Conventional amalgam	–	–	28.09	[100]
Vitremer GIC	–	–	42.30	[100]

[a] indicates a significant difference (p value < 0.05).

TiO_2 NPs [89,90]. These findings suggested that the concentration of TiO_2 NPs is inversely proportional to the flexural strength of reinforced PMMA.

5.1.2. GIC

GIC has some benefits including adhesion to moist tooth structure by which a little removal of the sound tooth is allowed, and fluoride ion release which renders anti-cariogenic qualities together with a similar coefficient thermal expansion to that of tooth structure [101]. However, their brittleness and low flexural strength limit their application as restorative materials. To overcome these shortcomings, TiO_2 NPs have been incorporated into GIC to augment their mechanical strength [102–106]. Garcia-Contreras et al. showed that the supplementation of 3 wt% and 5 wt% TiO_2 NP into the FX-II led to a significant increase in flexural strength compared to conventional GIC without compromising the adhesion to enamel and dentin [103]. El-Negoly et al. have found a significant increase in the flexural strength of conventional GIC by adding 3 wt% and 5 wt% TiO_2 NPs while further increase in the content of TiO_2 NPs decreased the flexural strength [102]. Ibrahim et al. have dually modified GIC with 3 wt% TiO_2 NPs and chitosan and their findings showed the enhancement in flexural strength which was attributed to the presence of TiO_2 NPs while the improvement in antibacterial properties was mainly ascribed to the chitosan in the liquid phase [107]. Fattah et al. have found that the incorporation of 5 wt% TiO_2 NPs into the conventional and resin-modified conventional GIC did not significantly change the shear bond strength which shows the chemical bonding of GIC capability [108]. Similar results were found in the study by Elaska et al., in which the incorporation of 3 wt% TiO_2 NPs into the GIC enhanced flexural strength compared to unmodified GIC without affecting the adhesion to enamel and dentin [109]. Overall, it can be understood that TiO_2 NPs were capable of improving the mechanical strength of PMMA particularly when used in low concentrations. The possible reasons for these positive effects could be explained as follows: (I) The NPs fill the empty voids within the matrix of the original material which further ameliorates the mechanical strength, (II) the large interfacial area of NPs provide more contact points with the material and interrupts the crack propagation through the transfer of stress from the weak original material to the strong NPs as fillers. Despite the potential and promising results regarding the effectiveness of TiO_2 NPs in various dental materials, some issues still need to be addressed. First is the tendency of NPs to agglomerate in dental materials. This reduces the surface energy of NPs and in turn, leads to the loss of NPs and alternations in their nano-properties. Therefore, a homogenous dispersion of NPs is required and this necessitates the use of NPs in low concentrations to eliminate their agglomeration [101]. Second, the optimum specifications need to be identified that suit specific dental applications. Third, these bench *in vitro* studies have not been followed up with clinical trials to support the obtained findings.

5.2. Orthodontic dental materials

The shear bond strength (SBS) of the orthodontic bracket plays an essential role in impairing the favourable treatment. This is because repeated breakage during treatment affects the treatment's quality and delays completion [110]. In contrast to restorative dentistry, very high bonding strength is not desired due to the destruction of the enamel surface at the time of debonding in the bracket [111]. A minimum value for SBS in the range of 6–10 MPa might be sufficient to keep the orthodontic bracket in place [112]. In the following section, the effects of TiO_2 on the shear bond strength (SBS) of orthodontic appliances are discussed. In a study, Behnaz et al. have added 0.1 wt% TiO_2 NP into the light-cured Transbond XT composite and their findings showed that the addition of TiO_2 NP reduced the SBS, however, the adhesion was still at an acceptable level [113]. Reddy et al. observed that the incorporation of 1 wt% TiO_2 NPs into the Transbond XT adhesive and they have revealed that the SBS on the stainless steel metal bracket was significantly decreased compared to that of unmodified Transbond XT [114]. In the study published by Sodagar et al., the addition of 1 wt% TiO_2 NP into the Transbond XT meaningfully reduced the SBS applied on the stainless steel metal bracket [68]. Poosti et al. have incorporated 1 wt% TiO_2 NP into the Transbond XT and found no significant difference in the SBS [71]. A summary of SBS values for TiO_2-incorporated orthodontic adhesive is shown in Table 4.

6. Effect of TiO_2 biomineralization

The dental plaques which are formed by the colonization of oral bacteria such as *S.mutans* demineralize the dental enamel and form cavities through the acidic products. This will have a substantial influence on the chewing functions of patients [115]. In addition, the demineralization and the degradation of the organic matrix in teeth can change their morphology and structure over time [116]. Therefore, it is important to repair demineralized enamel together with inhibition of plaque formation. The metallic NPs can spark biomineralization which promotes the remineralization in the demineralized dental tissues [117]. The TiO_2 NPs can have a positive effect on the remineralization of dental tissue which is briefly discussed in the following section. In a study, Welch et al. incorporated

Table 4
A summary of SBS values for TiO_2-incorporated orthodontic adhesive in the literature.

Orthodontic appliances	SBS (MPa) -control	SBS (MPa)-modified	NP (wt.%)	References
Orthodontic adhesive	143.66 ± 9.41[a]	124.33 ± 5.09	0.1	[113]
Orthodontic adhesive	34.47 ± 6.73	18.17 ± 4.65 [a]	1	[68]
Orthodontic adhesive	9.43 ± 3.03	6.33 ± 1.51 [a]	1	[114]
Orthodontic adhesive	14.4 ± 1.2	14.3 ± 1.26	1	[71]

[a] indicates a significant difference (p value < 0.05).

TiO_2 NPs into the Adper™ Scotchbond™ 1XT commercial dental adhesive and found the formation of HA crystals on their surface compared to pure dental adhesive [118]. In a study, Muhriz et al. coated TiO_2 NPs on GIC and revealed that the coating significantly affected the remineralization of dentine by increasing phosphorus content (P) compared to that of nano-HA with limited remineralization [119]. In another study, Wang et al., have demonstrated the accumulation of HA on TiO_2 NPs and their effectiveness in the remineralization of enamel with and without visible light irradiation [120]. Mollabashi et al., have reported that the TiO_2-modified orthodontic composite could prevent the demineralization around the bracket during orthodontic treatment after 6 months of bonding [121]. The effectiveness of TiO_2 in remineralization is associated with their surface chemistry and their charge. They can produce a surface with a negative charge which attracts the calcium (Ca) and phosphorous (P) ions to the surface and form the HA layer. A schematic representation of the remineralizing mechanism of TiO_2 NPs is shown in Fig. 4.

7. Effect of TiO_2 NPs on tooth glossiness

Colour and glossiness play an essential role in achieving aesthetics and this can positively affect the patient's satisfaction. Based on a survey conducted in the UK, 96.6 % of participants agreed that their self-confidence and psychological behaviour were affected by dental aesthetics [123]. It was found that a combination of intrinsic tooth colour and external stains on the surface of the tooth influence its colour. Particularly, the dentine determines the overall tooth colour [124]. Composite resin as one of the important materials for dental restoration should have acceptable optical and aesthetic properties in clinical applications as a key performance index [125,126]. However, the functional groups which exist in the molecular chains of polymers can absorb UV light. This UV light absorption increases the instability of the polymer. The excited molecules tend to disperse the excessive energy to make the structure more stable. As a consequence, the molecules are photochemically degraded and ruptured which ultimately changes the brightness or colour [127]. Another reason for colour change in acrylic resin is liquid absorption and the dispersion of this liquid into the polymer network [128]. To tackle this issue, the TiO_2 NPs can be applied as an additive or coating due to their whitish colour which is desired for dental applications [129]. In a study, Aziz et al. found that the addition of 3 wt% TiO_2 NPs into the PMMA matrix make it more opaque compared to pure PMMA due to the higher light absorption by TiO_2 NPs than polymer matrix [130]. In another report, the addition of TiO_2 NPs into dental resin composite was visually perceivable using different content of TiO_2 NPs [125]. This can be ascribed to the tooth-like colour of TiO_2 NPs. In another report, Pai et al. found that the addition of 0.5 wt% TiO_2 NPs revealed a minimal visible colour change [88]. Nonetheless, the addition of TiO_2 NPs into PMMA exhibited a light pink colour and the use of a modifier is required. Kashyap et al., have coated TiO_2 NPs on the PMMA denture base resin and found higher colour change levels for uncoated resin compared to TiO_2-coated PMMA in different beverages [131]. In a study published by Morie et al., the effect of TiO_2 NPs coating on the appearance of denture base resin was evaluated and their result showed no significant colour change after coating and the change was not easily perceivable by the human eye [132]. Nonetheless, the TiO_2-coated PMMA showed a significantly higher level of glossiness (12.8) compared to pure PMMA (3.06). In another study, the clinical appearance of TiO_2-coated PMMA was evaluated and the results showed no significant colour change between pure PMMA and TiO_2-coated PMMA. However, the glossiness of PMMA increased from 3.06 to 12.8 after TiO_2 NP coating [132]. AlQahtani et al., have used layering as a new approach to add TiO_2 NPs to PMMA and their finding showed a significant decrease in the translucency of PMMA using one-layer and double-layer. At the same time, this was not observed for 1 wt% dotted layering [93]. Altarazi et al. have shown that the addition of TiO_2 NPs to the acrylic denture revealed a noticeable change in colour by increasing the content of TiO_2 NPs which was attributed to the whitish colour of TiO_2 NPs (Fig. 5) [133]. This section showed that the addition of TiO_2 NPs as an additive and coating can enhance the glossiness and render the white colour to dental resin. However, further investigations need to be conducted to determine the suitable content of TiO_2 NPs to attain acceptable aesthetics [76].

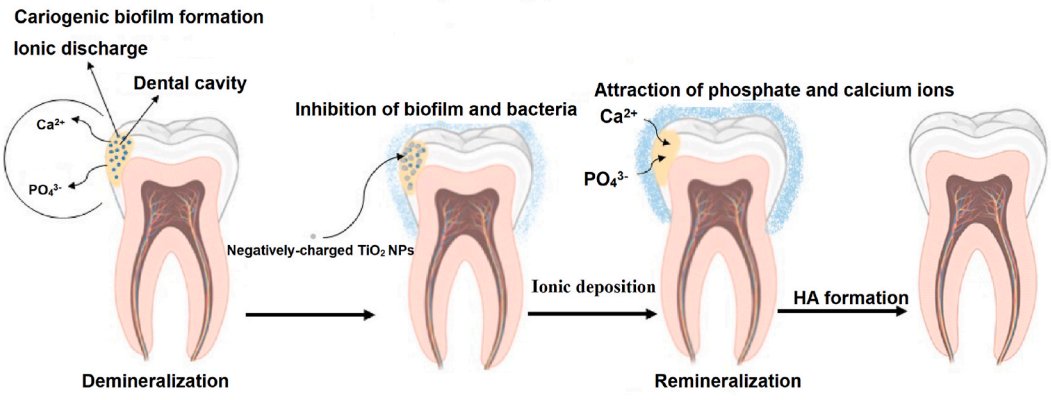

Fig. 4. Schematic representation of demineralization and remineralization process in the dental cavity. Reprinted with permission under Creative Commons CC-BY License [122].

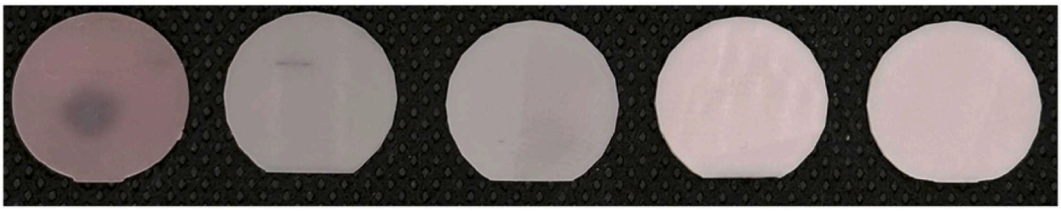

Fig. 5. The colour change in the acrylic denture for pure and TiO_2-modified counterparts (left to right). Reprinted with permission under Creative Commons CC-BY Ref. [133].

8. Photodynamic therapy in dentistry

8.1. Mechanism of PDT

Photodynamic therapy (PDT) is light therapy which works based on combinatory actions of three key constituents: (I) photosensitizer (PS), (II) light source, and (III) molecular oxygen [134]. The light-emitting diode (LED), laser, and incandescent lamp are the main types of light source used in PDT. The choice of light source relies on the target location, spectrum absorption related to PS, and the dose of light [135]. When the PS is activated at the target site under the appropriate irradiation of light, it absorbs and transfers electrons while the oxygen molecules act as electron acceptors [136]. Thus, ROS is generated which causes irreversible damage to microorganisms by rupturing their cell membrane [137]. There are two distinct mechanisms for PDT producing two main types of ROS. In the type I mechanism, oxygen radicals are produced by electron transfer. In this mechanism, the transition of PS molecules from the ground state to the singlet and triplet excited states is observed [138]. In the next step, these excited PS molecules form free radicals through the interaction with the substrate. Meanwhile, in the type II mechanism, the energy is transferred to the oxygen molecules by excited PS and consequently, highly active singlet oxygen is produced [138]. The mechanism of PDT is schematically represented in Fig. 6.

The PDT is advantageous over traditional alternatives due to its key advantages such as non-invasiveness, spatiotemporal selectivity, convenience and no drug resistance. These advantages mainly stem from the beneficial interactions between the light photosensitizer (photosensitive compound) [134,138]. The spatiotemporal selectivity allows for controlling the irradiation regarding time and position. This leads to minimal functional disturbances and minimization of systemic toxicity [142]. Nonetheless, the use of traditional PS in traditional PDT hinders its application. This is associated with poor solubility, limited light penetration, oxygen dependence, and instability in the PDT operation circumstances. Due to the challenges mentioned above for traditional PDT, PS has been integrated with nanotechnology to enhance the efficiency of therapy [138,143]. For this purpose, inorganic NPs are utilized as PS due to their higher light conversion efficiency, higher $^1O_2$, better stability, and excellent photochemical properties [143,144]. The TiO_2 NPs can be used as PS because of their antibacterial properties, excellent photosensitivity, and tuneable bandgap [145].

8.2. Photosensitive dental materials

When a dental material such as an orthodontic bracket, or restorations is entered into the oral cavity, it tends to accumulate biofilms which cause an imbalance in microbiota and cause oral diseases such as caries, and periodontal disease [146]. Thus, thoroughly eliminating those is the key objective of oral therapies [147]. Antibiotic therapy is the common choice to tackle microbial infections. Nonetheless, the rise in bacterial drug resistance poses significant challenges for their wide clinical applications. Alternatively, the incorporation of PS into dental materials has been developed as photosensitive materials allowing for targeted antibacterial treatment. This offers several benefits including the reduction in the need for patient cooperation during treatment as the material can be activated utilizing light without patient compliance, the minimization of chair time for patients compared to antibiotic treatment which requires extended contact time to achieve the desired effects, and rapid activation of antibacterial action upon

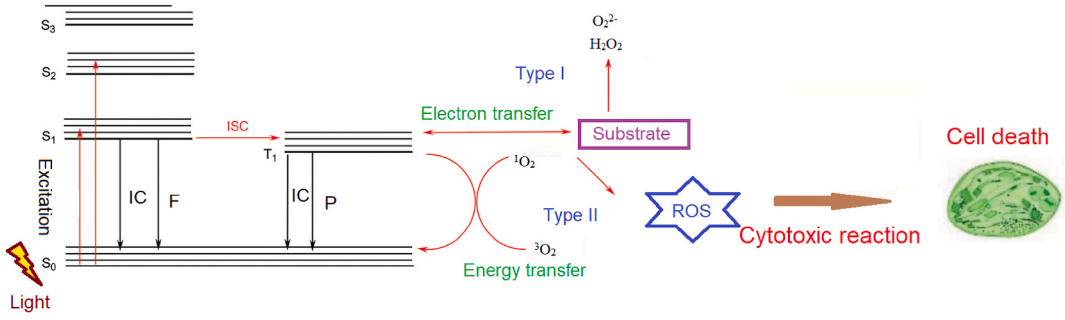

Fig. 6. A schematic representation of the mechanism of PDT. Replotted using the literature references [139–141].

exposure to light and which remarkably reduces the time needed for treatment. Incorporating inorganic PS such as TiO_2 into dental materials such as restorative composite can provide a continuous antibacterial effect. This is particularly to prevent the development of biofilm and secondary infection. For instance, light-activated TiO_2 NPs with UV light (400 nm), infrared light (300 nm), and laser (30 J) significantly decreased the viability of *P.gingivalis* [148]. Also, Cai et al. have reported that adding TiO_2 NPs to dental adhesive led to a significant reduction in the number of biofilm bacteria under low doses of UV-A irradiation compared to pure adhesive. The non-photocatalytic dental resin required a much higher dose (almost 10 times) of UV-A to have the equivalent effect on *S.mutans* cell viability [149].

Although PDT can potentially offer clinical benefits and is superior in preventing bacterial growth and colonization, the clinical application of PDT using TiO_2 as PS under UV irradiation is restricted due to the low penetration depth of UV and the wide bandgap of TiO_2 (3.2 eV) necessitating the photoactivation in the UV spectral range. This demands the exploration of strategies to extend its photoactivity into the visible spectral range. To achieve this, upconversion TiO_2 NPs by exposing them to highly penetrating near-infrared (NIR) were used. Qi et al. coated TiO_2 NPs on the upconversion luminescent β-$NaYF4:Yb^{3+}$, Tm^{3+} core [52]. Their results showed that applying 2 mM upconverted TiO_2 with near-infrared (NIR) light remarkably decreased the CFU counts (Fig. 7a) and metabolic activity (Fig. 7b) of *P.gingivalis* biofilm on dentin when compared to commercial antibacterial PDT and dark control. In another study, Tsai et al. optimized the antibacterial PDT using TiO_2 under LED by a synergistic strategy which combines the N doping, oxygen vacancies and reduced Ti species [150]. Their results showed that reduced N-doped TiO_2 NPs and N-doped TiO_2 NPs remarkably eradicated the *S.mutans* and *P.gingivalis* bacteria under visible light. This enhanced antibiofilm activity was attributed to the integration of Ti^{3+} species, oxygen defects and interstitial and substitutional N dopants.

The following section discusses the applicability of antibacterial PDT in dental materials. A study by Damrongrungruang et al., aimed to compare the antibacterial efficiency of PDT by erythrosine with TiO_2 NPs under stimulation of blue LED [151]. Their findings showed that the *C.albicans* biofilm was effectively inhibited on the acrylic denture resin by PDT utilizing erythrosine and 1 % TiO_2 NPs under irradiation of blue dental LED at 15 J/cm^2. This efficiency was superior to the Fluconazole as a denture cleaning agent. Barylyak et al. investigated the inhibitory effect of sulphur-doped TiO_2 NPs on *S.mutans* under blue LED [152]. Their findings revealed that incorporating S-TiO_2 into the orthodontic dental adhesive significantly enhanced the antibacterial activity under LED irradiation compared to pure orthodontic adhesive with no antibacterial effect. This was attributed to the photocatalytic generation of free radicals when excited by LED irradiation. Alanazi et al. assessed the impact of TiO_2-doped Rose Bengal (RB) on the survival rate of *S. mutans* on dental adhesive [153]. They have shown that the photoactivation by LED light (450 nm) significantly decreased the survival of *S.mutans*. This was due to electron transfer induced by light-activated TiO_2 NPs disrupting the DNA of bacteria. Wang et al. have fabricated HA/TiO_2 nanocomposite and found that TiO_2 NPs and TiO_2/HA dramatically destroyed *S.mutans* and Extracellular polymeric substances (EPS) of biofilm after exposure to LED [120]. This antibacterial property was mainly attributed to the presence of ROS. Furthermore, they have shown stronger tooth remineralization under UV light compared to dark counterparts. This was mainly due to the promotion of the release of insoluble TiO_2/HA and supersaturation of Ca and P ions. In another study, Ahmad Fauzi et al. incorporated the N-doped TiO_2 NPs into the dental resin and reported a reduction in the cell viability of *S.mutans* under visible light due to the presence of photo-induced ROS [51]. Esteban et al., have incorporated the N-doped TiO_2 NPs into the Optibond Solo Plus commercial dental resin and found that they strongly inhibited the activity of *S.mutans* cariogenic biofilm under LED irradiation [44]. This was ascribed to the restriction of EPS that forms biofilm and the presence of TiO_2 NPs itself. In a study, Salehi et al. coated a stainless steel orthodontic bracket with N-doped TiO_2 NPs and showed stronger antibacterial properties against *S.mutans* than the uncoated bracket over 90 days under irradiation of visible light and could effectively prevent enamel decalcification [70]. This section highlighted that PDT using TiO_2 as PS could suppress the growth of cariogenic bacteria under LED irradiation. Given patient safety, the PDT using visible light is a favourable condition as the patients desire visible light rather than UV. However, some challenges need further investigation in the future such as the selectivity of PS towards bacteria, the penetration depth and wavelength of light, and the availability of oxygen. Because they play an important role in optimising PDT and, in turn, its effectiveness in dentistry. For example,

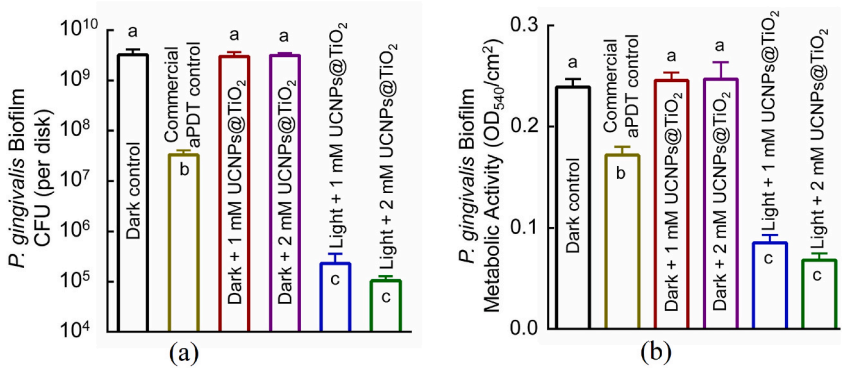

Fig. 7. The effect of 2 mM medication concentration of UCNPs@TiO_2 with and without the light on the activity of *P.gingivalis* on dentin: (a) CFU counts and (b) metabolic activity of *P.gingivalis* on dentin. Reprinted with permission [52]. Dissimilar alphabet shows significant differences (p value < 0.05).

Takahashi et al. measured the rate of $^1O_2$ formation under irradiation of LED light and found a decrease in the formation of $^1O_2$ using 365 nm–405 nm [154]. Maisch et al. have reported that the concentration of singlet oxygen inside the bacteria and its localisation to bacteria play a critical role in efficiently killing bacteria using PDT [155]. Komine et al., have assessed the antibacterial activity of PDT using TiO_2 as PS in dental treatment [156]. Their results revealed that both TiO_2 photocatalyst and LED light (405 nm) remarkably reduced the *P.gingivalis* (Gram-negative) but the effects on *S.mutans* (Gram-positive) were minimal. This can be due to the different thicknesses of peptidoglycan in G-positive and G-negative bacteria.

8.3. Tooth bleaching

The tooth-bleaching H_2O_2 is an amendable option to tackle tooth discolouration which is currently used in clinical applications for dental aesthetics. It produces free radicals (●OH and ●HOO) through dissociation in the alkaline environment which attack double bonds in the pigmented molecules inside the tooth tissue leading to the cleavage of double-bond conjugation [157,158]. Although H_2O_2 tooth-bleaching bleaching agents can decompose the pigment molecules and find clinical application, they can destroy the inorganic content of tooth structure and lead to side effects on enamel and dentin due to the direct contact between the bleaching agent and tooth tissue [159]. Moreover, it causes patient discomfort who suffers from soft tissue sensitivity and dental hypersensitivity [160]. These effects are directly associated with the concentration of H_2O_2 and the contact time of the bleaching agent with dental enamel [161]. For instance, Zhang et al. compared the enamel surface before (Fig. 8a–c) and after treatment with PDA-functionalized TiO_2 and 35 % H_2O_2 bleaching agents under LED irradiation. Their findings showed no enamel demineralization for PDA-functionalized TiO_2 (Fig. 8b) whereas 35 % H_2O_2 bleaching exhibited an obvious enamel demineralization (Fig. 8d) [43]. Thus, there is a need for an alternative material to achieve effective tooth bleaching and simultaneously reduce the side effects. To achieve this, PDT in the presence of PS is suggested to be used as an alternative tooth bleaching due to its non-invasiveness and selective therapeutic modality [162].

In PDT, the light units can deliver the required energy that accelerates chemical reactions in bleaching. Different irradiation energies such as halogen, LED, and laser have been used for this purpose. Furthermore, PS can absorb the photon energy when irradiated at the appropriate wavelength of light and transfer it to oxygen molecules to generate ROS via type I and II reaction mechanisms (refer to section 7.1). In the presence of TiO_2 NPs as a photosensitive agent, it can absorb the additional energy and accelerate the oxidation reactions of H_2O_2. This can be done by increasing the generation of superoxide rather than hydroxyl radicals which are related to dental sensitivity. In a study by Saita et al., the irradiation of UV to rutile and anatase TiO_2 led to a significant increase in the generation of superoxide compared to H_2O_2 which remarkably generated hydroxyl radicals [163]. This consequently ameliorates the effectiveness and speed of bleaching. Therefore, the mode of action of PDT during the bleaching process is different from that of H_2O_2.

As per request by patients, dental bleaching treatment should be safe, highly efficient, and minimally invasive. Moreover, they desire smile aesthetics. Therefore, colour change needs to be considered while using dental bleaching as dental bleaching can change the colour of the teeth [164]. The suggested method for the evaluation of dental colour change is the one that was defined by the Commission Internationale de l'Eclairage (CIE) in which colour is characterized based on human perception [165]. The color changes (ΔE*) are calculated using color coordinates L^*, a^*, and b^*:

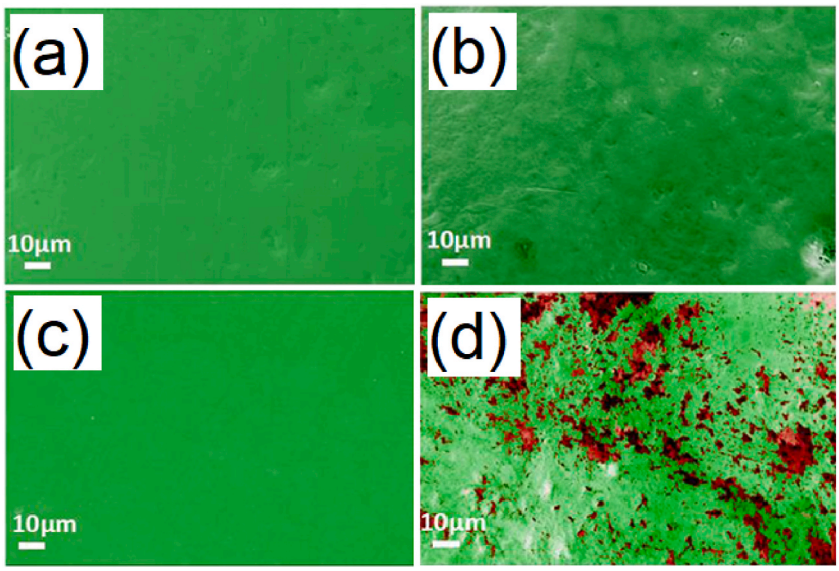

Fig. 8. The scanning electron microscopy (SEM) image of the enamel surface before (a,c) and after treatment with (b) PDA-functionalized TiO_2 NPs and (d) 35 % H_2O_2 dental bleaching under LED irradiation, respectively. Reprinted with permission Copyright (2018) American Chemical Society [43].

$$\Delta E^{*} = \left[\left(L_1^{*} - L_0^{*}\right) + \left(a_1^{*} - a_0^{*}\right) + \left(b_1^{*} - b_0^{*}\right)\right]^{1/2}$$

In this section, the effect of light-activated TiO_2 on the efficiency of conventional dental bleaching is discussed. In a study, Suyama et al. evaluated the effect of TiO_2 photocatalysts on H_2O_2 dental bleaching under different light irradiations [166]. They have shown that the high-intensity halogen lamp was more effective in dental bleaching than blue LED. Furthermore, the efficiency of tooth bleaching for the combination of H_2O_2 and TiO_2 was significantly higher compared to each constituent alone. In a clinical study by Dias et al., voluntary patients who were dissatisfied with the colour teeth and looking for bleaching were selected to evaluate the efficiency of different bleaching agents (Fig. 9a and b). Their results showed a similar bleaching effect for conventional H_2O_2 bleaching (Figs. 9c) and 6 % H_2O_2/N-doped TiO_2 dental bleaching under low-level laser therapy (780 nm) (Fig. 9d) [167]. In addition, the hypersensitivity was satisfactorily decreased while using a N-doped TiO_2-containing bleaching agent.

Trevisan et al. incorporated N-doped TiO_2 into the 6 % H_2O_2 dental bleaching and evaluated its clinical performance [168]. They have found that dental bleaching containing N-doped TiO_2 under irradiation of violet LED (405 nm) and blue LED (450 nm) caused less tooth sensitivity compared to in-office bleaching of 35 % H_2O_2 with comparable efficiency. However, the shorter wavelength and higher energy of violet LED compared to blue LED increased the interactions between the highly light-reactive pigmented molecules, leading to its better performance than blue LED. In another study, Bersezio et al. evaluated the effectiveness of light-activated TiO_2 6 % H_2O_2 dental bleaching [169]. They have reported that the TiO_2/6 % H_2O_2 under irradiation of LED/Laser (450 nm) showed comparable bleaching performance to H_2O_2 with a low incidence of sensitivity. Antunes et al., have shown that the incorporation of 5 % TiO_2 NPs into the H_2O_2 bleaching agent under the irradiation of poly-wave LED caused a greater bleaching outcome after the second clinical session and the irradiation of poly-wave LED light led to a noticeable colour change [170]. Cuppini et al. evaluated the performance of TiO_2/H_2O_2 and found a clinical colour change in bovine teeth. Furthermore, adding TiO_2 NPs into the dental bleaching accelerated the bleaching time and reduced the time required for bleaching [171]. This can lower the adverse effects and dentin sensitivity occurs in a longer time. Thacker et al. incorporated N-doped TiO_2 into calcium peroxide (CaO_2) dental bleaching in a study. They revealed an increase in colour change in bovine teeth coloured by coffee and black tea under LED irradiation which was significantly affected by the number of bleaching times [172]. Moreover, the dental bleaching exhibited no cytotoxicity towards 3T3 cells. In another study published by Kurzmann et al., photoactivated gel under blue LED light revealed that 6 % H_2O_2 significantly reduced the L929 cell viability compared to a gel containing TiO_2 NP with no obvious cytotoxicity [173].

Based on the previous reports in the literature, the threshold of perceptible and acceptable ΔE lies in the range of $1.0 \leq \Delta E \leq 3.7$ and $0.1.70 \leq \Delta E \leq 6.8$, respectively [174,175]. Johnston et al. reported that the average colour difference of $\Delta E = 3.3$ is rated as a match in the oral environment while $\Delta E = 6.8$ is rated as a mismatch in the oral environment but still within the acceptable range of tooth colour (marginally acceptable mismatch) [176]. The ΔE values for TiO_2/H_2O_2 dental bleaching are tabulated in Table 5. The data in the table indicated the effective bleaching effects for TiO_2/H_2O_2 dental bleaching. This section highlighted that PDT in the presence of TiO_2 as PS can be potentially used as an alternative tooth bleaching material. Moving forward, the dosage of TiO_2, intensities of light irradiation, and time need to be optimized to achieve the best scheme for tooth bleaching by PDT.

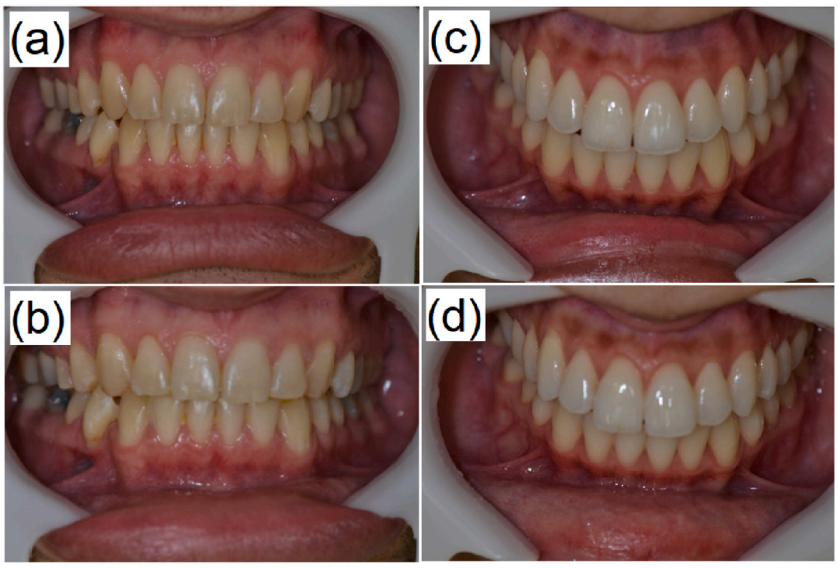

Fig. 9. The bleaching effects of 35 % H_2O_2 and 6%H_2O_2/N-TiO_2 effects on the colour of the right upper and lower incisors and premolars (a,b) before treatment and (c,d) after treatment, respectively. Reprinted with permission [167].

Table 5
A summary of dental bleaching in the presence of light-activated TiO_2.

Dental bleaching	ΔE (color change)	Light source	Reference
H_2O_2 6 %+N-TiO_2	<3.3	LED	[171,177]
H_2O_2 5%-TiO_2	>3.3	Poly-wave LED	[170]
CaO_2 10 %/N-TiO_2	4.82, 6.4	LED	[172]
H_2O_2 6 %+N-TiO_2	4.35, 4.02	Laser/LED	[169]
		Laser	[167]

9. Biosafety and nanotoxicology of TiO_2 NPs

9.1. Cytotoxicity

The smaller size and greater surface/volume ratio in NPs make them easily interact with living constituents. The exposure of NPs to cells may affect the cells via different routes such as the decrease in cell proliferation which can be attributable to the possible damage to the cells. This can be detected by cytotoxicity test while cell viability tests can quantify the growth of cells [178]. The cytotoxicity caused by NPs usually originates from their presence inside the cells [179]. When entered inside the cells, they cause metabolic changes and damage to proteins due to oxidative stress and inflammation [180]. The toxicity of NPs relies on various parameters including phase, mode of synthesis, concentration, and duration of exposure [181–183]. Mansoor et al. used the biogenic synthesis method to produce TiO_2 NPs and their results showed no change in the morphology of L929 fibroblast cells after exposure to TiO_2 NPs. This non-toxicity of TiO_2 NPs was ascribed to a mixture of anatase and rutile phases for TiO_2 making it less reactive and justifying its non-toxicity [184]. Garcia-Contreras et al. have shown that TiO_2 NPs with a size below 25 nm and in the anatase phase were not cytotoxic to HGF cells in the concentration range of 0.05–3.2 mM [185]. In another study, Chuang et *al.* compared the cell morphology and proliferation of the dental pulp stem cells (DSPC) control culture cell (Fig. 10a and b) with that of exposed to TiO_2 NPs in the rutile phase (Fig. 10c and d) after 2 days and 7 days, respectively [186]. They found that adding 0.1 mg/ml TiO_2 did not have a cytotoxic effect on the proliferation and morphology of DSPC. Furthermore, they evaluated the nucleation of banded collagen factors as a key requirement for *in vivo* hard tissue formation in the absence (Fig. 10e) and presence (Fig. 10f) of TiO_2 NPs, respectively. They showed that the addition of TiO_2 NPs enhanced the nucleation of banded collagen fibres. Nonetheless, increasing the concentration of TiO_2 NPs to 1 mg/ml led to a decrease in cell proliferation (Fig. 10g). Kim et al., have examined the cytotoxicity of TiO_2 NPs towards periodontal ligament cells (PDL) and they demonstrated that relatively low concentration of TiO_2 NPs (10 μg/mL) did not affect the cell viability [187]. Nonetheless, increasing the concentration of TiO_2 NPs led to a decrease in cell viability (20–50 μg/mL). Zane et al. have studied the biocompatibility of N-doped TiO_2 NPs under ambient and blue light irradiation when exposed to human gingival epithelial (hGEP). Their findings showed that the N-doped TiO_2 NPs were not toxic to hGEP cells. Cellular metabolism was remarkably elevated upon exposure to 50 and 100 μg/ml irrespective of the light treatment. Moreover, the blue light significantly increased the cellular metabolism compared to ambient light [188].

9.2. Inflammatory responses

The production of ROS is associated with the progression of inflammatory disease [189]. As the treatment with TiO_2 NPs gathers more ROS within the cells, the pro-inflammatory of TiO_2 NPs is of paramount importance in patients with chronic periodontitis in dentistry. The concentration of TiO_2 NPs exposed to cells plays an important role in the exertion of pro-inflammatory responses. Kim

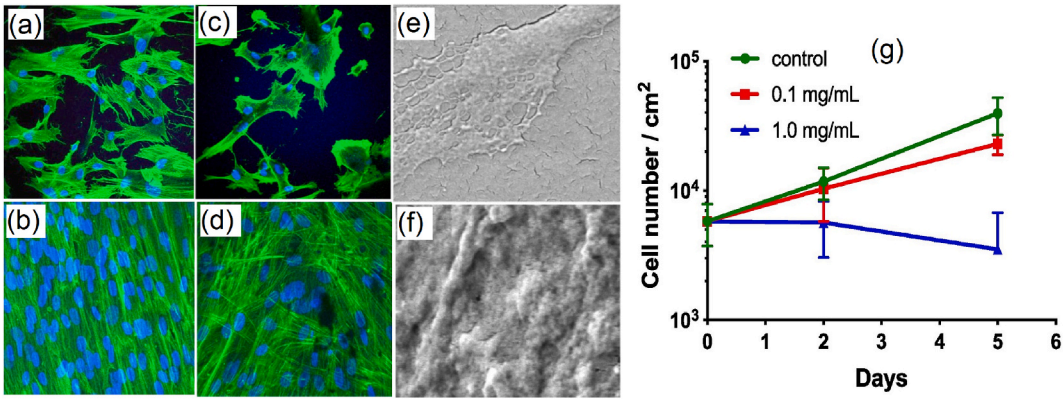

Fig. 10. The influence of TiO_2 NPs on the morphology of PDSC: Alex Flour 488 and DAPI staining for (a,b) control, (c,d) PDSC exposed to 0.1 mg/ml TiO_2 NPs after 2 and 7 days, (e,f) Scanning electron microscopy (SEM) micrographs of collagen fibres, in the presence and absence of TiO_2 NPs, and (g) PDSC cell proliferation. Reprinted with permission. Green and blue colours denote actin and nucleus [186].

et al. have reported that TiO_2 NPs (15 nm anatase) at the concentration of 2.5 μg/mL did not upregulate the COX-2 mRNA in PDL cells [187]. Nonetheless, increasing the concentration to 10 μg/mL significantly upregulated the levels of COX-2 mRNA in PDL which was attributed to overproduction of ROS. The inflammatory response was found to be through rapid activation of the extracellular signal-regulated kinase (ERK) and protein kinase B (Akt) which may be upstream of Nuclear factor-kappa B (NF-κB). Moreover, the pretreatment of ROS scavenger N-acetyl cysteine (NAC) before adding TiO_2 suppressed the increase in the expression of COX-2. For example, Garcia-Contreras et al. have investigated the effect of TiO_2 NPs (size below 25 nm in an anatase phase) on the inflammatory responses and found that the concentration of TiO_2 NPs higher than 0.2 mM exerted a pro-inflammatory response against HGF cells [185]. Other studies have investigated the pro-inflammatory reaction of TiO_2 NPs in the presence of interleukin 1β (IL-1β). For example, Garcia-Contreras et al. have monitored the metabolic profiles in a human gingivitis model exposed to TiO_2 NPs (18 nm, anatase phase) [190]. Their results showed that the TiO_2 NPs alone did not produce PGE_2 while their addition to Il-1β acted as a pro-inflammatory agent and led to a remarkable increase in the production of PGE_2 (Fig. 11a). Additionally, they showed TiO_2 NPs can be easily aggregated during culture incorporated into the cells demonstrating the intracellular uptake of TiO_2 NPs (Fig. 11b). Similarly, Garcia-Contreras et al. have impregnated TiO_2 NPs into GIC and found that TiO_2 itself did not produce PGE_2 while in the presence of Il-1β, the production of PGE_2 was aggravated when exposed to human pulp cells (HPC) and human gingival fibroblast (HGF) [191]. This section highlighted that the exposure of TiO_2 NPs at certain concentrations does not induce inflammatory reactions and a concentration of 0.1 mM or less for a safe dental application is suggested. Furthermore, it is recommended to carefully use TiO_2-modified dental materials in patients with gingivitis or periodontitis.

9.3. *Cytotoxicity of TiO_2-incorporated dental materials*

The PMMA denture base resin is not only in contact with the oral mucosa but also the skin of the wearer and dentist and dental technicians. Therefore, its biosafety needs to be carefully evaluated. In this regard, Raj et al. aimed to assess the effects of different concentrations of TiO_2 NPs on the biocompatibility of heat-cured PMMA resin [90]. They have shown that the TiO_2-coated PMMA resin was non-toxic to HGF cells within 7 days and significantly increased the cell viability compared to pure PMMA resin. Altazari et al. fabricated 3D printed TiO_2/PMMA composite denture base resin and revealed no cytotoxicity towards HGF cells [192]. Chen et al., have added TiO_2 NPs into PMMA denture base resin and found no adverse effects on L929 fibroblast cells after exposure to a 2-fold diluted extract of TiO_2-incorporated PMMA [193]. Tsuji et al. coated PMMA with TiO_2 NPs (5–10 nm) and conducted the oral mucosa irritation and intracutaneous tests [194]. The histological evaluation of mucosa exposed to elution from TiO_2-coated PMMA showed no irritation to the mucosa in the hamster. Moreover, TiO_2-coated PMMA did not cause skin sensitisation *in vivo* in the back skin of the guinea pig and rabbit.

The GIC dental material is made up of glass powders and polyacrylic acid liquids. The release of different chemicals during setting from the glass and the polyacrylic liquid may exert cytotoxicity. Previous studies have revealed a decline in cell viability in contact with GIC [195–197]. Thus, it is necessary to investigate the biocompatibility of TiO_2-incorporated GIC with pulp and the surrounding tissues. In a study, Cvjeticanin et al., have incorporated TiO_2 into commercial GIC Fuji IX [198]. Their results showed that TiO_2--modified GIC did not remarkably impact its biocompatibility and both Fuji IX and TiO_2-modified Fuji IX revealed a moderate decrease in cell viability of human dental pulp stem cell (hDPSC). This suggested the careful consideration of cement composition in the biological assessment. Cibim et al. studied the impact of TiO_2 addition to Ketac Molar as the conventional GIC. Their findings showed no cytotoxic effects on HGF cells and the incorporation of TiO_2 led to a significant increase in HGF cellular viability and formed collagenous and non-collagenous-rich ECM [199]. Garcia-Contreras et al. have impregnated TiO_2 NPs into GIC and revealed their acceptable biocompatibility after exposure to human pulp cells (HPC) and human gingival fibroblast (HGF) at low concentrations [191]. Garcia-Contreras et al. have impregnated TiO_2 NPs into GIC and found that TiO_2 itself did not produce PGE_2 while in the

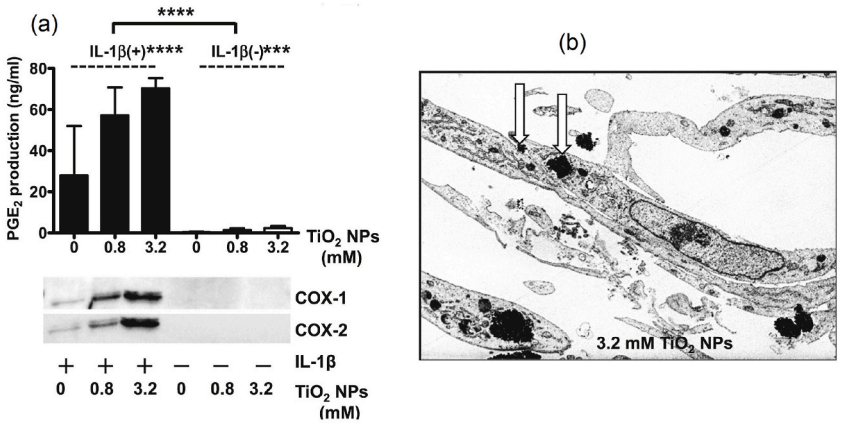

Fig. 11. The HGF cells with 3.2 mM TiO_2 NPs and their pro-inflammatory reactions (a) PGE_2 production of IL-1β in the presence and absence of TiO_2 NPs, and (b) Transmission electron microscopy (TEM) incubated HGF cells showing the intracellular uptake of TiO_2 NPs (Arrows indicated the agglomerated TiO_2 NPs). Reprinted with permission [190]. For full-size images please refer to the supplementary material S1.

presence of Il-1β, the production of PGE_2 was aggravated when exposed to human pulp cells (HPC) and human gingival fibroblast (HGF) [191].

The oral microenvironment during orthodontic treatment alters the properties of metal alloys and these changes cause degradation and corrosion (metal ion leaching). The leaching of metal ions causes adverse biological effects such as toxicity, genotoxicity and allergic reactions [200]. To control the corrosion of metals, the coating of orthodontic appliances is suggested. In this regard, Ahuja et al., aimed to investigate the risk associated with the corrosion of TiO_2-coated stainless brackets during orthodontic therapy [201]. Their genotoxic data have shown that it did not show cytoplasmic damage to buccal epithelial cells and HGF cells after exposure to corrosion eluates from TiO_2-coated stainless-steel bracket. Moreover, it showed higher cellular metabolic activities than uncoated stainless-steel counterparts. This showed the TiO_2 coating does not bring about inflammatory responses and improves biocompatibility due to better corrosion resistance. Heravi et al. investigated the cytotoxicity of TiO_2-incorporated orthodontic adhesive (Transbond XT) [202]. They found that the extract of TiO_2-incorporated Transbond XT was non-toxic to HGF and L929 cells after 14 days. This section highlighted that the incorporation of TiO_2 NPs in low concentrations does not cause additional health hazards making them a suitable candidate for dental applications. However, the research on the nano-toxicological studies on TiO_2-containing dental materials is still deficient and in its infancy. Thus, further investigations are warranted to investigate relevant toxicity data to the oral cavity to conclude the harm-benefit ratio of TiO_2 incorporation into dental applications [203–205]. A summary of evidence related to the *in vitro* and *in vivo* toxicity of TiO_2-incorporated dental materials is tabulated in Table 6.

10. Advantages and disadvantages of current material

Despite the widespread research on the application of TiO_2 NPs in dentistry as mentioned in the present article, this section provides a summary of the disadvantages and advantages of TiO_2 NPs themselves and TiO_2-incorporated dental materials for the readers to have a balanced view of the material:

Disadvantages:

(1) The wide band gap and truly antibacterial when it absorbs UV light (100–400 nm).
(2) Significant decrease of antibacterial activity under dark conditions [51,206].
(3) Effectively photocatalytic activity of traditional photocatalytic under UV light at levels harmful to human cells [51,207].
(4) Pro-inflammatory reaction of TiO_2 NPs in the presence of interleukin 1β (IL-1β) [190,191].
(5) Significant upregulation of the levels of COX-2 mRNA due to overproduction of ROS at high concentrations [187].

Advantages:

(1) Increased photocatalytic activity of the resin composite and no inhibition in photocatalytic activity after embedment in the resin matrix [51].
(2) Production of aesthetic resin composite under LED comparable to the available colours in the commercial dental shade guide [51].
(3) No long-lasting discolouration [51].
(4) Remarkable elevation in cellular metabolism irrespective of the light treatment [188].
(5) Significant increases in cellular metabolism under blue light compared to ambient light [188].

Table 6
A summary of evidence associated with toxicity of TiO_2 NPs in dental materials.

Material	Phase	Concentration	Control	Major findings	Reference
TiO_2/PMMA	–	3 %	Conventional PMMA resin	No cytotoxicity to HGF and significantly increased cell viability compared to pure PMMA resin.	[90]
TiO_2/3D printed denture base resin	Rutile	0.25 %	Commercial NextDent denture	No cytotoxicity to HGF	[192]
TiO_2-incorporated PMMA composite	–	3 %	PMMA composite	No adverse effect on L929 mouse fibroblast	[193]
TiO_2-coated PMMA	Anatase	2 %	PMM resin	No *in vivo* irritation to the mucosa no *in vivo* skin sensitisation	[194]
TiO_2-incorporated Transbond XT	Mixed anatase/ rutile	1 %	Pure orthodontic adhesive	Comparable or lower cytotoxicity to HGF and L929 cells	[202]
TiO_2-incorporated GIC	–	3 %	Commercial Ketac Molar	Higher HGF cell viability Significantly increased in the non-collagenous composition of ECM	[199]
TiO_2-incorporated GIC		3 %, 5 %	Commercial FX-II	No inflammatory reaction in the absence of IL-1β	[191]
TiO_2-incorporated GIC	Anatase	5 %	Commercial GIC (Fuji IX and Ketac Molar	No compromise on biocompatibility Moderate decrease in cell viability	[198]
TiO_2-incorporated GIC	Anatase	3 %, 5 %	Commercial GIC (Base cement, Core shade and FX-II)	Acceptable to moderate biocompatibility towards HGF, HPC, and HPLF Slightly higher pro-inflammatory reaction	[191]

(6) Potential long-term antibacterial properties (90 days) effective prevention of enamel decalcification [70].
(7) Enhanced nucleation of collagen fibres as a key requirement for *in vivo* hard tissue formation [186].
(8) No production of PGE_2 [190,191] and upregulation of COX-2 mRNA at low concentration [187].

11. Clinical trials and commercialization hurdles

According to the World Health Organization (WHO) 40, antimicrobial resistance is the third greatest peril to global health. This causes negative effects such as an increase in treatment prices for infectious diseases, failure of effective treatment, and ultimately an increase in infection-associated morbidity [208]. Furthermore, antibiotic resistance compromises the immune system's capability to combat infection in susceptible patients undergoing surgery or chemotherapy [209]. Also, the risk of additional issues may be raised by the long hospitalization of antibiotic-resistant patients such as outbreaks due to the easy transmission of germs from person to person [210]. The WHO has designated the effectiveness and selection of metal-based NPs against pathogens as the first and second priorities [211].

Based on the literature reviewed in the present work, widespread *in vitro* studies conducted a short and limited evaluation period and showed that the impregnation of TiO_2 NPs in dental materials can effectively enhance the antibacterial properties of dental materials. However, take the comprehensive orthodontic treatment as an example, it lasts more than 1.5 years [212] showing the necessity to conduct more long-term clinical trials to confirm the claimed outcomes of the *in vitro* studies. This will encourage manufacturers to include TiO_2 NPs as the standard ingredient in the composition of dental materials and facilitate the transition of TiO_2 NPs into clinical trials. The following section provides a summary of the current clinical trials conducted on TiO_2 NP in dental appliances. In a report, the effect of TiO_2 NP addition on the antibacterial properties of acrylic resin PMMA was investigated. Their findings showed that 3 % TiO_2 addition significantly reduced the colonization of *Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis* (*S.epidermidis*), and *C.albicans* after 1 month of follow-up in edentulous patients compared to conventional acrylic resin [42]. In another report, TiO_2 NP was incorporated into the acrylic baseplates of the maxillary part of a twin-block appliance to evaluate their antibacterial effects [213]. The findings showed that the addition of 1 % TiO_2 NPs significantly reduced the colonization of *S. mutans* on the baseplates after at least 4 months of application in orthodontic patients compared to unmodified twin-block acrylic resin. In a study, the effect of TiO_2 NPs on the *S.mutans* counts and the content of enamel minerals in fixed orthodontic patients were investigated. The findings showed that the addition of 1 % TiO_2 NPs to the orthodontic adhesive (Transbond X) in patients with supper second premolars and maxillary lateral incisors effectively reduced the counts of *S.mutans* after 6 months of orthodontic treatment without any significant difference in enamel mineral content [214]. Moustafa et al. have added 1 wt% TiO_2 NPs into the Transbond X and directly applied to the tooth surface of the Albino rat [73]. Their findings showed a significant decrease in colony counts of *S. mutans* after 3,4 and 5 weeks in modified adhesives than that of conventional adhesive. In another research, TiO_2 NPs were incorporated into the resin composite and adhesive and the findings demonstrated significant antibacterial activity against *S.mutans* after 1 month [215]. This antibacterial activity was significantly higher than that of unmodified Adper single bond 2 adhesive and Filtek 350 XT flowable composite in a time-dependent manner in patients with tooth cavities. In the next research, the effects of TiO_2-coated Nickel-Titanium (Ni-Ti) archwires on *S.mutans* and enamel mineralization were evaluated [216]. The results revealed that the adhesion of *S.mutans* on the archwires was lessened after 1 month of intraoral use in orthodontic patients due to the antibacterial properties of TiO_2 NPs compared to uncoated ones. However, the TiO_2-coated wires had a minimal role in the quality of enamel surrounding the orthodontic bracket. In a study published by Mollabashi et al., TiO_2 NPs were incorporated into the Transbond X dental composite, and the effects on the antibacterial properties against *S.mutans* and demineralization were investigated. They showed that the TiO_2-modified orthodontic composite could prevent demineralization around the bracket during orthodontic treatment after 6 months of bonding. However, the antibacterial effects were not significant [121]. This observation is an indication of an anti-caries effect rather than an antibacterial which may be due to different intra-oral conditions in patients. Although the above-mentioned clinical evidence indicated promising results, however, their clinical translation could be burdensome. Thus, the intersection of academia, industry, and regulatory agencies plays a key role. In addition, the role of industry in the acceptance of new TiO_2 NP-based dental appliances to regulatory agencies lies between the academic section and regulatory agencies which is through their expertise in commercial-scale manufacturing. From the commercial point of view, most of the TiO_2-based dental appliances did not receive regulatory approval even with positive clinical outcomes due to governmental concerns such as inappropriate design

Table 7
List of available clinical trials of TiO_2-incorporated dental appliances data retrieved from www.clinicaltrials.gov.

Dental appliance	Bacteria strain/disease	Study type	Phase	Reference
TiO_2-incorporated acrylic resin (denture)	Candida infection/denture stomatitis	Interventional	Not applicable	NCT03666195
TiO_2-modified GIC	Dental caries, pulpitis	Interventional	Phase 3	NCT04365270
TiO_2-modified acrylic resin (denture)	Candida aggregation	Interventional	Not applicable	NCT03700489
TiO_2-modified acrylic resin (denture)	Dental Anxiety	Interventional	Not applicable	NCT03006757
TiO_2-modified acrylic resin (denture)	Denture stomatitis	Interventional	Not applicable	NCT02950623
TiO_2-modified acrylic resin (denture)	Denture stomatitis	Interventional	Phase 1	NCT02950584
Stereolithographic TiO_2/PMMA composite	Mouth Edentulous Jaw Edentulous	Observational	Not provided	NCT02911038
TiO_2-modified GIC	Dental caries	Interventional	Not applicable	NCT05645029
TiO_2-modified baseplate	Gingival inflammation	Interventional	Not applicable	NCT06051487
TiO_2-reinforced bonding agent	Carious lesion	Interventional	Not applicable	NCT05744648

endpoints, and inadequate analysis methodology on clinical data. Therefore, conducting pre-clinical evaluations and getting approval from regulatory agencies are essential for the future. Besides, the potential issues that may bring about delayed regulatory approval should be avoided by companies by seeking suggestions from regulators. A summary of the list of clinical trials for TiO_2-incorporated dental appliances is shown in Table 7.

12. Conclusion

Nanotechnology is an integral part of clinical dental practice. In this review paper, the latest research advances in the application of TiO_2 NPs in dentistry were elaborated. It was shown that TiO_2 NPs are non-toxic and non-allergic to dental cells and can be used in orthodontic and endodontic dental materials. It was also discussed that their addition to conventional dental materials can enhance mechanical properties. It was shown that the concentration of TiO_2 NPs should not exceed a certain limit (5 %) as it compromises the mechanical properties of resin composite due to the aggregation and agglomeration of TiO_2 NPs acting as areas of stress concentration. The incorporation of TiO_2 NPs into dental materials also enhanced the antibacterial properties and suppressed biofilm formation both in dark and under light irradiation. Further, the incorporation of photocatalytic TiO_2 NP can develop bi-functional dental material which can not only destroy the dental plaque by the formation of phot-induced ROS but also promote remineralization simultaneously. This is particularly important in the treatment of dental caries and WSL. Finally, the TiO_2 NPs can accelerate the oxidation reactions of H_2O_2 by increasing the generation of superoxide enhancing the bleaching effect and reducing the dental sensitivity. However, vigorous *in vivo* studies are required before translating these into clinical performance and better guiding dental practitioners on these materials.

12.1. Future perspectives

In the author's opinion, TiO_2-based dental materials can hold a significant place in the future of dentistry and oral products. This is because the incorporation of TiO_2 NPs confers many advantages such as antibacterial, antibiofilm activities and enhanced mechanical properties over conventional dental materials for oral applications in dentistry. The ongoing research in this field can cause substantial changes in dental material science. For instance, the harmful effects of UV exposure to cells and tissues might not be an insurmountable challenge as strategies such as inducing oxygen deficiency in TiO_2 NPs (TiO_{2-x}) hydrogen-assisted magnesiothermic reduction (HAMR) process can narrow the bandgap and extend the optical absorbance to visible light region. This leads to a better photocatalytic performance which greatly extends their potential biomedical application. Thus, the future direction of the dental application of TiO_2 NPs is to conduct long-term preclinical studies on visible-light-driven photocatalysis for bacterial elimination. In the context of oral products, there is a demand to seek alternative options of low-cost and improved performance. For instance, H_2O_2 As the common tooth-whitening agent causes morphological change in dentin and enamel together with soft tissue irritation. In contrast, The TiO_2 NPs can firmly adhere to enamel and cover larger surfaces of teeth resulting in enhanced protection and whitening effects. Therefore, they can be potentially used in the next generation of oral care products.

12.2. Limitations

The current study has some limitations. The effect of different filler loading on the physical properties of a dental composite including solubility, and wettability needs to be studied by conducting further work. The testing of the antibacterial performance of TiO_2-based orthodontic and endodontic dental materials was limited to *S.mutans*. Thus, it might be useful as future work to take a look at the antibacterial effects on other species of cariogenic bacteria and the inhibitory role on biofilm formation. Furthermore, the behaviour of TiO_2-based orthodontic and endodontic materials needs to be investigated in real-world conditions or simulated oral environments and long-term exposure. Although recent studies have found no allergic reaction for TiO_2-containing orthodontic appliances after six months in patients [213] and the Ti release in the salvia of patients from TiO_2-containing dental composite was negligible after three months [62,121], however, the nano-toxicological studies are still deficient which necessitates further studies to collect toxicity data in the oral cavity in the long-term period before acquiring widespread acceptance and application in the dental industry.

CRediT authorship contribution statement

Hossein Mohammadi: Writing – original draft, Investigation. **Hedaiat Moradpoor:** Writing – review & editing. **Salmia Beddu:** Writing – review & editing. **Hamid Reza Mozaffari:** Writing – review & editing. **Roohollah Sharifi:** Writing – review & editing. **Razieh Rezaei:** Writing – review & editing. **Nima Fallahnia:** Writing – review & editing. **Mona Ebadi:** Writing – review & editing. **Saiful Amri Mazlan:** Writing – review & editing. **Mohsen Safaei:** Writing – review & editing, Supervision, Conceptualization.

Data availability

The data used to support the findings of this study are included in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e42169.

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