

How TiO₂ Nanomaterials are Emerging as Key Therapeutics in Stomatology

Junnan Qi^{1,2,*}, Huimin Liu^{3,*}, Huen Li^{1,2}, Haofeng Liu^{1,2}, Yawen Wang^{1,2}, Chunru Kong^{1,2}, Li Fu⁴, Bei Chang^{1,2}

¹Hospital of Stomatology, Jilin Provincial Key Laboratory of Tooth Development and Bone Remodeling, Jilin University, Changchun, 130021, People's Republic of China; ²Hospital of Stomatology, Department of Pediatric Dentistry, Jilin University, Changchun, 130021, People's Republic of China; ³Beijing Shunyi Hospital, Stomatology Department, Beijing, 101300, People's Republic of China; ⁴Hospital of Stomatology, Department of Oral Implantology, Jilin University, Changchun, 130021, People's Republic of China

*These authors contributed equally to this work

Correspondence: Li Fu; Bei Chang, Hospital of Stomatology, Jilin University, 1500 Qinghua Road, Changchun, 130021, People's Republic of China, Email fuli1127@jlu.edu.cn; bchang@jlu.edu.cn

Abstract: Conventional treatments for oral diseases—such as cancer and tissue defects—are often limited by high invasiveness, suboptimal efficacy, and drug resistance. In recent years, titanium dioxide (TiO₂) nanomaterials have demonstrated remarkable therapeutic potential in the field of oral medicine. This review systematically evaluates the current applications and future prospects of TiO₂ and its reduced form (TiO_{2-x}) nanomaterials across six major domains: cancer diagnosis and therapy, antibacterial treatment, tissue regeneration, drug delivery, restorative dental materials, and teeth whitening, based on an extensive literature search of databases including PubMed and Web of Science. The findings reveal that TiO₂ nanomaterials exhibit exceptional multifunctionality through various mechanisms: (1) surface-enhanced Raman spectroscopy (SERS) substrates achieve 100% sensitivity and 95.83% specificity in diagnosing oral squamous cell carcinoma; (2) reactive oxygen species (ROS)-mediated antibacterial efficiency exceeds 99% against key oral pathogens; (3) modified implant surfaces show a 1.5-fold increase in bone-implant contact; and (4) the incorporation of only 0.06% TiO₂ nanoparticles enhances resin hardness by over 200%. Notably, TiO_{2-x} exhibits visible/near-infrared responsiveness, photothermal conversion capacity, and peroxidase-like activity, enabling 12% H₂O₂-based whitening outcomes comparable to commercial 40% H₂O₂ products. Collectively, TiO₂-based nanomaterials represent a paradigm shift toward precision oral medicine, owing to their excellent biocompatibility, multifunctional therapeutic mechanisms, and broad application potential. Nonetheless, successful clinical translation requires addressing critical challenges, including synthesis standardization, comprehensive biosafety evaluation, optimization of interfacial bonding strength, and the development of regulatory frameworks tailored to dental nanomedicine.

Keywords: TiO₂ nanomaterials, stomatology, photodynamic therapy, dental biomaterials, nanozyme activity

Introduction

The oral cavity is characterized by its open, dynamic, and complex nature, rendering it highly vulnerable to a range of physical, chemical, and biological insults. These factors contribute to the high incidence of oral conditions, including trauma, neoplasms, and infections such as dental caries, pulpitis, and periodontal diseases. Although conventional therapeutic approaches in dentistry remain central to clinical practice, they are accompanied by significant limitations across diagnostic, therapeutic, antimicrobial, and restorative domains. For diagnosis, histopathological examination remains the gold standard for oral cancer but suffers from invasiveness, long processing time, and heavy reliance on skilled personnel—often delaying early detection.¹ Surgical resection, while primary for oral malignancies, is associated with high trauma, recurrence, and metastasis rates.² Antibiotic-based treatment of oral infections faces mounting challenges, including bacterial resistance, systemic side effects, and limited penetration through biofilms.³ Traditional mechanical debridement techniques, such as scaling and root planing, often fail to reach deep infections and may cause

secondary trauma.⁴ Current restorative materials, including resin composites, ceramics, and metal-based systems, face limitations in mechanical durability, esthetic outcomes, and long-term stability—leading to recurrent caries and restoration failure.³ These challenges collectively underscore the urgent need for advanced therapeutic strategies and materials with enhanced performance, multifunctionality, and clinical adaptability.

Driven by the rapid advances in nanotechnology, the design and application of nanomaterials are continuously expanding the frontiers of biomedical research and clinical practice. In recent years, a broad spectrum of nanomaterials—including carbon-based, polymeric, metallic, and metal oxide systems—have been developed for biomedical applications, demonstrating significant potential. However, each class of nanomaterials possesses distinct advantages and limitations. Carbon-based materials, such as graphene and carbon quantum dots, exhibit photoreactivity and the ability to induce oxidative stress, yet concerns remain regarding their long-term toxicity and inconsistent antibacterial performance.⁵ Polymeric nanomaterials are widely recognized for their excellent biocompatibility, but they often require co-administration with other agents to achieve adequate therapeutic efficacy.⁶ Noble metal nanoparticles (eg, gold and silver) show promising therapeutic potential; however, their high cost and potential cytotoxicity present substantial barriers to large-scale clinical adoption. Zinc oxide (ZnO), a classical photocatalyst, has demonstrated beneficial effects in infection control and tissue regeneration, but its chemical instability under physiological conditions limits its practical utility.⁷ In contrast, TiO₂ nanomaterials offer a unique combination of high photocatalytic activity, chemical inertness, excellent biocompatibility, and cost-effectiveness, positioning them as one of the most promising nanoplatforms for biomedical applications to date.⁸

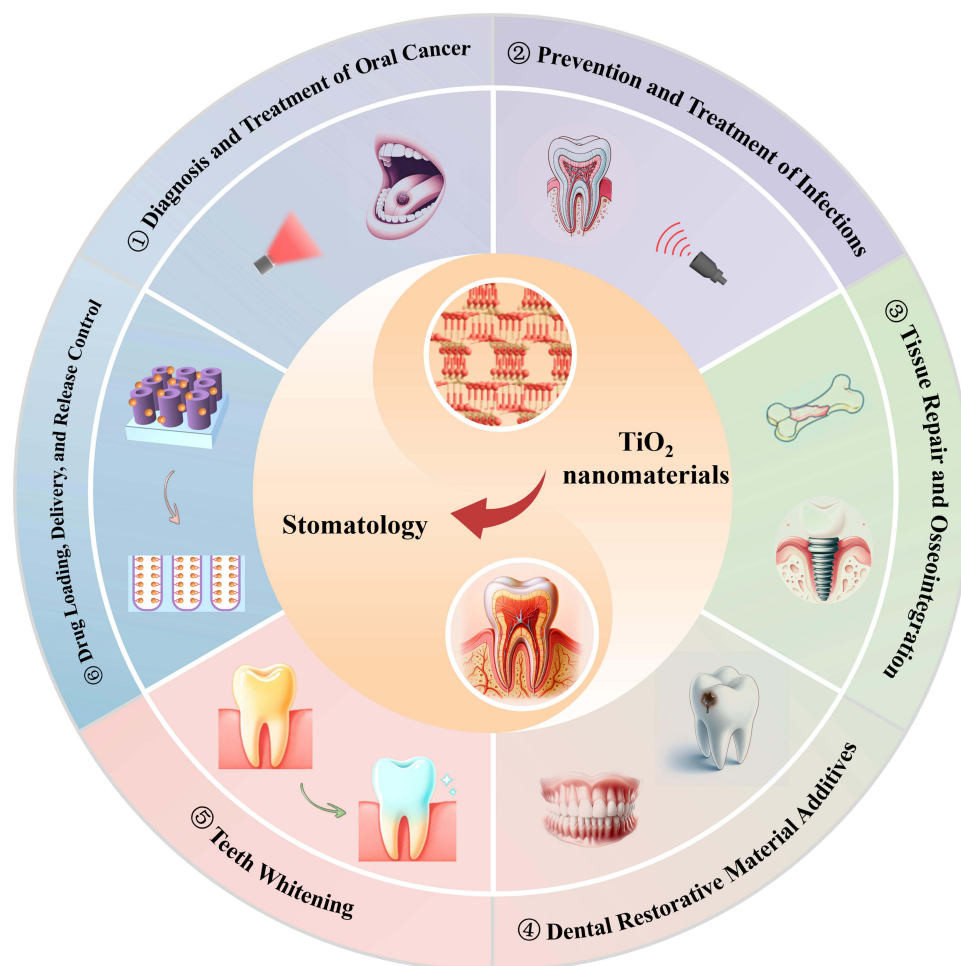
TiO₂, as a versatile and multifunctional nanomaterial, has demonstrated significant promise in the field of oral medicine. As early as the 1980s, pioneering studies by Matsunaga et al and Fujishima et al highlighted the potent cytotoxic effects of TiO₂ against both tumor and bacterial cells.^{9,10} In recent years, accumulating evidence has reinforced the broad potential of TiO₂ nanomaterials as innovative alternatives to conventional therapeutic modalities in oral healthcare. These nanomaterials have been applied across a wide spectrum of oral medical applications, including: diagnostic sensing for oral cancer; use as standalone agents or in composites for photodynamic therapy (PDT) and sonodynamic therapy (SDT) targeting tumors and bacterial infections; engineering into diverse nanostructures to modulate immune and regenerative cellular responses for guided tissue repair; surface modification of dental implants to enhance osseointegration; drug delivery and controlled-release systems; and functional enhancement of dental restorative materials such as composite resins.^{11–16} Despite the broad and versatile biomedical potential of TiO₂ in oral applications, its clinical translation still faces several inherent limitations, including its reliance on ultraviolet (UV) activation, low ROS yield in complex biological environments, and unresolved concerns regarding long-term biosafety. In response to the aforementioned limitations, a modified form of TiO₂—reduced TiO₂ (TiO_{2-x})—was first introduced in 2011.¹⁷ Characterized by the presence of Ti³⁺ species and oxygen vacancies, TiO_{2-x} exhibits a range of unique physicochemical properties, including peroxidase-mimetic activity and intrinsic photothermal effects.^{18,19} These features not only expand the utility of TiO₂-based materials in applications such as PDT, but also enable innovative functionalities in areas like photothermal antibacterial strategies and tooth whitening^{20,21} (Scheme 1 illustrates the multifaceted biomedical applications of TiO₂-based nanomaterials in stomatology).

Despite the growing global interest in TiO₂ nanomaterials and their demonstrated therapeutic efficacy in oral medicine, comprehensive reviews that systematically summarize their applications and underlying mechanisms remain limited. This review seeks to address this gap by critically examining the material properties, advanced biomedical applications, and mechanistic insights of TiO₂-based nanomaterials within the context of oral health. Moreover, we explore the current challenges hindering clinical translation and outline key directions for future research. By offering a thorough and focused analysis, this review aims to provide both researchers and clinicians with an integrated understanding of the opportunities and barriers associated with TiO₂-based nanoplatforms, ultimately advancing the development of innovative strategies in oral healthcare.

How TiO₂ Nanomaterials are Emerging as New Therapeutics?

Physicochemical Properties

TiO₂, a prominent metal oxide, has garnered considerable attention owing to its cost-effectiveness, structural robustness, low intrinsic toxicity, and strong photocatalytic activity.²⁷ It has been widely utilized as an additive in commercial



Scheme 1 Multifunctional applications of TiO_2 nanomaterials in stomatology. TiO_2 -based nanostructures exhibit broad clinical potential across six key domains in oral medicine:

1. Diagnosis and treatment of oral cancer – serving as SERS-active platforms for early detection and as photo/sonosensitive agents in photodynamic and sonodynamic therapies;^{12,22}
2. Antibacterial and anti-infective therapy – generating ROS via photocatalysis to eliminate pathogens and disrupt biofilms;²³
3. Tissue regeneration and osseointegration – enhancing bone–implant integration and mechanical stability through structural design and surface modification strategies;²⁴
4. Dental restorative material enhancement – improving the mechanical strength, biocompatibility, and longevity of composite resin-based materials;²⁵
5. Tooth whitening – enabling efficient bleaching under low-peroxide conditions while minimizing enamel damage;²⁰
6. Drug delivery and controlled release – supporting targeted, stimuli-responsive therapeutic systems to improve treatment precision.²⁶

products such as sunscreens, paints, and rubbers.²⁸ In addition, TiO_2 exhibits a range of favorable physicochemical properties—including high mechanical strength, hardness, hydrophilicity, self-cleaning capability, and a distinct pure white appearance—which collectively position it as a promising candidate for biomedical applications, particularly in the development of oral restorative materials.^{29–31}

The physicochemical attributes of TiO_2 align well with the stringent requirements for modern dental materials. When incorporated into next-generation oral repair systems such as dental filling composites or adhesives, TiO_2 not only enhances the aesthetic and mechanical performance of the material but also provides resilience against the chemically dynamic and mechanically demanding conditions of the oral cavity.^{32,33} These properties translate into improved clinical outcomes and prolonged material durability.

Nanostructure Fabrication Methods

The synthesis of TiO_2 nanomaterials generally follows two strategic paradigms: a bottom-up approach, wherein nanostructures are constructed from atomic or molecular precursors via homogeneous nucleation and controlled growth;

and a top-down approach, which involves the physical or chemical disintegration of bulk materials into nanoscale architectures.³⁴ For instance, the hydrothermal method enables the production of TiO₂ nanoparticles or nanosheets with controlled size and morphology,^{35,36} while electrochemical anodization has been widely employed to fabricate highly ordered TiO₂ nanotube arrays.³⁷ Notably, although the aforementioned fabrication techniques offer excellent controllability in laboratory settings, several challenges remain regarding their practical implementation. For instance, the hydrothermal method requires prolonged exposure to high temperature and pressure, resulting in high energy consumption and limited yield. Similarly, electrochemical anodization entails considerable equipment and electrolyte costs, making the overall process economically demanding. In addition, achieving batch-to-batch consistency and scalable production of high-quality nanostructures remains a critical bottleneck. While TiO₂ itself is relatively inexpensive, subsequent surface modification and functionalization steps substantially increase the total manufacturing cost. Therefore, advancing clinical translation requires a careful balance between structural precision, functional performance, and economic feasibility.

Despite these limitations, the diverse architectures of TiO₂ nanostructures offer substantial promise for biomedical applications. Their intrinsic advantages—including facile fabrication, tunable dimensions, large specific surface area, high modifiability, and strong loading capacity—render them ideal platforms for drug delivery systems.³⁸ By precisely tailoring their physical parameters (eg, diameter, length) and surface chemical characteristics (eg, surface charge, hydrophilicity), and further modifying their surfaces with functional polymers such as PLGA or chitosan, TiO₂ nanostructures enable controlled and targeted drug release.^{39,40} Additionally, stimuli-responsive strategies—triggered by magnetic fields, pH changes, or light—provide innovative avenues for achieving spatiotemporal control over therapeutic delivery.^{41,42}

Beyond drug delivery, TiO₂ exhibits excellent mechanical strength, corrosion resistance, and inherent biocompatibility, making it a promising material for implantable biomedical devices.⁴³ Rationally engineered TiO₂ nanostructures can promote the adhesion, proliferation, and functional modulation of various cell types involved in immune regulation, osteogenesis, and soft tissue regeneration.^{44–46} Furthermore, the interconnected porosity of certain three-dimensional TiO₂ architectures facilitates the efficient exchange of nutrients and metabolic waste, thereby supporting the regeneration of hard tissues.^{47,48} Within the domain of oral implantology, such nanostructures may significantly enhance implant osseointegration and long-term clinical performance.²¹

Photocatalytic Mechanism and Principles

As a classic photocatalyst, when TiO₂ is irradiated with photons with energy higher than its bandgap width, electrons in the valence band transition to the conduction band. This process leaves positively charged photogenerated holes in the valence band and negatively charged photoelectrons in the conduction band.⁴⁹ These photoelectrons and photogenerated holes react respectively with oxygen molecules, water molecules, or hydroxide ions to produce ROS such as hydrogen peroxide (H₂O₂), hydroxyl radicals (\cdot OH), and superoxide anions (\cdot O₂⁻).⁵⁰ These ROS can interact with cellular membranes or molecules within cells, thereby inducing apoptosis.⁵¹ In biomedical applications, this ROS-mediated oxidative stress forms the mechanistic basis of PDT.

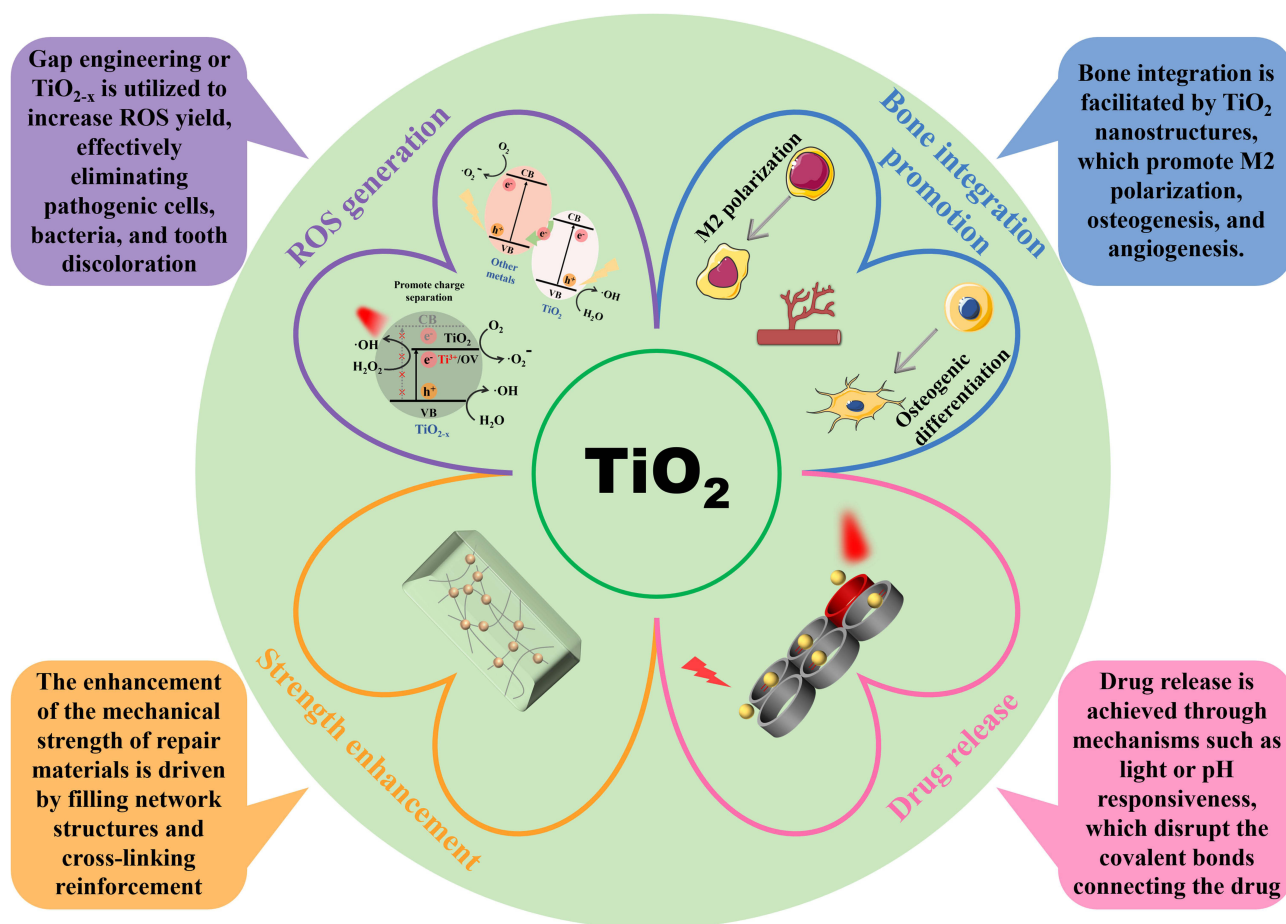
However, the clinical translation of TiO₂-based therapies is hampered by several intrinsic limitations. First, its wide bandgap restricts excitation to UV light, which suffers from poor tissue penetration and can induce phototoxicity.^{52,53} In addition, TiO₂ exhibits a high recombination rate of photoinduced electron–hole pairs and relatively low ROS quantum yield, both of which diminish therapeutic efficacy.⁵⁴

To address these challenges, several material engineering strategies have been developed. One foundational approach involves coupling TiO₂ with upconversion nanoparticles (UCNPs), such as NaYF₄:Yb,Tm. These UCNPs absorb near-infrared (NIR) light—which penetrates deeper into biological tissues—and emit UV light that overlaps with TiO₂'s absorption spectrum, thereby extending its activation depth.⁵⁵ However, this strategy primarily addresses the limitation of excitation depth without significantly enhancing TiO₂'s inherent photocatalytic efficiency and is further constrained by the low quantum yield of UCNPs. More advanced strategies focus on bandgap engineering, such as metal or non-metal doping to form TiO₂-based heterojunctions. These modifications red-shift the absorption spectrum, improve light harvesting, and facilitate charge separation while suppressing electron–hole recombination. Consequently, these systems exhibit elevated ROS generation and enhanced antibacterial or antitumor efficacy.⁵⁶

Despite these improvements, the use of multi-component systems introduces challenges related to synthetic complexity, structural stability, and long-term biosafety in biomedical applications. In response, TiO_{2-x} has emerged as a streamlined and promising alternative. Its enhanced physicochemical and biological properties will be discussed in the following section.

Enhanced Properties of TiO_{2-x}

In consideration of material simplicity, synthesis efficiency, long-term biological stability, and the reduction of potential *in vivo* side effects, reduced titanium dioxide (TiO_{2-x}) nanomaterials have attracted increasing research interest.^{57,58} Derived from TiO_2 precursors via methods such as hydrogenation or laser treatment, TiO_{2-x} features oxygen vacancies within its lattice structure that introduce defect states, effectively narrowing its bandgap. This modification significantly enhances its ability to absorb visible and even NIR light.^{57,59} Moreover, the heterogeneous interface between the amorphous shell and crystalline core of TiO_{2-x} facilitates synergistic charge transfer, enabling more efficient electron transport and rapid conduction. This contributes to improved redox reactivity and a higher quantum yield of ROS.⁶⁰ Additionally, the presence of Ti^{3+} ions and oxygen vacancies imparts intrinsic photothermal effects and peroxidase-like catalytic activity to TiO_{2-x} , further expanding its biomedical utility (Scheme 2c).^{61,62} Notably, these properties are closely linked to the specific synthetic pathways used. Collectively, these advances lay a robust foundation for harnessing TiO_2 -based photocatalytic activity in oral medicine. Among the various engineered forms, TiO_{2-x} nanomaterials stand out for their enhanced stability, superior photocatalytic performance, and emerging multifunctional capabilities—positioning them as a highly promising direction for future investigation. The mechanisms underlying the various applications of TiO_2 -based nanomaterials are illustrated in Scheme 2.



Scheme 2 Mechanisms of TiO_2 in Different Application Scenarios.

Structure–Function Characterization

The physicochemical characteristics of TiO₂-based nanomaterials are closely linked to their biomedical performance, and thus require systematic characterization. Transmission electron microscopy (TEM) reveals that pristine TiO₂ typically exhibits a well-ordered crystalline structure, while TiO_{2-x} shows a disordered shell induced by oxygen vacancy formation, which correlates with enhanced photocatalytic activity.⁶³ X-ray diffraction (XRD) patterns of TiO₂ generally display strong anatase or rutile phases with sharp peaks, whereas TiO_{2-x} exhibits peak broadening, reduced intensity, and occasional phase transitions, reflecting increased lattice distortion and defect formation.⁶⁴ X-ray photoelectron spectroscopy (XPS) of TiO₂ shows Ti⁴⁺ as the dominant oxidation state, while TiO_{2-x} presents additional Ti³⁺ peaks, confirming successful reduction and influencing peroxidase-like activity and antibacterial effects.⁶⁵ Electron paramagnetic resonance (EPR), typically silent for stoichiometric TiO₂, becomes active in TiO_{2-x} due to the emergence of unpaired electrons associated with oxygen vacancies.⁶⁶ UV–vis–NIR absorption spectroscopy reveals that TiO₂ absorbs mainly in the UV region, while TiO_{2-x} exhibits red-shifted absorption into the visible and NIR regions, enabling applications in deep-tissue phototherapy.⁶⁷ Electrochemical analysis demonstrates that TiO_{2-x} has significantly reduced interfacial resistance and stronger photocurrent response compared to TiO₂, suggesting improved charge separation and enhanced ROS generation potential.⁶⁸ Other techniques such as FTIR, Raman spectroscopy, and photoluminescence provide further insights into surface functional groups, lattice disorder, and electron–hole recombination behavior, but are not detailed here due to space limitations.

While TiO₂ exhibits excellent physicochemical properties, its long-term toxicity and biocompatibility remain areas that require further investigation. These issues are thoroughly discussed in Section Biocompatibility, where we delve into the current limitations in clinical safety data and the need for additional studies to assess its long-term effects.

What are the Key Applications of TiO₂ in Stomatology?

TiO₂ Nanomaterials in Oral Cancer Diagnosis and Therapy

Diagnostic Applications of TiO₂ Nanomaterials in Oral Cancer

Oral cancer currently ranks sixth in global cancer incidence. Traditional treatment primarily relies on surgical resection, often combined with radiotherapy and chemotherapy.⁶⁹ Although these comprehensive approaches can achieve partial therapeutic efficacy, they are insufficient to ensure complete eradication of malignant cells. The 5-year survival rate for oral cancer remains below 50%, and patients frequently face reduced quality of life, along with high risks of recurrence and metastasis.⁷⁰ These challenges underscore the critical importance of early detection and highlight the urgent need for more effective and minimally invasive diagnostic and therapeutic strategies.

Histopathological analysis remains the clinical gold standard for early cancer diagnosis.⁷¹ However, its invasive nature, time-intensive procedures, and dependence on skilled personnel severely limit its utility for routine screening and early intervention.^{72,73} In this context, researchers have been actively pursuing rapid, accurate, and noninvasive diagnostic alternatives. Raman spectroscopy technology based on TiO₂ nanomaterials is used for the diagnosis of oral cancer, primarily leveraging the fingerprint recognition function of Raman spectroscopy.⁷⁴ This technique provides information on the structure and pathological state of biomolecules through molecular vibrational energy levels. Changes in cellular components in cancer can be detected through Raman fingerprint spectra, improving the specificity and sensitivity of the detection.⁷⁵ Nevertheless, conventional Raman spectroscopy suffers from inherently low scattering cross-sections and significant interference from tissue autofluorescence, necessitating prolonged signal integration times and the use of costly background-free optical substrates—factors that hinder clinical translation. These limitations can be addressed by surface-enhanced Raman scattering (SERS), wherein Raman signals are significantly amplified when analyte molecules are adsorbed near noble metal surfaces such as silver (Ag) or gold (Au).⁷⁶ By sputter-coating Ag nanoparticles onto TiO₂ nanostructures to generate “hot spots”, researchers have developed hybrid SERS substrates that synergistically combine the highly tunable architectures of TiO₂ with the plasmonic enhancement properties of Ag, rendering them highly effective for biomedical sensing.⁷⁷ In addition, TiO₂ offers inherent advantages including excellent biocompatibility, chemical stability, mechanical strength, low cost, and scalability—making it a compelling platform for point-of-care diagnostics.

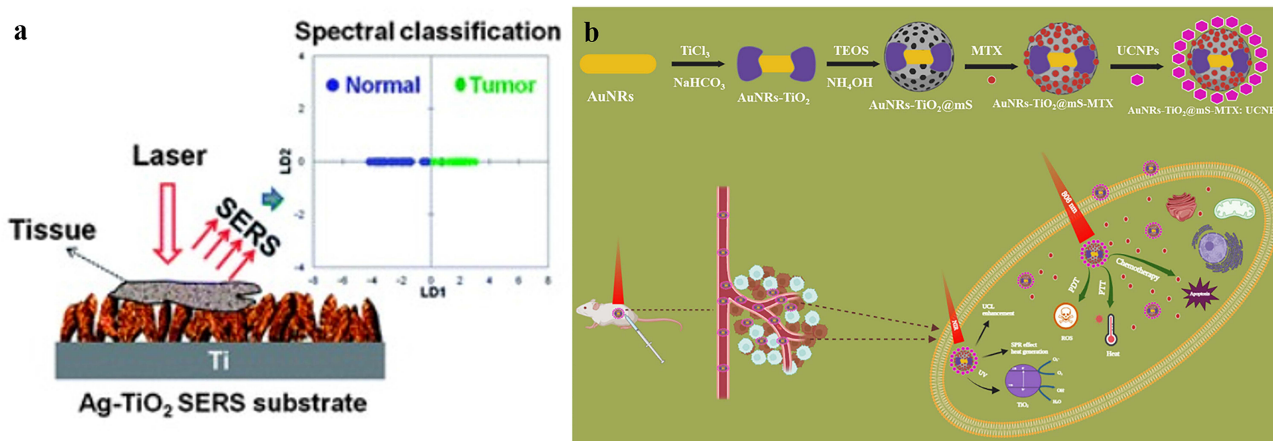


Figure 1 (a) Ag-TiO₂ SERS substrate used for the analysis of oral squamous cell carcinoma tissue sections, demonstrating ideal sensitivity and specificity. Reproduced with permission from Girish CM, Iyer S, Thankappan K, et al. Rapid detection of oral cancer using Ag-TiO₂ nanostructured surface-enhanced Raman spectroscopic substrates. *J Mater Chem B*. 2014;2(8):989–998. Royal Society of Chemistry 2014.¹¹ (b) Synergistic effect of PDT/PTT/Chemotherapy using Au NRs-TiO₂@mS-MTX:UCNP nanocomposites for effective treatment of oral squamous cell carcinoma. Reproduced with permission from Dash P, Thirumurugan S, Tseng C-L, et al. Synthesis of methotrexate-loaded dumbbell-shaped titanium dioxide/gold nanorods coated with mesoporous silica and decorated with upconversion nanoparticles for near-infrared-driven trimodal cancer treatment. *ACS Appl Mater Interfaces*. 2023;15(28):33335–33347. © American Chemical Society 2023.⁷⁸

Manzoor et al fabricated a SERS-active substrate by hydrothermally growing TiO₂ nanostructures and subsequently depositing Ag nanoparticles onto their surfaces (Figure 1a). This sensor achieved a remarkable 100% sensitivity and 95.83% specificity in detecting tongue squamous cell carcinoma across 56 clinical samples, with an average analysis time of only 15–20 minutes—demonstrating the feasibility of SERS-based approaches for rapid and accurate cancer screening.¹¹ In a subsequent study, the same group engineered an innovative Raman-sensing catheter device, wherein the key detection unit consisted of leaf-shaped TiO₂ nanostructures coated with Ag nanoparticles.²² The closely packed configuration of TiO₂ nanosheets and Ag particles facilitated the generation of a high density of Raman hotspots, enabling effective differentiation of normal, precancerous, and malignant tissues. Applied to 37 clinical samples—including oral squamous cell carcinoma (OSCC), verrucous carcinoma, leukoplakia, and healthy controls—the device achieved an overall diagnostic accuracy of 97.24%, with a remarkable 97.84% accuracy in grading OSCC. These results collectively underscore the transformative potential of TiO₂-based SERS systems for the noninvasive, real-time, and high-precision detection of oral malignancies.

Despite the tremendous potential of SERS in the early diagnosis of oral cancer, several challenges hinder its clinical translation. One major limitation is the strong autofluorescence emitted by oral tissues, which can significantly interfere with the detection and interpretation of Raman signals. To address this issue, a variety of strategies have been proposed, including the use of NIR excitation sources to reduce background signals⁷⁹ and time-gated detection techniques to temporally separate fast Raman responses from delayed fluorescence.⁸⁰ Within the TiO₂ material family, TiO_{2-x} has emerged as a promising candidate for SERS substrates due to its extended NIR absorption, which may enhance the signal-to-noise ratio. Furthermore, the lack of standardized strategies and practical pathways for the clinical translation of SERS systems remains a major bottleneck. Future efforts should focus on establishing robust clinical validation protocols and promoting large-scale, cost-effective manufacturing—such as the development of reusable and reproducible SERS substrates—will be essential to facilitate broader biomedical adoption.⁸¹

Therapeutic Applications of TiO₂ Nanomaterials in Oral Cancer

In recent years, PDT has garnered considerable attention in cancer treatment owing to its simplicity, minimally invasive nature, and therapeutic efficacy. PDT utilizes light of specific wavelengths to activate photosensitizers, generating cytotoxic ROS within tumor cells, and has demonstrated promising outcomes across various malignancies.⁸² As a highly promising photosensitizer, titanium dioxide (TiO₂) has been increasingly applied in oncological contexts, including recent advances in oral cancer therapy. One notable example involves the development of Au NRs-TiO₂@mS-methotrexate (MTX):UCNP nanocomposites.⁷⁸ This system employs a classical upconversion nanoparticle UCNP-TiO₂ model, allowing TiO₂ to achieve deep-tissue PDT under NIR irradiation. Concurrently, the visible light emitted by UCNP is absorbed by gold nanorods (Au NRs), enabling a strong

photothermal therapy (PTT) effect. The thermal electrons generated by Au NRs further enhance TiO₂-mediated PDT. Additionally, the incorporated chemotherapeutic agent MTX inhibits tumor proliferation (Figure 1b). In vitro studies confirmed that under NIR laser irradiation, this nanoplatform exhibited a synergistic effect, effectively eradicating oral squamous carcinoma (HSC-3) cells. In a murine tumor model, after 16 days of treatment, the tumor volume in the Au NRs-TiO₂@mS-MTX:UCNP group was reduced to less than one-quarter of that in the control group.

The primary anticancer mechanism of TiO₂ involves ROS generation upon light exposure. TiO₂ NPs can be internalized by cells and accumulate in lysosomes, where ROS-mediated disruption of the lysosomal membrane leads to leakage of its contents and consequent cellular damage. ROS can also impair mitochondrial function, triggering apoptosis or necrosis. Moreover, TiO₂-mediated PDT has been shown to induce pyroptosis—a form of programmed cell death characterized by inflammasome activation, gasdermin D (GSDMD) cleavage, and cell membrane rupture. This process results in the release of damage-associated molecular patterns (DAMPs), such as HMGB1 and IL-24, which activate immune cells and enhance antitumor immunity.¹² Collectively, TiO₂ nanomaterials exert both direct cytotoxic effects and indirect immunomodulatory functions, underscoring their therapeutic promise in oral cancer management.

Given the limited light penetration and photosensitivity constraints within biological tissues, SDT has emerged as a complementary approach. Like PDT, SDT relies on the activation of sonosensitizers by ultrasound to generate ROS, leading to tumor cell apoptosis and necrosis.⁸³ Compared with light, ultrasound offers deeper tissue penetration and is associated with lower cost and enhanced safety, attributes that have led to its widespread use in clinical imaging.⁸⁴ Owing to its high catalytic activity and physicochemical stability under both photonic and ultrasonic stimulation, TiO₂ has become one of the most widely explored semiconductor materials in SDT.^{85,86} During SDT, the cavitation effect induced by ultrasound generates microbubbles, which collapse to produce shock waves, localized high temperatures, and sonoluminescence—all of which can damage tumor tissue. Importantly, the sonoluminescence spectrum overlaps with the absorption spectrum of TiO₂, facilitating electron excitation and the formation of electron–hole pairs. These carriers react with oxygen and water molecules to produce ROS, which then attack cellular membranes, proteins, and nucleic acids.⁸⁷ Moosavi et al investigated TiO₂-mediated SDT in oral squamous carcinoma models and found that under 73 W/cm² ultrasound irradiation, the survival rate of cancer cells was reduced by more than 50% compared to controls.⁸⁸ Histopathological analysis confirmed significant hemorrhage and necrosis in tumor tissues treated with TiO₂ and ultrasound, and the therapeutic effect correlated positively with TiO₂ concentration. These findings establish a strong rationale for the future clinical application of minimally invasive or non-invasive SDT-based treatments for oral malignancies.

In summary, although conventional modalities such as surgery, radiotherapy, and chemotherapy remain the standard of care for oral cancer, recent progress in early diagnosis and innovative therapeutic approaches—including PDT and SDT—offers promising directions for clinical translation. However, studies on TiO₂'s role in oral cancer remain limited, primarily due to reliance on in vitro and small-animal models. The field lacks large-scale, multicenter clinical trials and standardized diagnostic protocols. Moreover, long-term biosafety concerns regarding TiO₂ exposure remain inadequately addressed. Overcoming these barriers is essential to fully realize the clinical potential of TiO₂ nanomaterials, enabling more effective and less invasive cancer treatment strategies while improving patient quality of life.

TiO₂ Nanomaterials in the Prevention and Treatment of Oral Infections

The oral cavity, as a complex microecosystem harboring diverse microbial populations, is particularly susceptible to bacterial infections, which can lead to a spectrum of diseases such as periodontitis, dental caries, pulpitis, and periapical periodontitis. Globally, approximately 60%–90% of school-aged children are affected by dental caries, and nearly half of the adult population suffers from at least one tooth with periapical periodontitis. Periodontitis alone has a global prevalence of nearly 10%, posing a serious public health burden worldwide.^{89–91} Left untreated, dental caries can progress gradually into irreversible pulpitis and periapical periodontitis. Moreover, inadequate removal of bacterial biofilms during root canal therapy is a common cause of endodontic treatment failure. For patients who experience tooth loss due to periodontitis or periapical pathology, dental implants have become increasingly preferred for oral rehabilitation—yet this trend has also contributed to a rising incidence of peri-implantitis.

Although antibiotics remain the primary therapeutic strategy for infectious diseases, the growing prevalence of antibiotic resistance and the protective nature of bacterial biofilms significantly complicate treatment outcomes.³ In

diseases such as periodontitis and peri-implantitis, conventional instruments often fail to eliminate bacterial biofilms located deep within periodontal pockets, risking secondary trauma and insufficient debridement.⁹² Orthodontic patients are also at elevated risk for both caries and periodontal disease, and standard oral hygiene measures frequently fall short in eliminating plaque biofilms localized around brackets and wires.^{93,94} These challenges highlight the urgent need for novel, minimally invasive, and highly effective antimicrobial strategies.

TiO₂ nanomaterials, as potent antibacterial metal oxides, have attracted extensive attention. Their bactericidal activity has been validated against common Gram-positive and Gram-negative strains, including *Escherichia coli* and *Staphylococcus aureus*, as well as key oral pathogens such as *Porphyromonas gingivalis* and *Fusobacterium nucleatum*.^{13,95} Accordingly, TiO₂ nanomaterials are considered promising candidates for the treatment of oral infectious diseases.

TiO₂-mediated PDT and SDT antibacterial strategies primarily function through the generation of ROS. These reactive species not only damage bacterial proteins and DNA but also suppress the expression of virulence factors in key oral pathogens. For example, PDT has been shown to reduce the expression of the *FimA* gene (encoding fimbrial proteins related to bacterial adhesion and invasion), *RgpA* and *RgpB* (encoding gingipains involved in tissue degradation), and *Kgp* (a protease implicated in host tissue destruction) in *P. gingivalis*.^{96–98} Additionally, ROS disrupt bacterial ATP production, impair ribosomal activity, and interfere with the tricarboxylic acid (TCA) cycle—mechanisms that collectively impair bacterial viability and pathogenicity.⁹⁹ These multifaceted antimicrobial actions support the utility of TiO₂ nanomaterials in combating biofilm-associated oral infections.

TiO₂ Nanomaterials in Dental Caries Prevention and Treatment

Resin-based composites are widely used for the restoration of carious lesions. However, microleakage and residual bacterial contamination around restorations can still lead to secondary caries and treatment failure.¹⁰⁰ To address these issues and enhance the therapeutic durability of restorations, researchers have explored novel antibacterial composite materials. Wang et al developed a TiO₂/hydroxyapatite composite which, when irradiated with dental curing lights (385–515 nm), exhibited potent bactericidal activity against *Streptococcus mutans*. Furthermore, it suppressed biofilm formation and promoted remineralization through the release of calcium and phosphate ions.¹⁰¹ Separately, Andrew et al incorporated nitrogen-doped TiO₂ (N-TiO₂) nanoparticles into dental resins. Upon stimulation with 480 nm blue light, these TiO_{2-x}-modified resins generated ROS that significantly inhibited *S. mutans* proliferation.¹⁰²

TiO₂ Nanomaterials in Endodontic Infection Treatment

Irrigation is a critical step in endodontic therapy. While sodium hypochlorite (NaClO) is a widely used irrigant, higher concentrations can induce severe cytotoxicity and tissue damage.¹⁰³ To overcome this, Xu et al proposed a novel irrigation system combining TiO_{2-x} nanomaterials with a low-concentration NaClO solution (0.5%). Under visible light irradiation, this system rapidly generated ROS and active chlorine species, achieving 99.3% and 100% inhibition of planktonic and biofilm forms of *Enterococcus faecalis*—a resilient species often implicated in persistent root canal infections—within 5 minutes of treatment. Notably, this antibacterial effect approached that of 3% NaClO while maintaining efficient pulp tissue dissolution (Figure 2a).²³

TiO₂ Nanomaterials in the Treatment of Periodontitis

In PDT for periodontitis, Qi et al employed UCNPs to indirectly activate TiO₂ for ROS generation. Upon excitation with 980 nm NIR light, this system facilitated deep tissue penetration, significantly reducing bacterial biofilm colony counts by approximately three orders of magnitude—surpassing both the negative control and conventional PDT treatment groups (Figure 2b).¹⁰⁴ Nonetheless, the limited ROS yield and wide bandgap of TiO₂ continue to constrain its antibacterial efficacy.

Recent studies suggest that TiO_{2-x} exhibits enhanced photocatalytic activity and superior photothermal performance. Tan et al developed Ag-TiO_{2-x}@alginate (ATA) hydrogel microspheres, which exhibited dual PDT and PTT functions under 808 nm NIR irradiation. Furthermore, low concentrations of H₂O₂ were found to stimulate the peroxidase-like activity of TiO_{2-x}, promoting ROS generation. The ATA system achieved nearly 100% bactericidal efficiency against

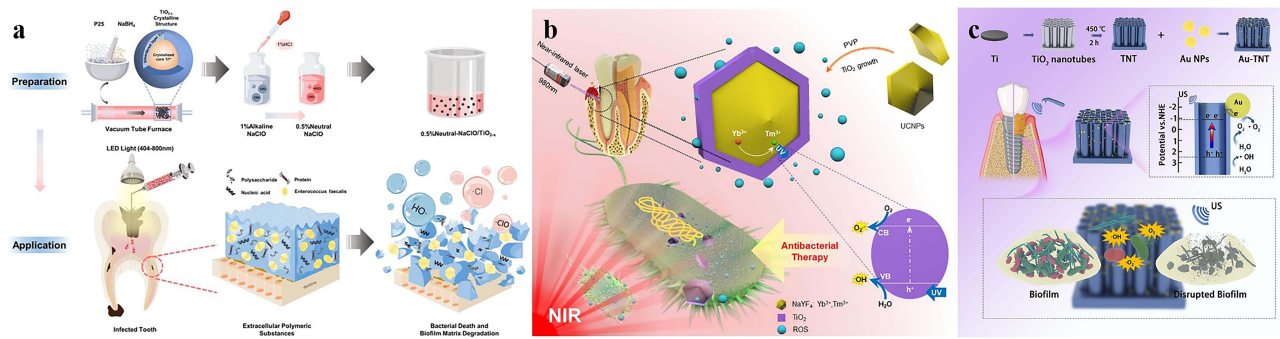


Figure 2 (a) Preparation of 0.5% NaClO/TiO_{2-x} and its application in root canal irrigation: TiO_{2-x} nanoparticles efficiently generate ROS and active chlorine under visible light exposure, significantly inhibiting endodontic pathogens. Reprinted from *Chem Engine J.* Volume 431. Xu Z, Hu X, Xie L, et al. Visible light-induced photocatalytic chlorine activation enhanced the 0.5% neutral-NaClO/TiO_{2-x} system as an efficient and safe root canal irrigant. 134119. © Elsevier B.V. 2022, with permission from Elsevier.²³ (b) NIR light-triggered UCNPs@TiO₂ generating ROS to effectively eliminate periodontal pathogens. Reprinted from *Dental Mater.* Volume 35(11). Qi M, Li X, Sun X, et al. Novel nanotechnology and near-infrared photodynamic therapy to kill periodontitis-related biofilm pathogens and protect the periodontium. 1665–1681. © Elsevier B.V. 2019, with permission from Elsevier.¹⁰⁴ (c) The SDT function of Au-TNT efficiently eradicates peri-implant pathogens, promoting bone integration. Reprinted from *Chem Engine J.* Volume 460. Li F, Pan Q, Ling Y, et al. Gold – Titanium dioxide heterojunction for enhanced sonodynamic mediated biofilm eradication and peri-implant infection treatment. 141791. © Elsevier B.V. 2023, with permission from Elsevier.¹³

Streptococcus gordonii and *Porphyromonas gingivalis*, and its therapeutic efficacy was further validated in a rat model of periodontal inflammation.⁶⁵

Additionally, TiO₂ can be incorporated into polymethyl methacrylate (PMMA) to inhibit the adhesion and proliferation of *Candida albicans*, providing a promising strategy for the prevention and management of denture stomatitis in elderly populations.¹⁰⁵

TiO₂ Nanomaterials in Peri-Implantitis Treatment

Titanium (Ti) implants are widely used in clinical dentistry; however, their susceptibility to bacterial colonization poses a significant risk of peri-implant infections and implant failure. TiO₂, which naturally forms as a surface oxide layer on Ti implants, has been extensively investigated for surface modification aimed at infection control. Its strong oxidative properties enable robust bactericidal activity. Various TiO₂-based nanostructures—used alone or in combination with nanoparticles such as Au, Ag, Cu, and ZnO—have demonstrated excellent antimicrobial effects against key oral pathogens, including *Porphyromonas gingivalis*, *Aggregatibacter actinomycetem-comitans*, *Tannerella forsythia*, and *Fusobacterium nucleatum*.^{106–109}

Notably, Li et al fabricated TiO₂ nanotubes (TNTs) via anodic oxidation on Ti implant surfaces and deposited gold nanoparticles to construct an Au-TNT nanoplatform (Figure 2c). Under ultrasound irradiation, this system generated oxygen to support SDT and alleviate peri-implant hypoxia—thereby compromising anaerobic bacterial survival. Gold nanoparticles also enhanced ROS production. In vivo studies demonstrated that Au-TNT treatment reduced bacterial colony counts by three logs compared to the control group. Furthermore, Au-TNT significantly alleviated inflammation and promoted peri-implant bone regeneration.¹³ This approach offers a non-invasive strategy for effective peri-implant infection management.

TiO₂ Nanomaterials in Orthodontic Treatment

Orthodontic appliances such as brackets and retainers can serve as microbial niches, predisposing patients to dental caries and periodontal complications. During orthodontic therapy, the incidence of caries has been reported to exceed 45%, while biofilm accumulation on wires and brackets can disrupt periodontal health.^{94,110} To address these challenges, researchers have developed antimicrobial orthodontic materials.

Studies have demonstrated that coating or doping TiO₂ onto orthodontic wires or resin retainers can significantly inhibit *Streptococcus* species, *Porphyromonas gingivalis*, and *Lactobacillus acidophilus* via PDT activation.^{111–113} In a clinical study involving 68 patients, Vahid et al evaluated the antimicrobial efficacy of TiO₂-coated orthodontic wires. Compared to the control group, the TiO₂-coated group exhibited significantly lower *Streptococcus mutans* colony counts in both the first and third weeks of treatment.¹¹⁴ Moreover, Fauzi et al incorporated TiO_{2-x} (N-doped TiO₂) into

orthodontic resin adhesives. This modified resin generated ROS upon exposure to standard dental light-curing units, effectively suppressing *S. mutans* growth. It also demonstrated advantages in ease of use, reduced phototoxicity, and maintenance of aesthetic properties during clinical application.¹¹⁵

In summary, TiO₂ nanomaterials exhibit broad potential for the prevention and treatment of oral infectious diseases. However, current research—particularly in the context of chronic or recurrent conditions such as dental caries and periodontitis—remains largely confined to in vitro and small animal studies, with limited clinical evidence on long-term efficacy. To overcome the persistent challenge of biofilm-associated infections, a multimodal therapeutic approach combining TiO₂ with other antimicrobial agents or complementary treatments (eg, PTT or SDT) may enhance overall outcomes.

Moreover, in-depth mechanistic studies are urgently needed to elucidate the molecular pathways involved in TiO₂-mediated antimicrobial effects, enabling the rational optimization of treatment strategies. Future efforts should focus on translating laboratory findings into clinically viable protocols, thereby establishing a solid foundation for the integration of TiO₂ nanomaterials into routine oral healthcare.

TiO₂ Nanomaterials in Oral Tissue Repair and Regeneration

Craniofacial bone defects caused by tumors, trauma, or infections often impair the intrinsic regenerative capacity of bone tissue. Particularly in critical-sized defects, spontaneous healing is unlikely, necessitating external interventions to restore function and structural integrity. Although numerous biomaterials and pharmacologic agents have been developed to facilitate hard tissue repair, limitations such as insufficient mechanical strength and suboptimal osteoinductive capacity remain significant hurdles.¹¹⁶ Furthermore, long-term clinical success following dental or orthopedic implantation relies heavily on robust osseointegration. However, Ti implants—despite their widespread use—exhibit biological inertness, stress-shielding effects, and limited space for inward bone ingrowth. These factors collectively contribute to bone resorption and eventual implant loosening.¹¹⁷ To overcome these limitations, extensive research has focused on modifying and enhancing implant surfaces to achieve long-term osseointegration. The native TiO₂ layer that forms spontaneously on titanium surfaces offers excellent chemical stability, corrosion resistance, and biocompatibility, serving as a critical interface for tissue integration. In particular, functionalizing this TiO₂ layer at the micro/nanoscale significantly improves implant-tissue interactions, leading to enhanced biological performance.^{118,119} Therefore, TiO₂ nanomaterials may represent a promising avenue for addressing the aforementioned issues.

In tissue engineering, TiO₂ has garnered attention for its bioactivity and ability to promote matrix mineralization.¹²⁰ Incorporating nano-TiO₂ into scaffolds composed of bioceramics or polymers enhances both mechanical strength and osteoinductive potential.^{121,122} Furthermore, some studies directly utilize TiO₂ as a raw material to fabricate bio-scaffolds, which exhibit mesoporous structures capable of storing proteins, supporting bone cell growth, and demonstrating favorable osteogenic effects.^{123,124} In a minipig model, Hanna et al fabricated TiO₂ scaffolds with ~400 μm pores and 83% porosity, which showed excellent socket preservation after tooth extraction. Notably, ~50% of the scaffold was in direct contact with bone, and ~74% of the pores were filled with new bone. The regenerated bone displayed density comparable to native cortical bone, with internal vascularization and bone spicules surrounding newly formed blood vessels.¹²⁵ In another study, Anders et al demonstrated that TiO₂ scaffolds achieved bone-implant contact levels comparable to autologous grafts in a porcine model, withstanding functional loads and showing 3% higher average contact area than controls.¹²⁶ These findings underscore TiO₂'s promise as a scaffold material in bone tissue engineering.

The design of implants must thoroughly consider the interaction between cells and the material surface. In order to achieve enhanced nutrient perfusion and aggregation, provide robust anchoring points for cell adhesion and proliferation, and promote the osseointegration of surrounding cells for the desired bone integration effect, various micro-nano structures have been developed.^{47,127} The latest research reveals that the hydrophilic surface of a nanostructured TiO₂ layer promotes blood wetting and shear flow, thereby accelerating clot formation. These clots contribute to anti-inflammatory responses and osteogenesis, resulting in a 1.5-fold increase in bone-implant contact and a 1.8-fold improvement in early mechanical anchorage.²⁴ At the cellular and molecular levels, research has revealed that carefully designed personalized micro-nanostructures, such as TiO₂ nano-clusters, nanorods, and nanotubes, can effectively enhance protein adsorption, improve macrophage adhesion to the surface, induce macrophages to transition towards the anti-inflammatory M2 phenotype, thereby alleviating the inflammation response induced by surgery.¹²⁸ This

modulation of immune response supports osteogenic differentiation of mesenchymal stem cells, facilitated by pathways such as FAK-Erk1/2-Runx2¹²⁹ and PKC α -ERK1/2.¹³⁰ TiO₂ nanotubes have also been shown to enhance F-actin polymerization and upregulate GCN5, a key regulator of osteogenic gene expression.¹³¹ Additionally, these nanostructures stimulate the osteogenic activity of periodontal ligament stem cells (PDLSCs) and adipose-derived stem cells (ADSCs), and support epithelial cell adhesion to form a protective peri-implant barrier.^{132–134}

Beyond pristine TiO₂, TiO_{2-x} exhibits enhanced bioactivity in tissue regeneration. TiO_{2-x} promotes adhesion, proliferation, and differentiation of osteoblasts and MSCs more effectively than unmodified TiO₂.^{135,136} This is attributed to increased hydrophilicity, improved protein adsorption, and the formation of Ti-OH groups that attract Ca²⁺ and PO₄³⁻ ions, facilitating hydroxyapatite nucleation and bone mineralization.^{135,137} Recent work by Su et al developed Ti-S-TiO_{2-x}-modified implant surfaces that significantly enhanced MC3T3-E1 cell proliferation and bone formation in vivo. Bone volume/tissue volume (BV/TV) and bone formation rate in the Ti-S-TiO_{2-x} group were nearly twice that of controls. Additionally, the surface exhibited strong photothermal and acoustic properties with antibacterial activity against *S. aureus* and *P. gingivalis*.¹³⁸ Yang et al further demonstrated that TiO_{2-x} metasurfaces improved human gingival fibroblast (HGF) proliferation and upregulated key adhesion-related genes, while also reducing peri-implant fibrosis.¹³⁹

Taken together, these findings highlight TiO₂ and TiO₂ nanomaterials as versatile and highly promising candidates for hard tissue regeneration and implant integration. Their physicochemical properties, biological responsiveness, and multifunctionality position them at the forefront of next-generation biomaterials in regenerative oral medicine. Next, a systematic comparison of the effects of different sizes and morphologies of TiO₂-based nanomaterials on tissue regeneration is critical for advancing their clinical translation. Recent studies have begun to explore this issue. For instance, within the 10–50 nm range, smaller TiO₂ nanoparticles are more effective in promoting fibroblast migration, thereby accelerating soft tissue healing.¹⁴⁰ In the context of hard tissue repair, smaller-scale honeycomb-like TiO₂ structures have been shown to significantly promote macrophage polarization toward an anti-inflammatory phenotype. Specifically, the 90 nm structure was found to activate the RhoA/Rho signaling pathway, leading to optimal expression levels of anti-inflammatory markers and osteogenic genes.⁴⁴ Although these findings highlight the importance of controlling particle size, morphology, and surface architecture, there remains a lack of systematic and comparative studies. Future research should focus on evaluating various TiO₂ nanostructures under standardized conditions to elucidate their regenerative mechanisms and facilitate clinical application. Furthermore, additional research may be necessary to explore the critical thresholds of TiO₂ nanomaterials in repairable tissues, essential for elucidating the application methods and scope of TiO₂.

TiO₂ Nanomaterials in Drug Loading, Delivery, and Release Control

Despite notable advances in antibacterial strategies such as PDT and SDT, their clinical application remains limited. Currently, antibiotic regimens are the mainstay for preventing and treating peri-implant infections. However, systemic administration is often associated with adverse effects and uneven drug distribution at the infection site.¹⁴¹ Owing to its excellent biosafety and stability, TiO₂ has been widely explored in the biomedical field, particularly in oral implantology. Numerous studies have validated the benefits of TiO₂ nanotube structures for implant surface modification.^{142,143} These nanotubes not only enhance bone regeneration and promote osseointegration but also show great potential as drug delivery vehicles for antimicrobial agents and bioactive molecules. Nevertheless, uncontrolled local drug release can lead to cytotoxicity and hinder therapeutic efficacy.¹⁴⁴

To address these concerns, researchers have developed TiO₂-based surface drug delivery systems to enable sustained and localized antimicrobial release. Among these, coating or encapsulating TNTs with polymeric layers has proven effective in modulating drug release kinetics. Several studies have utilized TNTs as drug reservoirs and applied biodegradable polymer coatings to regulate the release profile by adjusting film thickness and degradation rates.^{145,146} In a representative study, Seyed et al fabricated a drug-releasing antibacterial system on a Ti-6Al-4V surface incorporating chitosan nanofibers (CH), reduced graphene oxide (RGO), TNTs, and vancomycin. This hybrid structure prolonged the drug release duration up to 11 days, significantly improved antibacterial efficacy, and promoted osteoblast viability compared to uncoated controls.¹⁴⁷

In another approach, Dong et al developed a pH-sensitive aldehyde-linked TNT-Ag NP platform (TNT-AL-Ag) capable of releasing Ag NPs under acidic conditions induced by bacterial metabolism (pH 5.5), thereby exhibiting potent antibacterial activity against periprosthetic infections.¹⁴⁸ Li et al further advanced this concept by incorporating Ag NPs into TNTs on sandblasted and acid-etched (SLA) titanium surfaces. Their platform exhibited an initial “release-killing” phase followed by sustained “contact-killing” activity, mitigating Ag-related cytotoxicity and addressing antimicrobial needs at different post-implantation stages.¹⁴⁹ Collectively, these multifunctional TNT-based platforms—tailored through polymeric encapsulation, pH responsiveness, or staged release—represent promising strategies for implant surface engineering.

Beyond passive coatings, light-triggered intelligent drug release has emerged as a precise and controllable delivery approach. Zhao et al designed an amphiphilic TNT system (UC/Au/TiO₂) responsive to NIR light (Figure 3).²⁶ The system comprises a hydrophobic top layer modified with UCNPs and gold for NIR absorption and drug leakage prevention, and a hydrophilic bottom layer containing ampicillin sodium. Upon NIR irradiation, UCNPs convert NIR into visible light, activating the TiO₂/Au interface to generate ROS, which cleaves the AMP-TiO₂ bond, enabling on-demand release. The hydrophobic upper layer also minimizes ROS-induced cytotoxicity to adjacent normal tissues. Even after drug release, residual ROS continue to exert antibacterial effects, demonstrating the system’s promise for spatiotemporally controlled antimicrobial therapy.

In addition to antibiotics, TNTs can also serve as carriers for bioactive growth factors. Sebastian et al covalently immobilized epidermal growth factor (EGF) and bone morphogenetic protein-2 (BMP-2) onto TNT surfaces. Functionalization with EGF on 100 nm TNTs significantly enhanced the proliferation and activity of mesenchymal stem cells, thereby promoting osseointegration.¹⁵⁰ Interestingly, TiO_{2-x} appears to outperform pristine TNTs in growth factor delivery. Hydrogenated TiO_{2-x} showed superior protein adsorption and loading capacity, slower release rates, and greater retention of osteogenic bioactivity, particularly for MG-63 cell modulators.¹³⁵ Chen et al developed a TiO_{2-x} nanotube-based system (B-TNT) coated with polydopamine and loaded with interleukin-4 (IL-4). Upon NIR activation, this system enabled on-demand IL-4 release, significantly attenuating inflammation and enhancing osseointegration relative to bare Ti implants.¹⁵¹ However, this study did not directly compare the performance of TiO_{2-x} with conventional TNTs.

Together, the diverse drug delivery mechanisms of TiO₂ and TiO_{2-x} nanostructures offer a rich toolkit for surface modification and controlled therapeutic release. However, there is a notable lack of direct comparisons between the two in terms of their drug delivery performance. This may be due to the fact that research on TiO_{2-x} has primarily focused on

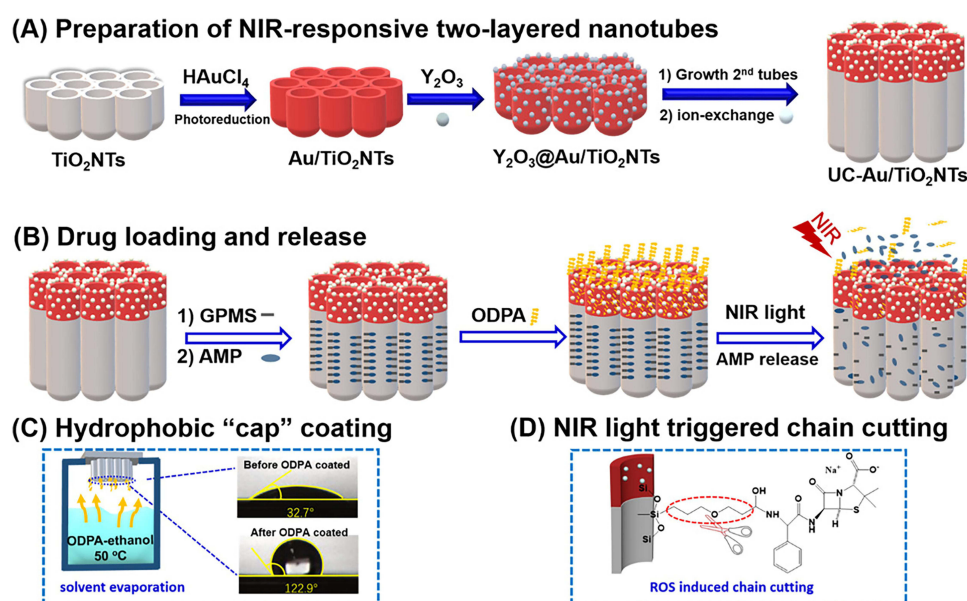


Figure 3 UC-Au/TiO₂ nanotubes exhibit smart drug release control under NIR irradiation, reducing cytotoxicity while maintaining effective antibacterial activity. Reproduced with permission from Zhao J, Xu J, Jian X, Xu J, Gao Z, Song -Y.Y. NIR light-driven photocatalysis on amphiphilic TiO₂ nanotubes for controllable drug release. *ACS Appl Mater Interfaces*. 2020;12(20):23606–23616. © American Chemical Society 2020.²⁶

enhancing photocatalytic activity, improving visible light absorption, and its applications in photothermal therapy, whereas TiO₂ nanotubes have been more extensively studied for their role as implant surface modifiers and drug carriers. Importantly, regardless of their intended function—be it drug delivery or promoting osseointegration—TiO₂-based surface modifications must also ensure robust interfacial bonding with the implant substrate to maintain long-term functionality.

TiO₂ Nanomaterials as Additives in Dental Restorative Materials

Given the complex and repetitive masticatory forces experienced by human dentition in daily life, the mechanical performance of dental restorative materials plays a crucial role in ensuring clinical success. These materials must undergo rigorous evaluation—not only for their biological compatibility but also for their chemical, mechanical, and physical properties. In this context, TiO₂ has garnered substantial attention in dentistry due to its outstanding performance profile.¹⁵² Characterized by low cost, excellent stability, high compressive strength, and superior hardness, TiO₂ is widely incorporated into various restorative materials to enhance their mechanical durability, prolong service life, and improve overall restoration outcomes.

For localized hard tissue damage—commonly resulting from dental caries—adhesive agents are typically combined with resin or glass ionomer cement (GIC) for restorative purposes. Material selection must be tailored to the anatomical and functional needs of different oral regions: for example, high mechanical strength is essential for occlusal surfaces, whereas esthetic properties are prioritized in the anterior zone. Furthermore, the long-term exposure of restorative materials to the dynamic oral fluid environment necessitates exceptional chemical and hydrolytic stability. Recent studies have shown that the incorporation of low concentrations of TiO₂ NPs into resin-based materials significantly enhances flexural strength, wear resistance, and hardness.¹⁵³ In addition, TiO₂ doping effectively reduces water sorption and polymerization shrinkage, contributing to longer restoration lifespans.^{154,155}

Sun et al systematically examined the effects of acid-modified TiO₂ on the properties of dental resins. A 0.08 wt% addition of TiO₂ NPs increased vinyl conversion by approximately 5%, while just 0.06 wt% raised the elastic modulus by ~48% and surface hardness by over 200%.³³ These improvements have also been validated in flowable composite resins, with favorable outcomes reported for mechanical performance and water resistance.^{156,157} Moreover, resin composites containing 0.1–0.25 wt% TiO₂ NPs can mimic the natural opalescence of enamel, thus enhancing esthetic results in restorative procedures.¹⁵⁸

In GIC-based systems, TiO₂ nanofillers also significantly improve mechanical performance. Their inclusion enhances flexural strength, compressive strength, surface hardness, and bonding strength to both enamel and dentin.^{159–161} However, the effects are concentration-dependent. For example, the incorporation of 0–10 wt% TiO₂ NPs in GIC composites initially enhances flexural and compressive strengths up to 5 wt%, beyond which the performance declines.¹⁶² Additionally, Sun et al reported that the addition of 2 wt% TiO₂ and 1 wt% cellulose nanocrystals (CnC) improved compressive strength and enamel shear bond strength by 18.9% and 51%, respectively.¹⁶³ Despite these advancements, few studies have examined whether the improved mechanical properties of TiO₂-enhanced resin or GIC materials match those of natural enamel or dentin in terms of hardness and elastic modulus.

The longevity of dentin-resin bonding is often compromised due to hydrolytic degradation of covalent bonds formed by traditional adhesives, a consequence of dentin's intrinsic structural characteristics.¹⁶⁴ Incorporating TiO₂ NPs into dental adhesives has been shown to reduce solubility and water sorption, thereby extending bond durability.¹⁶⁵ Moreover, TiO₂ addition increases the degree of vinyl conversion and significantly enhances both mechanical and physicochemical properties.¹⁶⁶ Sun et al demonstrated that adding just 0.1 wt% acid-modified TiO₂ NPs to dentin adhesive increased shear bond strength by 130%.³³ Collectively, these findings establish a robust foundation for optimizing the performance of bonding agents and restorative materials via TiO₂ nanotechnology.

For large-scale dental tissue loss or complete tooth loss, resin-based bonding agents alone are often insufficient. Full restorations—such as inlays, onlays, crowns, or removable dentures—become necessary. Despite the extensive clinical application of ceramic materials for crowns and bridges, their brittleness limits mechanical reliability.¹⁶⁷ Mechanical ball-milling of 0–2 wt% TiO₂ and Al₂O₃ into 3 mol% yttria-stabilized tetragonal zirconia polycrystals (3Y-TZP) has shown promising outcomes. A composition of 0.5 wt% TiO₂ and 1 wt% Al₂O₃ yielded optimal hardness (13.05 ± 0.22 GPa) and fracture toughness (4.74 ± 0.30 MPa·m^{1/2}) without affecting the ceramic phase, while also enhancing L929 cell

adhesion and proliferation.¹⁶⁸ Additionally, varying titanium doping levels and sintering conditions affect ceramic color and strength. For instance, 7.5 mol% titanium exhibited better color brightness and lower red saturation than 12.5 mol%, and sintering at 1300 °C for 2 hours achieved high densification and flexural strength up to 670 MPa.²⁵ These results highlight TiO₂'s potential in improving both the aesthetic and mechanical performance of advanced ceramic restorations.

Polymethyl methacrylate (PMMA) remains the dominant material for denture bases due to its esthetic appeal, low density, and affordability.¹⁶⁹ However, its poor mechanical and chemical durability results in fatigue, porosity, and reduced strength over time.^{170–173} The strengthening effect of TiO₂ in PMMA is attributed to the homogeneous dispersion of small, low-concentration (≈ 3 wt%) NPs within the matrix,^{174,175} which restricts polymer chain mobility through strong interfacial interactions.¹⁷⁵ Nonetheless, certain studies report that high TiO₂ concentrations may induce discoloration and reduce esthetic appeal.¹⁷⁶ Furthermore, TiO₂'s photocatalytic activity may degrade polymer components over time.¹⁷² Therefore, surface coating rather than direct doping has been proposed as a superior reinforcement strategy. Atomic layer deposition (ALD) of a ~ 30 nm TiO₂ film on PMMA significantly increased surface roughness and improved abrasion resistance. Notably, surface roughness remained stable after brushing, and the TiO₂ film remained intact after 100,000 brushing cycles.^{177,178} However, excessive nanoparticle loading may negatively impact mechanical properties and processing behavior.¹⁷⁹

In summary, current evidence supports the integration of TiO₂ nanomaterials into various dental restorative systems to enhance mechanical strength, esthetics, and longevity. Future efforts should focus on developing patient-specific formulations tailored to functional demands of different tooth regions. Given the variable mechanical and optical requirements across anterior and posterior teeth, careful modulation of TiO₂ content is essential to optimize performance without compromising aesthetics or durability.

TiO₂ Nanomaterials in Teeth Whitening

With the advancement of aesthetic standards and medical technologies, both patients and clinicians have placed increasing emphasis on the concept of red-white aesthetics. Within this framework, “white aesthetics”—pertaining to tooth color—has gained particular attention, with rapid and minimally invasive tooth-whitening treatments emerging as a preferred clinical option.¹⁸⁰ Owing to their unique physicochemical properties, TiO₂ nanomaterials have demonstrated considerable promise in the domain of dental whitening.

Although commercially available whitening agents are effective, many contain H₂O₂ concentrations ranging from 30% to 40%, which significantly raises the risk of enamel erosion, tooth hypersensitivity, and gingival irritation.¹⁸¹ Acting as a photosensitizer, TiO₂ absorbs photons with energies exceeding its bandgap, thereby generating reactive oxygen species (ROS) such as singlet oxygen (¹O₂), superoxide anions ($\cdot\text{O}_2^-$), and hydroxyl radicals ($\cdot\text{OH}$), which degrade the organic chromophores responsible for tooth discoloration.¹⁸²

TiO_{2-x}, a reduced form of TiO₂ enriched with Ti³⁺ and oxygen vacancies, further enhances this effect by mimicking Fenton-like catalytic activity—reacting with H₂O₂ to generate $\cdot\text{OH}$ —making it particularly well-suited for safer and more efficient whitening formulations. In a study by Hu et al, TiO_{2-x} demonstrated not only strong Fenton-like catalytic properties but also excellent photothermal performance under NIR irradiation, which further amplified its ROS production (Figure 4). The presence of oxygen vacancies also facilitated greater adsorption of chromogenic compounds, enhancing whitening efficacy. Remarkably, the whitening outcome achieved with TiO_{2-x}/12% H₂O₂ under NIR stimulation was comparable to that of the commercial product Opalescence Boost, which contains 40% H₂O₂.²⁰

Clinical studies have reinforced these findings. In a randomized trial by Martin et al, nitrogen-doped TiO_{2-x} was combined with 6% H₂O₂ for the experimental group, while 35% H₂O₂ was used in the control group. Among 31 patients, the TiO_{2-x}-assisted group achieved comparable whitening results with significantly fewer adverse effects.¹⁸³ Similarly, Bortolatto et al compared a 15% H₂O₂/TiO_{2-x} formulation with a 35% H₂O₂ control and reported superior whitening efficacy and reduced tooth sensitivity in the TiO_{2-x} group.¹⁸⁴

In addition to its ROS-mediated mechanisms, TiO₂ may also influence dental aesthetics by altering enamel microstructure. Previous studies have shown that the incorporation of Ti into dental enamel reduces hydroxyapatite crystal size, which enhances light scattering and contributes to increased brightness and visual whiteness of teeth.^{185–187} Taken together, these findings highlight TiO₂ nanomaterials—particularly TiO_{2-x}—as promising candidates for the development

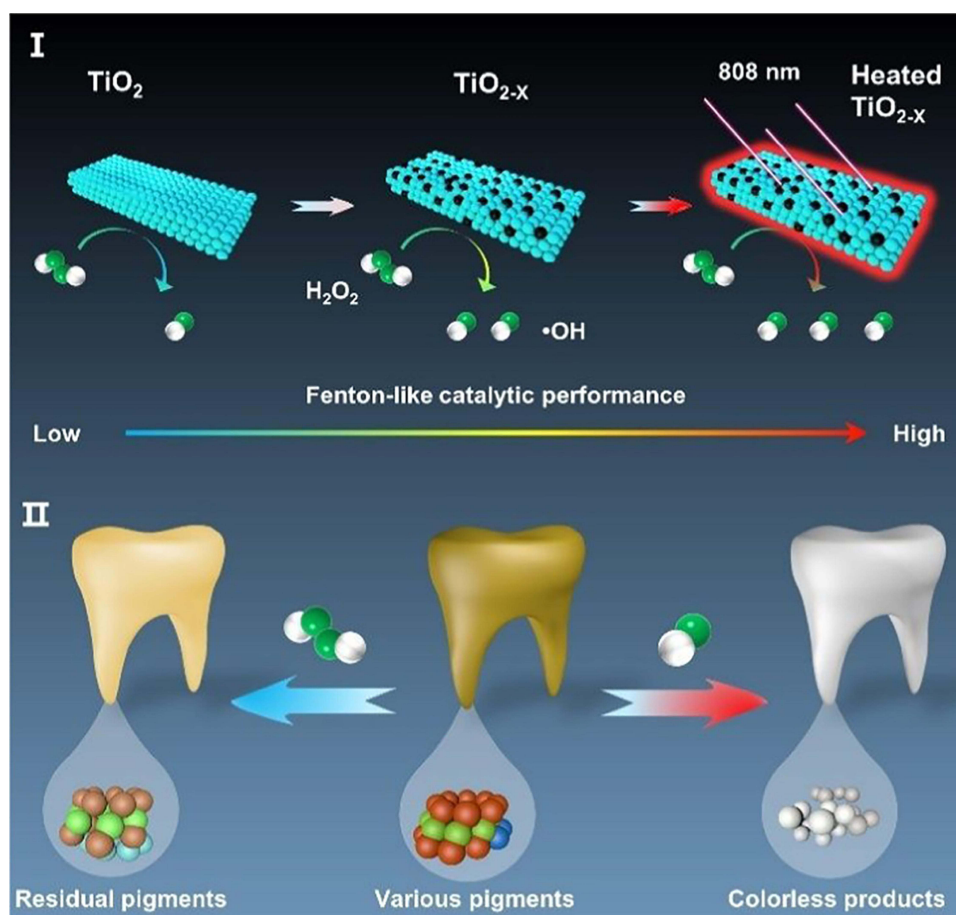


Figure 4 The Fenton-like reactivity of TiO_{2-x} is significantly enhanced under NIR-induced photothermal effects, providing an efficient and low-sensitivity tooth whitening solution. Reproduced with permission from Hu X, Xie L, Xu Z, et al. Photothermal-enhanced fenton-like catalytic activity of oxygen-deficient nanotitania for efficient and safe tooth whitening. *ACS Appl Mater Interfaces*. 2021;13(30):35315–35327. © American Chemical Society 2021.²⁰

of next-generation, high-efficacy, low-toxicity tooth-whitening agents, offering a compelling alternative to conventional peroxide-based treatments.

It is particularly important to consider the changes in tooth composition and sensitivity in tooth whitening applications. Currently, the whitening effect of TiO_2 nanomaterials is primarily achieved through photocatalysis, generating ROS or assisting H_2O_2 . First, UV leakage can lead to phototoxicity and excessive heat generation, which may cause damage to the teeth. Therefore, using visible light as the excitation source may be a more ideal option.¹⁸⁰ The generation of ROS can accelerate the loss of tooth minerals or reduce hardness,¹⁸⁸ which makes the teeth more fragile, leading to surface damage and the formation of microcracks. High concentrations of H_2O_2 not only have the potential to cause soft tissue damage but may also penetrate the dental pulp, leading to further risks.¹⁸⁹ These side effects may contribute to the occurrence of tooth sensitivity. Although some studies suggest that TiO_2 does not induce these adverse effects, inconsistent conclusions highlight the need for close attention to these potential issues.

Key cases on the applications of TiO_2 -based nanomaterials in stomatology have been summarized in Table 1 for ease of reference.

Biocompatibility

Due to its exceptional physicochemical properties, TiO_2 is anticipated to witness a growing breadth of applications in oral medicine in the near future. However, to mitigate potential risks and adverse effects associated with TiO_2 nanomaterials, a comprehensive evaluation of their biocompatibility is essential. Furthermore, given that TiO_{2-x} represents a reduced and optimized derivative of TiO_2 with superior properties in certain studies, and shares overlapping

Table 1 TiO₂ Nanomaterials in Typical Applications in Stomatology

Application Area	Treatment System	Action Mechanism	Therapeutic Outcomes	Ref.
Cancer diagnosis	TiO ₂ nanostructures/Ag NPs Leaf-like TiO ₂ nanostructures/Ag nanoparticles.	SERS signal enhancement SERS signal enhancement	Sensitivity: 100%, Specificity: 95.83% 97.24% accuracy in tissue detection and 97.84% classification	[11] [22]
Cancer therapy	AuNRs-TiO ₂ @mS-MTX: UCNP nanocomposites TiO ₂ NPs@Ru@siRNA TiO ₂ NPs	PDT+PTT+ immune activation Photo-immunotherapy SDT	>75% tumor volume reduction in vivo Tumor weight reduced by ~10-fold Damage effect on tumor cells correlates with TiO ₂ concentration	[78] [12] [88]
Antibacterial therapy (Dental Caries)	TiO ₂ -HAP nanorods	PDT	Concentration-dependent antibacterial effect for 24 h, promotes remineralization by releasing calcium and phosphate ions	[101]
Antibacterial therapy (Endodontic Infections)	N-TiO ₂ NPs NaClO/TiO _{2-x} NPs	PDT PDT	Dose-dependent antibacterial 99.3% antibacterial rate for <i>E. faecalis</i>	[102] [23]
Antibacterial therapy (Periodontitis)	UCNPs@TiO ₂ NPs Alginate-Ag-TiO _{2-x} NPs	PDT PDT+PTT+POD+ ion release	Biofilm CFU reduced by 3–4 orders of magnitude 83.3% antibacterial rate for <i>S. gordonii</i> and 87.9% for <i>P. gingivalis</i>	[104] [65]
Antibacterial therapy (Peri-Implantitis)	Au NPs-TiO ₂ nanotubes	SDT	Biofilm CFU reduced by 3 orders of magnitude in vivo	[13]
Antibacterial therapy (Orthodontic treatment)	TiO ₂ coating N-TiO ₂	Catalysts PDT	Significant reduction in <i>S. mutans</i> colonies Significant reduction in <i>S. mutans</i> viability	[114] [115]
Tissue regeneration	TiO ₂ bone scaffolds (mean pore size ~400 μm, porosity >83%) Half-cylindrical TiO ₂ scaffolds (~6 mm diameter, 10 mm height) Nanoscaled TiO ₂ layer TiO ₂ nanotube arrays/CaP Nanoscale laminated protuberance structure of S-TiO _{2-x} TiO ₂ /TiO _{2-x} array of nanorods	3D microenvironment promoting osteogenesis and mechanical stability High compressive strength, porosity, and interconnectivity, low cytotoxicity Enhanced blood shear rate on the hydrophilic surface Micro-/nano-topographies affecting cell behavior Increased hydrophilicity, more contact anchors for filopodia Nanoscale topographic manipulation	73.6 ± 11.1% of pore space occupied by newly formed bone tissue Similar to autologous bone block Blood shear rate increased by 1.2x, bone-implant contact increased by 1.5x, mechanical anchorage increased by 1.8x Promotes adhesion and proliferation of HGFs Promotes cell adhesion, proliferation and bone integration Promotes HGFs proliferation, activity, and adhesion.	[125] [126] [24] [134] [138] [139]
Drug Loading, Delivery, and Release Control	Ag NPs-acetal linker-TiO ₂ nanotube arrays UCNPs/Au/TiO ₂ nanotubes PDA-black TiO ₂ nanotubes	pH-dependent NIR light-driven Photothermal-controlled release	pH 5.5 enhances Ag NPs release, improving antibacterial activity and cell proliferation/differentiation Drug release rate modulated by NIR light Photothermal activation of IL-4 release regulates immune response and promotes bone integration	[148] [26] [151]

(Continued)

Table 1 (Continued).

Application Area	Treatment System	Action Mechanism	Therapeutic Outcomes	Ref.
Dental materials	TiO ₂ NPs	Mechanical properties and photoactivities	DC of resin mixture improved by ~7%, elastic modulus increased by 48%, hardness more than doubled, SBS increased by ~30% (vs NP-free resin)	[33]
	TiO ₂ NPs/CNCs	Mechanical properties	Compressive strength increased by 18.9%, SBS by 51%, dissolution reduced by 18.3%, volume wear rate reduced by 5% (vs conventional GIC)	[163]
	3Y-TZP/TiO ₂	Esthetics and mechanical properties	7.5 mol% TiO ₂ shows higher brightness, more yellow and less red, 12.5 mol% TiO ₂ flexural strength: 670 MPa (in dental ceramics)	[25]
	TiO ₂ NPs	Mechanical properties	Flexural strength, impact strength, and wear resistance increase with low TiO ₂ concentration, hardness increases with high TiO ₂ concentration (in PMMA)	[175]
Teeth Whitening	TiO _{2-x} NPs	Photothermal-enhanced Fenton-like performance	Equivalent whitening effect to a product containing 40% H ₂ O ₂	[20]
	N-TiO ₂	Activated by light	6% H ₂ O ₂ + N-TiO ₂ similar effect on tooth whitening and sensitivity as 35% H ₂ O ₂	[183]

application prospects, we have also summarized its biocompatibility profile. The toxicity of nanomaterials is governed by multiple factors, including particle size, surface charge, morphology, and crystalline structure,¹⁹⁰ making it inherently challenging to obtain a unified understanding of TiO₂'s biological toxicity. To ensure biosafety, numerous *in vitro* and *in vivo* investigations have been undertaken.

Despite extensive research, findings on the biotoxicity of TiO₂ remain somewhat contradictory. Several studies regard TiO₂ as one of the least toxic nanomaterials. Its approval by the US Food and Drug Administration (FDA) for use in food contact materials and pharmaceuticals suggests a favorable safety profile.^{191,192} Conversely, other studies report significant toxicological effects. For instance, exposure of HGFs to TiO₂ NPs above 0.1 mg/mL was shown to significantly reduce cell viability in CCK-8 assays.¹⁹³ *In vivo* studies in rodents have revealed organ-level toxicity. A meta-analysis encompassing 62 studies concluded that high doses of TiO₂ NPs may induce damage to the liver, spleen, kidneys, lungs, brain, and heart.¹⁹⁴ Specifically, TiO₂-induced oxidative stress and inflammation have been implicated in hepatic fibrosis, steatosis, and edema.^{195,196} Sang et al further demonstrated that TiO₂ exposure (10 mg/kg) activated the MAPKs/PI3K/Akt signaling pathway, resulting in spleen inflammation and injury in mice.¹⁹⁷ Prolonged accumulation of TiO₂ in the kidneys may activate the Nrf2/Keap1 pathway, causing renal dysfunction and inflammation.¹⁹⁸ Similarly, oral administration of TiO₂ NPs (2.5–10 mg/kg/day for 90 days) in mice induced cardiac histopathologies, including myocardial fiber rarefaction, necrosis, inflammation, and biochemical dysfunction.¹⁹⁹ Other studies have shown that TiO₂ NPs disrupt gut microbiota homeostasis and trigger colonic inflammation,²⁰⁰ disturb endocrine signaling and reproductive function, and even pose potential genotoxic risks such as DNA damage, gene deletions, and mutations.^{201,202} Alarming, TiO₂ has been reported to cross the placental barrier, causing developmental toxicity in fetuses,²⁰³ and to penetrate the brain via the blood–brain and olfactory-brain barriers, raising concerns about neurotoxicity.^{204,205}

Compared to TiO₂, research on the biosafety of TiO_{2-x} is relatively nascent, and systematic evaluations are still lacking. However, several studies have reported promising results. For example, co-culture of TiO_{2-x} NPs (1 mg/mL) with liver cells (BRL), renal tubular epithelial cells (NRK-52E), and brain capillary endothelial cells (BCECs) for 24 hours showed no significant cytotoxicity.²⁰⁶ Similarly, TiO_{2-x} at 50 µg/mL had negligible impact on human A549 lung cell viability within 24 hours, likely due to the absence of intracellular ROS elevation—suggesting lower toxicity than TiO₂.²⁰⁷ Moreover, TiO_{2-x} NPs with varying Ti³⁺/Ti⁴⁺ ratios have been shown to be well tolerated by fibroblasts.²⁰⁸ In long-term biosafety evaluations, mice injected with TiO_{2-x} for 90 days displayed no abnormalities in hematological parameters or in the morphology of the heart, liver, spleen, kidneys, lungs, or brain.²⁰⁶ Behavioral analyses in a 1-month dosing study also showed no significant differences in feeding, excretion, activity, or neurological signs compared to controls.²⁰⁹ Clearance studies using ICP-MS and electron microscopy confirmed that TiO_{2-x} can be broken down into smaller fragments or ions and eliminated via hepatic and renal excretory pathways. Notably, throughout these experiments, animals exhibited no signs of pain, distress, or discomfort.^{210,211}

It is important to note that most current biosafety studies rely heavily on rodent models, and data regarding the organ-specific and systemic toxicity of TiO₂ in humans remain insufficient. Thus, more robust and predictive preclinical models are urgently needed. In future research, it will be crucial to tailor TiO₂ nanomaterials based on their physicochemical properties and intended clinical applications. For instance, while smaller TiO₂ NPs offer a larger surface area and enhanced photodynamic performance, they may also induce stronger inflammatory responses—posing a design trade-off. Application-specific structural optimization of TiO₂ remains an ongoing challenge in the field.

In summary, further research is warranted to establish standardized biosafety models and thoroughly evaluate the interactions of TiO₂ nanomaterials with different organs and biological systems under practical use conditions. Through meticulous optimization and application-specific design, the safe and effective clinical deployment of TiO₂-based nanomaterials in oral medicine can be more reliably achieved.

Risks and Limitations

The aforementioned properties and related studies underscore the considerable potential of TiO₂-based nanomaterials in oral medicine, signaling meaningful progress toward their clinical translation and eventual commercialization. However, several critical challenges remain to be addressed.

First, the biocompatibility of TiO₂ remains a subject of debate, highlighting the urgent need for validation through more robust and predictive biosafety models to ensure its safety in human applications. For TiO_{2-x}, despite its promising enhancements over pristine TiO₂, a comprehensive and systematic evaluation of its biological safety is still lacking. Further investigations into its *in vivo* behavior—including biodistribution, metabolism, and excretion—are essential to fully understand its biocompatibility and potential toxicity. Moreover, our current understanding of the adverse effects potentially induced by ion release from TiO₂-based nanomaterials remains incomplete. In particular, the biological transformation of these ions and their interactions with endogenous ions within complex physiological environments warrant deeper mechanistic exploration. Addressing these gaps will be crucial for the safe and effective clinical deployment of TiO₂ series nanomaterials in oral healthcare. Early studies have shown that Ti⁴⁺ ions can bind to serum transferrin (sTf), a critical iron transport protein, and enter cells through endocytosis.²¹² However, the exact role and potential toxicity of this interaction remain unclear. Recent research has demonstrated that enterobactin can bind to TiO₂ nanoparticles, leading to the dissolution of TiO₂ from its surface in biological media. Consequently, long-term exposure and ingestion of TiO₂ may pose potential biosafety risks, including gastrointestinal diseases and immune system disorders.²¹³

Additionally, the complex oral environment presents significant challenges for the clinical application of TiO₂-based diagnostic sensors. First, the relationship between biomarkers and diseases remains incompletely understood, and the correlation between disease progression and biomarker levels is not well-established, particularly for biomarkers with low expression levels.²¹⁴ Given the abundance of interfering biomolecules, dynamic pH fluctuations, the nature of saliva, and the formation of biofilms, sensors must possess high sensitivity and resolution. Therefore, future research should focus on developing robust sensors with antifouling properties and establishing standardized protocols that better reflect the real oral conditions. In the context of tumor therapy, although TiO₂ nanomaterials exhibit inherently low toxicity, their effective delivery to tumor sites remains hindered by immune system clearance during systemic circulation. To minimize the potential side effects associated with high dosages, surface modification strategies—such as cloaking TiO₂-based nanomaterials with macromolecules or vesicles—have been proposed to prolong their blood circulation time and evade immune recognition.^{215,216} Moreover, elevated local temperatures have been reported to facilitate enhanced accumulation of nanomaterials within tumor tissues via improved vascular permeability.²¹⁷ These findings collectively suggest that TiO_{2-x} nanomaterials, with their superior photothermal and catalytic properties, hold significant promise for advancing oral cancer therapeutics through rational design and targeted delivery approaches.

Differences in immune regulation and osteogenic outcomes have been observed with mesoporous and nanotubular TiO₂ structures of varying dimensions. In advancing toward clinical applications, it is imperative to conduct comprehensive comparisons among diverse synthesis methods to ensure both cost-efficiency and optimal performance in large-scale production. Although certain fabrication strategies have demonstrated greater suitability for biological applications, there remains a paucity of comparative studies evaluating their relative advantages. Establishing standardized, reproducible protocols for the preparation and characterization of TiO₂ nanomaterials is therefore critical to ensuring data consistency and facilitating translational research. Such standardization would offer a robust foundation for the application of TiO₂-based platforms in oral tissue regeneration and accelerate their transition from bench to bedside.

Furthermore, the regenerative potential of TiO₂ nanomaterials in promoting soft and hard tissue healing within the oral cavity warrants deeper investigation. Identifying the optimal physiological conditions and threshold parameters for defect repair is crucial for achieving precision in clinical interventions. A more nuanced understanding of the structure–function relationships across various application contexts will inform the strategic deployment of TiO₂-based systems. Comparative studies examining the influence of nanomaterial morphology, dimensionality, and surface chemistry on biological outcomes are particularly needed. Parallel efforts to establish standardized evaluation criteria and preclinical models will enable more accurate quantification of therapeutic efficacy and promote the development of targeted, evidence-based regenerative therapies.

Additionally, the mechanical integrity and long-term adhesion of TiO₂ nanostructures to implant surfaces remain key challenges limiting clinical deployment. Strengthening the interface between nanomaterials and implant substrates is vital for enhancing therapeutic reliability and ensuring mechanical stability under functional load. Continued investigation into interface engineering strategies will therefore play a pivotal role in advancing clinical outcomes.

At the same time, addressing issues of phototoxicity and limited tissue penetration associated with UV–visible light activation of TiO₂ remains a major research priority. Although material modifications—such as doping and structural engineering—have successfully extended TiO₂'s excitation range into the visible and NIR regions, further in vivo validation is essential. In particular, clinical studies are needed to assess the penetration depth of NIR irradiation in human tissues, evaluate its ability to activate TiO₂-based nanomaterials in situ, and confirm therapeutic efficacy in relevant disease models. Such efforts will be instrumental in translating photoactivated TiO₂ systems into clinically viable treatments.

The Future Prospective

Titanium dioxide (TiO₂) and its reduced form (TiO_{2-x}) have emerged as promising multifunctional platforms in the field of oral medicine. This review systematically summarizes the latest progress in six key application areas—oral cancer diagnosis and therapy, antibacterial infection control, tissue repair, drug delivery, restorative dental materials, and tooth whitening—highlighting the transformative potential of TiO₂-based nanomaterials in advancing precision oral healthcare.

Despite these promising prospects, several significant barriers still hinder the clinical translation of TiO₂-based materials. These include the lack of comprehensive long-term biosafety evaluations, the absence of standardized synthesis and characterization protocols, and an underdeveloped regulatory framework—all of which critically limit their path toward clinical application.

Future research should focus on the precise engineering of TiO₂ nanostructures to enhance their functional integration, biological stability, and targeting specificity. It is equally essential to establish unified standards for synthesis, characterization, and toxicity assessment, and to integrate advanced tools—such as artificial intelligence—to accelerate the development of personalized therapeutic strategies. Additionally, thorough consideration of the complexity of the oral microenvironment, along with dosage optimization tailored to specific indications, will be crucial to ensuring safe and effective clinical translation.

As nanotechnology and oral medicine continue to converge, TiO₂ and its derivatives are poised to serve as foundational materials for next-generation precision therapies, laying a solid groundwork for intelligent, systematic management of oral health.

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Disclosure

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References

- Essat M, Cooper K, Bessey A, Clowes M, Chilcott JB, Hunter KD. Diagnostic accuracy of conventional oral examination for detecting oral cavity cancer and potentially malignant disorders in patients with clinically evident oral lesions: systematic review and meta-analysis. *Head Neck*. 2022;44(4):998–1013. doi:10.1002/hed.26992
- Zhang S, Li Z, Xu Z, et al. Reactive oxygen species-based nanotherapeutics for head and neck squamous cell carcinoma. *Mater Design*. 2022;223:111194. doi:10.1016/j.matdes.2022.111194
- Qi J, Si C, Liu H, et al. Advances of metal-based nanomaterials in the prevention and treatment of oral infections. *Advanced Healthcare Mater*. 2025;14(15):2500416. doi:10.1002/adhm.202500416
- Qi M, Ren X, Li W, et al. NIR responsive nitric oxide nanogenerator for enhanced biofilm eradication and inflammation immunotherapy against periodontal diseases. *Nano Today*. 2022;43:101447. doi:10.1016/j.nantod.2022.101447
- Cui F, Li T, Wang D, et al. Recent advances in carbon-based nanomaterials for combating bacterial biofilm-associated infections. *J Hazard Mater*. 2022;431:128597. doi:10.1016/j.jhazmat.2022.128597
- Xia D, Chen J, Zhang Z, Dong M. Emerging polymeric biomaterials and manufacturing techniques in regenerative medicine. *Aggregate*. 2022;3(5):e176. doi:10.1002/agt2.176
- Weng Z, Xu Y, Gao J, Wang X. Research progress of stimuli-responsive ZnO-based nanomaterials in biomedical applications. *Biomater Sci*. 2023;11(1):76–95. doi:10.1039/D2BM01460B

8. Shi J, Li J, Wang Y, Zhang CY. TiO₂-based nanosystem for cancer therapy and antimicrobial treatment: a review. *Chem Engine J.* 2022;431:133714. doi:10.1016/j.cej.2021.133714
9. Matsunaga T, Tomoda R, Nakajima T, Wake H. Photoelectrochemical sterilization of microbial cells by semiconductor powders. *FEMS Microbiol Letters.* 1985;29(1–2):211–214. doi:10.1111/j.1574-6968.1985.tb00864.x
10. Fujishima A. Behavior of tumor cells on photoexcited semiconductor surface. *Photomed Photobiol.* 1986;8:45–46.
11. Girish CM, Iyer S, Thankappan K, et al. Rapid detection of oral cancer using Ag–TiO₂ nanostructured surface-enhanced Raman spectroscopic substrates. *J Mater Chem B.* 2014;2(8):989–998. doi:10.1039/C3TB21398F
12. Zhou J-Y, Wang W-J, Zhang C-Y, et al. Ru(II)-modified TiO₂ nanoparticles for hypoxia-adaptive photo-immunotherapy of oral squamous cell carcinoma. *Biomaterials.* 2022;289(121757):121757. doi:10.1016/j.biomaterials.2022.121757
13. Li F, Pan Q, Ling Y, et al. Gold – Titanium dioxide heterojunction for enhanced sonodynamic mediated biofilm eradication and peri-implant infection treatment. *Chem Engine J.* 2023;460:141791. doi:10.1016/j.cej.2023.141791
14. Salahuddin N, Abdelwahab M, Gaber M, Elneaeay S. Synthesis and design of norfloxacin drug delivery system based on PLA/TiO₂ nanocomposites: antibacterial and antitumor activities. *Mater Sci Engine.* 2020;108:110337. doi:10.1016/j.msec.2019.110337
15. Xiao F, Ye J-H, Huang C-X, et al. Gradient gyroid Ti₆Al₄V scaffolds with TiO₂ surface modification: promising approach for large bone defect repair. *Biomater Adv.* 2024;161:213899. doi:10.1016/j.bioadv.2024.213899
16. Wang R, Wang Y, Chen J, et al. Photocatalytic TiO₂/HAP nanocomposite for antimicrobial treatment, remineralization, and tooth whitening. *RSC Adv.* 2025;15(17):13453–13467. doi:10.1039/D5RA00792E
17. Chen X, Liu L, Yu PY, Mao SS. Increasing solar absorption for photocatalysis with black hydrogenated titanium dioxide nanocrystals. *Science.* 2011;331(6018):746–750. doi:10.1126/science.1200448
18. Jiang X, Huang Z, Liu Z, et al. MOF-derived oxygen-deficient titania-mediated photodynamic/photothermal-enhanced immunotherapy for tumor treatment. *ACS Appl Mater Interfaces.* 2024;16(27):34591–34606. doi:10.1021/acsami.4c04985
19. Liu X, Qian R, Li B, Zhang Y, Han Y. Sono-catalytic tooth whitening and oral health enhancement with oxygen vacancies-enriched mesoporous TiO₂ nanospheres: a nondestructive approach for daily tooth care. *ACS Biomater Sci Engine.* 2024;10(10):6634–6647. doi:10.1021/acsbmaterials.4c01185
20. Hu X, Xie L, Xu Z, et al. Photothermal-enhanced fenton-like catalytic activity of oxygen-deficient nanotitania for efficient and safe tooth whitening. *ACS Appl Mater Interfaces.* 2021;13(30):35315–35327. doi:10.1021/acsami.1c06774
21. Wu S, Zhang Q, Lin D, et al. Near-infrared responsive biomimetic Titanate/TiO₂-xHeterostructure: a therapeutic strategy for combating implant-associated infection and enhancing osseointegration. *ACS Appl Mater Interfaces.* 2024;16(33):43227–43243. doi:10.1021/acsami.4c06154
22. Chundayil Madathil G, Iyer S, Thankappan K, Gowd GS, Nair S, Koyakutty M. A novel surface enhanced Raman catheter for rapid detection, classification, and grading of oral cancer. *Adv Healthcare Mater.* 2019;8(13):1801557. doi:10.1002/adhm.201801557
23. Xu Z, Hu X, Xie L, et al. Visible light-induced photocatalytic chlorine activation enhanced the 0.5% neutral-NaClO/TiO₂-x system as an efficient and safe root canal irrigant. *Chem Engine J.* 2022;431:134119. doi:10.1016/j.cej.2021.134119
24. Shu T, Wang X, Li M, et al. Nanoscaled Titanium oxide layer provokes quick osseointegration on 3D-printed dental implants: a domino effect induced by hydrophilic surface. *ACS Nano.* 2024;18(1):783–797. doi:10.1021/acsnano.3c09285
25. de Paula Miranda RB, Ussui V, Ricci Lazar DR, de Lima NB, Marchi J, Cesar PF. Characterization of 3Y-TZP/TiO₂ hybrid experimental dental ceramics. *Ceramics Inter.* 2023;49(10):15734–15740. doi:10.1016/j.ceramint.2023.01.167
26. Zhao J, Xu J, Jian X, Xu J, Gao Z, Song -Y-Y. NIR light-driven photocatalysis on amphiphilic TiO₂ nanotubes for controllable drug release. *ACS Appl Mater Interfaces.* 2020;12(20):23606–23616. doi:10.1021/acsami.0c04260
27. Ahasan T, Edirisooriya EMNT, Senanayake PS, Xu P, Wang H. Advanced TiO₂-based photocatalytic systems for water splitting: comprehensive review from fundamentals to manufacturing. *Molecules.* 2025;30(5):1127. doi:10.3390/molecules30051127
28. Barcelos DA, Gonçalves MC. Daylight photoactive TiO₂ sol-gel nanoparticles: sustainable environmental contribution. *Materials.* 2023;16(7):2731. doi:10.3390/ma16072731
29. Ahmad S, Tian Y, Hashmi AW, et al. Experimental studies on mechanical properties of Al-7075/TiO₂ metal matrix composite and its tribological behaviour. *J Mater Res Technol.* 2024;30:8539–8552. doi:10.1016/j.jmrt.2024.05.227
30. Zeng Q, Liu K. Surface characterization and superhydrophilic properties of TiO₂ nanopores prepared by multi-step anodizing process. *Appl Surface Sci.* 2025;690:162617. doi:10.1016/j.apsusc.2025.162617
31. Zhang W, Ye C, Liu Q. Development of anti-reflective coatings with photocatalytic and hydrophobic self-cleaning property for solar cells. *SurfacesInterfaces.* 2025;65:106454. doi:10.1016/j.surfin.2025.106454
32. Van Landuyt KL, Snauwaert J, De Munck J, et al. Systematic review of the chemical composition of contemporary dental adhesives. *Biomaterials.* 2007;28(26):3757–3785. doi:10.1016/j.biomaterials.2007.04.044
33. Sun J, Forster AM, Johnson PM, et al. Improving performance of dental resins by adding titanium dioxide nanoparticles. *Dental Mater.* 2011;27(10):972–982. doi:10.1016/j.dental.2011.06.003
34. Rathod Y, Natu V. TiO₂ spaghetti for sustainable future. *Matter.* 2024;7(8):2735–2737. doi:10.1016/j.matt.2024.06.015
35. Huang B, Wang X, Sun S, et al. A room temperature ammonia sensor based on MoTe₂ nanosheets modified with TiO₂ nanoparticles. *J Hazard Mater.* 2025;494:138522. doi:10.1016/j.jhazmat.2025.138522
36. Dong Y, Tian X, Zhao H. Highly dispersed Pt on N-doped TiO₂ nanosheets for highly efficient selective hydrogenation of furfural. *J Molecular Struct.* 2025;1321:140107. doi:10.1016/j.molstruc.2024.140107
37. Boykobilov D, Thakur S, Samiev A, et al. Electrochemical synthesis and modification of novel TiO₂ nanotubes: chemistry and role of key synthesis parameters for photocatalytic applications in energy and environment. *Inorganic Chem Commun.* 2024;170:113419. doi:10.1016/j.inoche.2024.113419
38. Zuo F, Zhu Y, Wu T, et al. Titanium dioxide nanomaterials: progress in synthesis and application in drug delivery. *Pharmaceutics.* 2024;16(9):1214. doi:10.3390/pharmaceutics16091214
39. Ganesh SK, Chakravorty A, Raghavan V, Subathra Devi C. Chitosan coated ZnO/TiO₂/Gd₂O₃ nano composites for improved rapamycin delivery in non-small cell lung cancer. *International Jo Biolog Macromol.* 2025;319:145439. doi:10.1016/j.ijbiomac.2025.145439

40. Baranwal AK, Keerthiga G, Mohan L, et al. Controlled and localized drug delivery using Titania nanotubes. *Mater Today Commun.* 2022;32:103843. doi:10.1016/j.mtcomm.2022.103843
41. Ganguly S, Das P, Srinivasan S, Rajabzadeh AR, Tang XS, Margel S. Superparamagnetic amine-functionalized maghemite nanoparticles as a thixotropy promoter for hydrogels and magnetic field-driven diffusion-controlled drug release. *ACS App Nano Mater.* 2024;7(5):5272–5286. doi:10.1021/acsanm.3c05543
42. Liu N, Tu S, Zhang S, et al. A pH and near-infrared light dual-responsive drug delivery system based on TiO₂ nanotube arrays modified with polydopamine and Fe³⁺. *J Drug Delivery Sci Technol.* 2024;99:106003. doi:10.1016/j.jddst.2024.106003
43. Wang M-F, Yan T, Gao M-C, et al. A review of the advances in implant technology: accomplishments and challenges for the design of functionalized surface structures. *Biomed Mater.* 2025;20(3):032003. doi:10.1088/1748-605X/adca7c
44. Zhu Y, Liang H, Liu X, et al. Regulation of macrophage polarization through surface topography design to facilitate implant-to-bone osteointegration. *Sci Adv.* 2021;7(14):eabf6654. doi:10.1126/sciadv.abf6654
45. Yu D, Guo S, Yang D, Li B, Guo Z, Han Y. Interrod spacing dependent angiogenesis and osseointegration of Na₂TiO₃ nanorods-patterned arrays via immunoregulation. *Chem Engine J.* 2021;426:131187. doi:10.1016/j.cej.2021.131187
46. Li R, Zhang H, Yao X, Tang B, Chu PK, Zhang X. Regulation of TiO₂ nanoarrays on titanium implants for enhanced osteogenic activity and immunomodulation. *J Mater Sci Technol.* 2023;150:233–244. doi:10.1016/j.jmst.2022.12.023
47. Pei Y, Wang Y, Chen J, et al. Bionic nanostructures create mechanical signals to mediate the composite structural bone regeneration through multi-system regulation. *Adv Sci.* 2025;e02299. doi:10.1002/advs.202502299
48. Wang S, Zhang S, Cui Y, et al. Titanium dioxide bioceramics prepared by 3D printing method and its structure effect on stem cell behavior. *Ceramics Inter.* 2024;50(11):20410–20420. doi:10.1016/j.ceramint.2024.03.164
49. Peiris S, de Silva HB, Ranasinghe KN, Bandara SV, Perera IR. Recent development and future prospects of TiO₂ photocatalysis. *J Chin Chem Soc.* 2021;68(5):738–769. doi:10.1002/jccs.202000465
50. Romero-Morán A, Sánchez-Salas JL, Molina-Reyes J. Influence of selected reactive oxygen species on the photocatalytic activity of TiO₂/SiO₂ composite coatings processed at low temperature. *Appl Catalysis B Environ.* 2021;291:119685. doi:10.1016/j.apcatb.2020.119685
51. Tang D, Cui M, Wang B, Liang G, Zhang H, Xiao H. Nanoparticles destabilizing the cell membranes triggered by NIR light for cancer imaging and photo-immunotherapy. *Nat Commun.* 2024;15(1):6026. doi:10.1038/s41467-024-50020-w
52. Chi M, Sun X, Lozano-Blanco G, Tatarchuk BJ. XPS and FTIR investigations of the transient photocatalytic decomposition of surface carbon contaminants from anatase TiO₂ in UHV starved water/oxygen environments. *Appl Surface Sci.* 2021;570:151147. doi:10.1016/j.apsusc.2021.151147
53. Guo J, Feng K, Wu W, et al. Smart 131 I-labeled self-illuminating photosensitizers for deep tumor therapy. *Angewandte Chemie Inter Edition.* 2021;60(40):21884–21889. doi:10.1002/anie.202107231
54. Jiang X, Xu L, Ji W, et al. One plus one greater than two: ultrasensitive surface-enhanced raman scattering by TiO₂/ZnO heterojunctions based on electron-hole separation. *Appl Surface Sci.* 2022;584:152609. doi:10.1016/j.apsusc.2022.152609
55. Linghu X, Shu Y, Liu L, et al. Enhanced photocatalytic degradation of organic pollutants and pathogens in wastewater using a full-spectrum response NaYF₄:Yb,Tm@TiO₂/Ag₃PO₄ nanoheterojunction. *Enviro Technol Innov.* 2022;28:102927. doi:10.1016/j.eti.2022.102927
56. Nair RV, Gummaluri VS, Matham MV, C V. A review on optical bandgap engineering in TiO₂ nanostructures via doping and intrinsic vacancy modulation towards visible light applications. *J Phys Appl Phys.* 2022;55(31):313003. doi:10.1088/1361-6463/ac6135
57. Junnan Q, Huimin L, Guihong L, Yao C. Innovation of TiO₂-x nanomaterials in the biomedical field: synthesis, properties, and application prospects. *Chem Engine J.* 2024;491:151773. doi:10.1016/j.cej.2024.151773
58. Loh JYY. Could metamaterials be the next frontier of catalysis? *Small.* 2025;21(4):2405140. doi:10.1002/smll.202405140
59. Lv K, Hou M, Kou Y, et al. Black Titania Janus mesoporous nanomotor for enhanced tumor penetration and near-infrared light-triggered photodynamic therapy. *ACS Nano.* 2024;18(21):13910–13923. doi:10.1021/acsnano.4c03652
60. Yu T, Zhang W, Hou C, et al. Confined growth of oxygen-vacancy rich TiO₂-x nanoparticles with heterophase junction for high-efficiency photocatalytic water purification. *Surfaces Interfaces.* 2024;48:104323. doi:10.1016/j.surfin.2024.104323
61. Li Y, Zhu Y, Wang M, et al. Recent progress on titanium sesquioxide: fabrication, properties, and applications. *Adv Funct Mater.* 2022;32(33):2203491. doi:10.1002/adfm.202203491
62. Liu Q, Sun Q, Gao W, et al. Turning built-in electric field of porphyrin on Ti³⁺ self-doped blue-TiO₂ hollow nanospheres boosts peroxidase-like activity for high-performance biosensing. *Chem Engine J.* 2022;441:136070. doi:10.1016/j.cej.2022.136070
63. Yin G, Huang X, Chen T, et al. Hydrogenated Blue Titania for efficient solar to chemical conversions: preparation, characterization, and reaction mechanism of CO₂ reduction. *ACS Catalysis.* 2018;8(2):1009–1017. doi:10.1021/acscatal.7b03473
64. Komtchou S, Dirany A, Drogui P, et al. Degradation of atrazine in aqueous solution with electrophotocatalytic process using TiO₂-x photoanode. *Chemosphere.* 2016;157:79–88. doi:10.1016/j.chemosphere.2016.05.022
65. Tan X, Liu S, Hu X, et al. Near-infrared-enhanced dual enzyme-mimicking Ag–TiO₂-x@alginate microspheres with antibactericidal and oxygenation abilities to treat periodontitis. *ACS Appl Mater Interfaces.* 2023;15(1):391–406. doi:10.1021/acsami.2c17065
66. Wu S-M, Liu X-L, Lian X-L, et al. Homojunction of oxygen and titanium vacancies and its interfacial n–p effect. *Adv Mater.* 2018;30(32):1802173. doi:10.1002/adma.201802173
67. Zhang S, Cao S, Zhang T, Lee JY. Plasmonic oxygen-deficient TiO₂-x Nanocrystals for dual-band electrochromic smart windows with efficient energy recycling. *Adv Mater.* 2020;32(43):2004686. doi:10.1002/adma.202004686
68. Xiong J, Zhang M, Cheng G. Facile polyol-triggered anatase–rutile heterophase TiO₂-x nanoparticles for enhancing photocatalytic CO₂ reduction. *J Colloid Interface Sci.* 2020;579:872–877. doi:10.1016/j.jcis.2020.06.103
69. Subash A, Bylapudi B, Thakur S, Rao VUS. Oral cancer in India, a growing problem: is limiting the exposure to avoidable risk factors the only way to reduce the disease burden? *Oral Oncol.* 2022;125:105677. doi:10.1016/j.oraloncology.2021.105677
70. Ekanayaka RP, Tilakaratne WM. Impact of histopathological parameters in prognosis of oral squamous cell carcinoma. *Oral Dis.* 2025;31(5):1420–1438. doi:10.1111/odi.15035
71. Agrawal R, Tofighbakhsh A, Davidson J, Gabriele J. Early detection of oral cavity cancer: a comprehensive literature review of risk factors and latest techniques in diagnosis. *Curr Surg Rep.* 2025;13(1):15. doi:10.1007/s40137-024-00442-8

72. van den Einden LCG, De hullu JA, Massuger LFAG, et al. Interobserver variability and the effect of education in the histopathological diagnosis of differentiated vulvar intraepithelial neoplasia. *Modern Pathol.* 2013;26(6):874–880. doi:10.1038/modpathol.2012.235
73. Cooper L, Sertel O, Kong J, Lozanski G, Huang K, Gurcan M. Feature-based registration of histopathology images with different stains: an application for computerized follicular lymphoma prognosis. *Comp Meth Program Biomed.* 2009;96(3):182–192. doi:10.1016/j.cmpb.2009.04.012
74. Singh R, Yadav V, Dhillon AK, Sharma A, Ahuja T, Siddhanta S. Emergence of raman spectroscopy as a probing tool for theranostics. *Nanotheranostics.* 2023;7(3):216–235. doi:10.7150/ntno.81936
75. Zhang S, Qi Y, Tan SPH, Bi R, Olivo M. Molecular fingerprint detection using Raman and infrared spectroscopy technologies for cancer detection: a progress review. *Biosensors.* 2023;13(5):557. doi:10.3390/bios13050557
76. Yang D, Youden B, Carrier A, et al. Nanomaterials for surface-enhanced Raman spectroscopy-based metal detection: a review. *Environ Chem Letters.* 2024;22(5):2425–2465. doi:10.1007/s10311-024-01758-8
77. Zhao X, Xu W, Tang X, Wen J, Wang Y. Design of Ag/TiO₂/Ag composite nano-array structure with adjustable SERS-activity. *Materials.* 2022;15(20):7311. doi:10.3390/ma15207311
78. Dash P, Thirumurugan S, Tseng C-L, et al. Synthesis of methotrexate-loaded dumbbell-shaped titanium dioxide/gold nanorods coated with mesoporous silica and decorated with upconversion nanoparticles for near-infrared-driven trimodal cancer treatment. *ACS Appl Mater Interfaces.* 2023;15(28):33335–33347. doi:10.1021/acsami.3c04300
79. Zhu S, Deng B, Liu F, Li J, Lin L, Ye J. Surface-enhanced Raman scattering bioimaging with an ultrahigh signal-to-background ratio under ambient light. *ACS Appl Mater Interfaces.* 2022;14(7):8876–8887. doi:10.1021/acsami.2c01063
80. Lipiäinen T, Pessi J, Movahedi P, et al. Time-gated Raman spectroscopy for quantitative determination of solid-state forms of fluorescent pharmaceuticals. *Analyt Chem.* 2018;90(7):4832–4839. doi:10.1021/acs.analchem.8b00298
81. Sloan-Dennison S, Wallace GQ, Hassanain WA, Laing S, Faulds K, Graham D. Advancing SERS as a quantitative technique: challenges, considerations, and correlative approaches to aid validation. *Nano Conver.* 2024;11(1):33. doi:10.1186/s40580-024-00443-4
82. Sun B, Bte Rahmat JN, Zhang Y. Advanced techniques for performing photodynamic therapy in deep-seated tissues. *Biomaterials.* 2022;291:121875. doi:10.1016/j.biomaterials.2022.121875
83. Huang H, Miao Y, Li Y. Recent advances of piezoelectric materials used in sonodynamic therapy of tumor. *Coord Chem Rev.* 2025;523:216282. doi:10.1016/j.ccr.2024.216282
84. Huang H, Zheng Y, Chang M, et al. Ultrasound-based micro-/nanosystems for biomedical applications. *Chem Rev.* 2024;124(13):8307–8472. doi:10.1021/acs.chemrev.4c00009
85. Zhu K, Wang J, Wang Z, Chen Q, Song J, Chen X. Ultrasound-activated theranostic materials and their bioapplications. *Angewandte Chemie International Edition.* 2025;64(22):e202422278. doi:10.1002/anie.202422278
86. Chen Z, Sang L, Liu Y, Bai Z. Sono-piezo dynamic therapy: utilizing piezoelectric materials as sonosensitizer for sonodynamic therapy. *Adv Sci.* 2025;12(12):2417439. doi:10.1002/adv.202417439
87. Cui H, Zhu W, Yue C, Yang M, Ren W, Wu A. Recent progress of ultrasound-responsive titanium dioxide sonosensitizers in cancer treatment. *Chin Chem Letters.* 2024;35(10):109727. doi:10.1016/j.ccl.2024.109727
88. Moosavi Nejad S, Takahashi H, Hosseini H, et al. Acute effects of sono-activated photocatalytic titanium dioxide nanoparticles on oral squamous cell carcinoma. *Ultrason Sonochem.* 2016;32:95–101. doi:10.1016/j.ulsonch.2016.02.026
89. Janakiram C, Dye BA. A public health approach for prevention of periodontal disease. *Periodontol 2000.* 2020;84(1):202–214. doi:10.1111/prd.12337
90. Tibúrcio-Machado CS, Michelin C, Zanatta FB, Gomes MS, Marin JA, Bier CA. The global prevalence of apical periodontitis: a systematic review and meta-analysis. *Inter Endodontic J.* 2021;54(5):712–735. doi:10.1111/iej.13467
91. Hummel R, Akveld NAE, Bruers JJM, van der Sanden WJM, Su N, van der Heijden GJMG. Caries progression rates revisited: a systematic review. *J Dental Res.* 2019;98(7):746–754. doi:10.1177/0022034519847953
92. Peterson BW, He Y, Ren Y, et al. Viscoelasticity of biofilms and their recalcitrance to mechanical and chemical challenges. *FEMS Microbiol Rev.* 2015;39(2):234–245. doi:10.1093/femsre/fuu008
93. Opsahl Vital S, Haignere-Rubinstein C, Lasfargues -J-J, Chaussain C. Caries risk and orthodontic treatment. *Inter Orthodont.* 2010;8(1):28–45. doi:10.1016/j.ortho.2009.12.003
94. Bollen A-M, Cunha-Cruz J, Bakko DW, Huang GJ, Hujoel PP. The effects of orthodontic therapy on periodontal health: a systematic review of controlled evidence. *J Am Dent Assoc.* 2008;139(4):413–422. doi:10.14219/jada.archive.2008.0184
95. Yong -S-S, Lee J-I, Kang D-H. TiO₂-based photocatalyst Generated reactive oxygen species cause cell membrane disruption of staphylococcus aureus and escherichia coli O157:H7. *Food Microbiol.* 2023;109:104119. doi:10.1016/j.fm.2022.104119
96. Kong Q, Qi M, Li W, et al. A novel Z-scheme heterostructured Bi₂S₃/Cu-TCPP nanocomposite with synergistically enhanced therapeutics against bacterial biofilm infections in periodontitis. *Small.* 2023;19(43):2302547. doi:10.1002/sml.202302547
97. Sun Y, Sun X, Li X, et al. A versatile nanocomposite based on nanoceria for antibacterial enhancement and protection from aPDT-aggravated inflammation via modulation of macrophage polarization. *Biomaterials.* 2021;268:120614. doi:10.1016/j.biomaterials.2020.120614
98. Sun X, Sun J, Sun Y, et al. Oxygen self-sufficient nanoplatform for enhanced and selective antibacterial photodynamic therapy against anaerobe-induced periodontal disease. *Adv Funct Mater.* 2021;31(20):2101040. doi:10.1002/adfm.202101040
99. Cheng S, Qi M, Li W, et al. Dual-responsive nanocomposites for synergistic antibacterial therapies facilitating bacteria-infected wound healing. *Adv Healthcare Mater.* 2023;12(6):2202652. doi:10.1002/adhm.202202652
100. Li H, Huang Y, Zhou X, et al. Intelligent pH-responsive dental sealants to prevent long-term microleakage. *Dental Mater.* 2021;37(10):1529–1541. doi:10.1016/j.dental.2021.08.002
101. Wang R, Jia C, Zheng N, et al. Effects of photodynamic therapy on streptococcus mutans and enamel remineralization of multifunctional TiO₂-HAP composite nanomaterials. *Photodiagn Photodynamic Therapy.* 2023;42:103141. doi:10.1016/j.pdpdt.2022.103141
102. Zane A, Zuo R, Villamena FA, et al. Biocompatibility and antibacterial activity of nitrogen-doped titanium dioxide nanoparticles for use in dental resin formulations. *Inter J Nanomed.* 2016;11:6459–6470. doi:10.2147/IJN.S117584
103. Prasad N, Dasson Bajaj P, Shenoy R, Dutta A, Thomas MS. Sodium hypochlorite concentration and postendodontic pain - unveiling the optimal balance: a systematic review and meta-analysis. *J Endodont.* 2024;50(9):1233–1244. doi:10.1016/j.joen.2024.06.005

104. Qi M, Li X, Sun X, et al. Novel nanotechnology and near-infrared photodynamic therapy to kill periodontitis-related biofilm pathogens and protect the periodontium. *Dental Mater.* 2019;35(11):1665–1681. doi:10.1016/j.dental.2019.08.115
105. Cascione M, De Matteis V, Pellegrino P, et al. Improvement of PMMA dental matrix performance by addition of titanium dioxide nanoparticles and clay nanotubes. *Nanomaterials.* 2021;11(8):2027. doi:10.3390/nano11082027
106. Rajeswari SR, Nandini V, Perumal A, Rajendran, Gowda T, Gowda T. Influence of titania nanotubes diameter on its antibacterial efficacy against periodontal pathogens: an in vitro analysis. *J Pharm Bioall Sci.* 2021;13(Suppl 1):S284–s88. doi:10.4103/jpbs.JPBS_743_20
107. Yeniyl S, He Z, Yüksel B, et al. Antibacterial activity of as-annealed TiO₂ nanotubes doped with Ag nanoparticles against periodontal pathogens. *Bioinorganic Chem Appl.* 2014;2014:829496. doi:10.1155/2014/829496
108. Wen Z, Shi X, Li X, et al. Mesoporous TiO₂ coatings regulate ZnO nanoparticle loading and Zn²⁺ release on titanium dental implants for sustained osteogenic and antibacterial activity. *ACS Appl Mater Interfaces.* 2023;15(12):15235–15249. doi:10.1021/acsami.3c00812
109. Rosenbaum J, Versace DL, Abbad-Andaloussi S, et al. Antibacterial properties of nanostructured Cu–TiO₂ surfaces for dental implants. *Biomater Sci.* 2017;5(3):455–462. doi:10.1039/C6BM00868B
110. Sundararaj D, Venkatachalapathy S, Tandon A, Pereira A. Critical evaluation of incidence and prevalence of white spot lesions during fixed orthodontic appliance treatment: a meta-analysis. *J Inter Soc Prev Commun Dentist.* 2015;5(6):433–439. doi:10.4103/2231-0762.167719
111. Chun M-J, Shim E, Kho E-H, et al. Surface modification of orthodontic wires with photocatalytic titanium oxide for its antiadherent and antibacterial properties. *Angle Orthodontist.* 2007;77(3):483–488. doi:10.2319/0003-3219(2007)077[0483:SMOOWW]2.0.CO;2
112. Kuroiwa A, Nomura Y, Ochiai T, et al. Antibacterial, hydrophilic effect and mechanical properties of orthodontic resin coated with UV-responsive photocatalyst. *Materials.* 2018;11(6):889. doi:10.3390/ma11060889
113. Sodagar A, Akhoundi MSA, Bahador A, et al. Effect of TiO₂ nanoparticles incorporation on antibacterial properties and shear bond strength of dental composite used in orthodontics. *Dental Press J Orthodont.* 2017;22(5):67–74. doi:10.1590/2177-6709.22.5.067-074.oar
114. Mollabashi V, Farmany A, Alikhani MY, et al. Effects of TiO₂-coated stainless steel orthodontic wires on streptococcus mutans bacteria: a clinical study. *Inter J Nanomed.* 2020;15:8759–8766. doi:10.2147/IJN.S258440
115. Ahmad Fauzi NA, Ireland AJ, Sherriff M, Bandara HMHN, Su B. Nitrogen doped titanium dioxide as an aesthetic antimicrobial filler in dental polymers. *Dental Mater.* 2022;38(1):147–157. doi:10.1016/j.dental.2021.10.019
116. Zhao X, Li N, Zhang Z, et al. Beyond hype: unveiling the Real challenges in clinical translation of 3D printed bone scaffolds and the fresh prospects of bioprinted organoids. *J Nanobiotechnol.* 2024;22(1):500. doi:10.1186/s12951-024-02759-z
117. Ji Y, Zhang J, Hou M, et al. Review: osseointegration of titanium-based and zirconia implants: novel perspective on features, influencing factors and improvements. *J Mater Sci.* 2024;59(34):16020–16037. doi:10.1007/s10853-024-10126-4
118. Zhao L, Mei S, Chu PK, Zhang Y, Wu Z. The influence of hierarchical hybrid micro/nano-textured titanium surface with titania nanotubes on osteoblast functions. *Biomaterials.* 2010;31(19):5072–5082. doi:10.1016/j.biomaterials.2010.03.014
119. Zhao X, Wang G, Zheng H, et al. Delicate refinement of surface nanotopography by adjusting TiO₂ coating chemical composition for enhanced interfacial biocompatibility. *ACS Appl Mater Interfaces.* 2013;5(16):8203–8209. doi:10.1021/am402319a
120. Zhang X, Zhang G, Chai M, Yao X, Chen W, Chu PK. Synergistic antibacterial activity of physical-chemical multi-mechanism by TiO₂ nanorod arrays for safe biofilm eradication on implant. *Bioact Mater.* 2021;6(1):12–25. doi:10.1016/j.bioactmat.2020.07.017
121. Stipnice L, Narkevica I, Sokolova M, Loos J, Ozolins J. Novel scaffolds based on hydroxyapatite/poly(vinyl alcohol) nanocomposite coated porous TiO₂ ceramics for bone tissue engineering. *Ceramics Inter.* 2016;42(1):1530–1537. doi:10.1016/j.ceramint.2015.09.101
122. Pelaseyed SS, Madaah Hosseini HR, Samadikuchaksaraei A. A novel pathway to produce biodegradable and bioactive PLGA/TiO₂ nanocomposite scaffolds for tissue engineering: air–liquid foaming. *J Biomed Mater Res Part A.* 2020;108(6):1390–1407. doi:10.1002/jbm.a.36910
123. Mirhadi SM, Hassanzadeh Nemati N, Tavangarian F, Daliri Joupari M. Fabrication of hierarchical meso/macroporous TiO₂ scaffolds by evaporation-induced self-assembly technique for bone tissue engineering applications. *Mater Characteriz.* 2018;144:35–41. doi:10.1016/j.matchar.2018.06.035
124. Wan Y, Chang P, Yang Z, Xiong G, Liu P, Luo H. Constructing a novel three-dimensional scaffold with mesoporous TiO₂ nanotubes for potential bone tissue engineering. *J Mater Chem B.* 2015;3(27):5595–5602. doi:10.1039/C5TB00609K
125. Tiainen H, Wohlfahrt JC, Verket A, Lyngstadaas SP, Haugen HJ. Bone formation in TiO₂ bone scaffolds in extraction sockets of minipigs. *Acta Biomaterialia.* 2012;8(6):2384–2391. doi:10.1016/j.actbio.2012.02.020
126. Verket A, Müller B, Wohlfahrt JC, et al. TiO₂ scaffolds in peri-implant dehiscence defects: an experimental pilot study. *Clin Oral Implants Res.* 2016;27(10):1200–1206. doi:10.1111/clr.12725
127. Dong Y, Hu Y, Hu X, et al. Synthetic nanointerfacial bioengineering of Ti implants: on-demand regulation of implant–bone interactions for enhancing osseointegration. *Mater Horizons.* 2025;12(3):694–718. doi:10.1039/D4MH01237B
128. Wu B, Tang Y, Wang K, Zhou X, Xiang L. Nanostructured titanium implant surface facilitating osseointegration from protein adsorption to osteogenesis: the example of TiO₂ NTAs. *Inter J Nanomed.* 2022;17:1865–1879. doi:10.2147/IJN.S362720
129. Chang Y, Shao Y, Liu Y, et al. Mechanical strain promotes osteogenic differentiation of mesenchymal stem cells on TiO₂ nanotubes substrate. *Biochem Biophys Res Commun.* 2019;511(4):840–846. doi:10.1016/j.bbrc.2019.02.145
130. Wang C, Liu Y, Hu X, et al. Titanium dioxide nanotubes increase purinergic receptor P2Y₆ expression and activate its downstream PKC α -ERK1/2 pathway in bone marrow mesenchymal stem cells under osteogenic induction. *Acta Biomaterialia.* 2023;157:670–682. doi:10.1016/j.actbio.2022.11.045
131. Liu Y, Tong Z, Wang C, et al. TiO₂ nanotubes regulate histone acetylation through F-actin to induce the osteogenic differentiation of BMSCs. *Artifi Cells Nanomed Biotechnol.* 2021;49(1):398–406. doi:10.1080/21691401.2021.1910282
132. Li Z, Qiu J, Du LQ, Jia L, Liu H, Ge S. TiO₂ nanorod arrays modified Ti substrates promote the adhesion, proliferation and osteogenic differentiation of human periodontal ligament stem cells. *Mater Sci Engine.* 2017;76:684–691. doi:10.1016/j.msec.2017.03.148
133. Sabino RM, Mondini G, Kipper MJ, Martins AF, Popat KC. Tanfloc/heparin polyelectrolyte multilayers improve osteogenic differentiation of adipose-derived stem cells on titania nanotube surfaces. *Carbohydrate Polymers.* 2021;251:117079. doi:10.1016/j.carbpol.2020.117079
134. Xu R, Hu X, Yu X, et al. Micro-/nano-topography of selective laser melting titanium enhances adhesion and proliferation and regulates adhesion-related gene expressions of human gingival fibroblasts and human gingival epithelial cells. *Inter J Nanomed.* 2018;13:5045–5057. doi:10.2147/IJN.S166661

135. Lu R, Wang C, Wang X, et al. Effects of hydrogenated TiO₂ nanotube arrays on protein adsorption and compatibility with osteoblast-like cells. *Inter J Nanomed.* 2018;13:2037–2049. doi:10.2147/IJN.S155532
136. Zhang W, Gu J, Li K, et al. A hydrogenated black TiO₂ coating with excellent effects for photothermal therapy of bone tumor and bone regeneration. *Mater Sci Engine.* 2019;102:458–470. doi:10.1016/j.msec.2019.04.025
137. Jiang P, Liang J, Song R, et al. Effect of octacalcium-phosphate-modified micro/nanostructured titania surfaces on osteoblast response. *ACS Appl Mater Interfaces.* 2015;7(26):14384–14396. doi:10.1021/acsami.5b03172
138. Su K, Tan L, Liu X, et al. Rapid photo-sonotherapy for clinical treatment of bacterial infected bone implants by creating oxygen deficiency using sulfur doping. *ACS Nano.* 2020;14(2):2077–2089. doi:10.1021/acsnano.9b08686
139. Yang M, Qiu S, Coy E, et al. NIR-responsive TiO₂ biometasurfaces: toward in situ photodynamic antibacterial therapy for biomedical implants. *Adv Mater.* 2022;34(6):2106314. doi:10.1002/adma.202106314
140. Venkataprasanna KS, Prakash J, Anusuya T, Devanand Venkatasubbu G. Size dependent mechanistic activity of titanium dioxide nanoparticles for enhanced fibroblast cell proliferation and anti-bacterial activity. *J Sol-Gel Sci Technol.* 2021;99(3):565–575. doi:10.1007/s10971-021-05600-3
141. Zhao L, Chu PK, Zhang Y, Wu Z. Antibacterial coatings on titanium implants. *J Biomed Mater Res.* 2009;91B(1):470–480. doi:10.1002/jbm.b.31463
142. Shen S-C, Letchmanan K, Chow PS, Tan RBH. Antibiotic elution and mechanical property of TiO₂ nanotubes functionalized PMMA-based bone cements. *J Mech Behav Biomed Mater.* 2019;91:91–98. doi:10.1016/j.jmbm.2018.11.020
143. Lin W-T, Tan H-L, Duan Z-L, et al. Inhibited bacterial biofilm formation and improved osteogenic activity on gentamicin-loaded titania nanotubes with various diameters. *Inter J Nanomed.* 2014;9(null):1215–1230. doi:10.2147/IJN.S57875
144. Li Y, Ji T, Torre M, et al. Aromatized liposomes for sustained drug delivery. *Nat Commun.* 2023;14(1):6659. doi:10.1038/s41467-023-41946-8
145. Hashemi A, Ezati M, Mohammadnejad J, Houshmand B, Faghihi S. Chitosan coating of tio2 nanotube arrays for improved metformin release and osteoblast differentiation. *Inter J Nanomed.* 2020;Volume 15:4471–4481. doi:10.2147/IJN.S248927
146. Abbasnezhad N, Zirak N, Shirinbayan M, Tcharkhtchi A, Bakir F. On the importance of physical and mechanical properties of PLGA films during drug release. *J Drug Delivery Sci Technol.* 2021;63:102446. doi:10.1016/j.jddst.2021.102446
147. Rahnamaee SY, Bagheri R, Heidarpour H, Vossoughi M, Golizadeh M, Samadikuchaksaraei A. Nanofibrillated chitosan coated highly ordered titania nanotubes array/graphene nanocomposite with improved biological characters. *Carbohydr Polym.* 2021;254:117465. doi:10.1016/j.carbpol.2020.117465
148. Dong Y, Ye H, Liu Y, et al. pH dependent silver nanoparticles releasing titanium implant: a novel therapeutic approach to control peri-implant infection. *Colloids Surfaces B.* 2017;158:127–136. doi:10.1016/j.colsurfb.2017.06.034
149. Li B, Ma J, Wang D, et al. Self-adjusting antibacterial properties of Ag-incorporated nanotubes on micro-nanostructured Ti surfaces. *Biomater Sci.* 2019;7(10):4075–4087. doi:10.1039/C9BM00862D
150. Bauer S, Park J, Pittrof A, Song -Y-Y, von der Mark K, Schmuiki P. Covalent functionalization of TiO₂ nanotube arrays with EGF and BMP-2 for modified behavior towards mesenchymal stem cells. *Integra Biol.* 2011;3(9):927–936. doi:10.1039/c0ib00155d
151. Chen B, Liang Y, Song Y, et al. Photothermal-controlled release of IL-4 in IL-4/PDA-immobilized black titanium dioxide (TiO₂) nanotubes surface to enhance osseointegration: an in vivo study. *Materials.* 2022;15(17):5962. doi:10.3390/ma15175962
152. Liu S, Chen X, Yu M, et al. Applications of titanium dioxide nanostructure in stomatology. *Molecules.* 2022;27(12):3881. doi:10.3390/molecules27123881
153. Azmy E, Al-Kholi MRZ, Fattouh M, Kenawi LMM, Helal MA, Wu F-G. Impact of nanoparticles additions on the strength of dental composite resin. *Inter J Biomater.* 2022;2022:1165431. doi:10.1155/2022/1165431
154. Raorane DV, Chaughule RS, Pednekar SR, Lokur A. Experimental synthesis of size-controlled TiO₂ nanofillers and their possible use as composites in restorative dentistry. *Saudi Dental J.* 2019;31(2):194–203. doi:10.1016/j.sdentj.2019.01.008
155. Mirjalili A, Zamanian A, Hadavi SMM. The effect of TiO₂ nanotubes reinforcement on the mechanical properties and wear resistance of silica micro-filled dental composites. *J Comp Mater.* 2019;53(23):3217–3228. doi:10.1177/0021998318818882
156. Dafar MO, Grol MW, Canham PB, Dixon SJ, Rizkalla AS. Reinforcement of flowable dental composites with titanium dioxide nanotubes. *Dental Mater.* 2016;32(6):817–826. doi:10.1016/j.dental.2016.03.022
157. Karaca MK, Kam Hepdeniz O, Esencan Turkaslan B, Gurdal O. Correction to: the effect of functionalized titanium dioxide nanotube reinforcement on the water sorption and water solubility properties of flowable bulk-fill composite resins. *Odontology.* 2022;110(2):329. doi:10.1007/s10266-022-00695-8
158. Yu B, Ahn J-S, Lim JI, Lee Y-K. Influence of TiO₂ nanoparticles on the optical properties of resin composites. *Dental Mater.* 2009;25(9):1142–1147. doi:10.1016/j.dental.2009.03.012
159. Kantovitz KR, Fernandes FP, Feitosa IV, et al. TiO₂ nanotubes improve physico-mechanical properties of glass ionomer cement. *Dental Mater.* 2020;36(3):e85–e92. doi:10.1016/j.dental.2020.01.018
160. Hamid N, Telgi RL, Tirth A, Tandon V, Chandra S, Chaturvedi RK. Titanium dioxide nanoparticles and cetylpyridinium chloride enriched glass-ionomer restorative cement: a comparative study assessing compressive strength and antibacterial activity. *J Clin Pediatr Dentist.* 2019;43(1):42–45. doi:10.17796/1053-4625-43.1.8
161. Garcia-Contreras R, Scougall-Vilchis RJ, Contreras-Bulnes R, Sakagami H, Morales-Luckie RA, Nakajima H. Mechanical, antibacterial and bond strength properties of nano-titanium-enriched glass ionomer cement. *J Appl Oral Sci.* 2015;23(3):321–328. doi:10.1590/1678-775720140496
162. Mansoor A, Khan MT, Mehmood M, Khurshid Z, Ali MI, Jamal A. Synthesis and characterization of titanium oxide nanoparticles with a novel biogenic process for dental application. *Nanomaterials.* 2022;12(7):1078. doi:10.3390/nano12071078
163. Sun J, Xu Y, Zhu B, et al. Synergistic effects of titanium dioxide and cellulose on the properties of glassionomer cement. *Dental Mater J.* 2019;38(1):41–51. doi:10.4012/dmj.2018-001
164. Amin F, Fareed MA, Zafar MS, Khurshid Z, Palma PJ, Kumar N. Degradation and stabilization of resin-dentine interfaces in polymeric dental adhesives: an updated review. *Coatings.* 2022;12(8):1094. doi:10.3390/coatings12081094
165. Esteban Florez FL, Kraemer H, Hiers RD, et al. Sorption, solubility and cytotoxicity of novel antibacterial nanofilled dental adhesive resins. *Scie Rep.* 2020;10(1):13503. doi:10.1038/s41598-020-70487-z
166. Ramos-Tonello CM, Lisboa-Filho PN, Arruda LB, et al. Titanium dioxide nanotubes addition to self-adhesive resin cement: effect on physical and biological properties. *Dental Mater.* 2017;33(7):866–875. doi:10.1016/j.dental.2017.04.022

167. Shahmiri R, Standard OC, Hart JN, Sorrell CC. Optical properties of zirconia ceramics for esthetic dental restorations: a systematic review. *J Prosth Dentist*. 2018;119(1):36–46. doi:10.1016/j.prosdent.2017.07.009
168. Agac O, Gozutok M, Sasmazel HT, Ozturk A, Park J. Mechanical and biological properties of Al₂O₃ and TiO₂ co-doped zirconia ceramics. *Ceramics Inter*. 2017;43(13):10434–10441. doi:10.1016/j.ceramint.2017.05.080
169. Ladha K, Shah D. An in-vitro evaluation of the flexural strength of heat-polymerized poly (methyl methacrylate) denture resin reinforced with fibers. *J Indian Prosthodont Soc*. 2011;11(4):215–220. doi:10.1007/s13191-011-0086-5
170. Zhang X, Zhang X, Zhu B, Lin K, Chang J. Mechanical and thermal properties of denture PMMA reinforced with silanized aluminum borate whiskers. *Dental Mater J*. 2012;31(6):903–908. doi:10.4012/dmj.2012-016
171. Kasina SP, Ajaz T, Attili S, Surapaneni H, Cherukuri M, Srinath HP. To evaluate and compare the porosities in the acrylic mandibular denture bases processed by two different polymerization techniques, using two different brands of commercially available denture base resins - an in vitro study. *J Inter Oral Health*. 2014;6(1):72–77.
172. Tsuji M, Ueda T, Sawaki K, Kawaguchi M, Sakurai K. Biocompatibility of a titanium dioxide-coating method for denture base acrylic resin. *Gerodontology*. 2016;33(4):539–544. doi:10.1111/ger.12204
173. Silva CDS, Machado AL, Chaves Cd CDAL, Pavarina AC, Vergani CE. Effect of thermal cycling on denture base and autopolymerizing relines resins. *J Appl Oral Sci*. 2013;21(3):219–224. doi:10.1590/1679-775720130061
174. Bangera MK, Kotian R, N R. Effect of titanium dioxide nanoparticle reinforcement on flexural strength of denture base resin: a systematic review and meta-analysis. *Japanese Dental Sci Rev*. 2020;56(1):68–76. doi:10.1016/j.jdsr.2020.01.001
175. Azmy E, Al-kholy MRZ, Al-Thobity AM, Gad MM, Helal MA, Chen W-C. Comparative effect of incorporation of ZrO₂, TiO₂, and SiO₂ nanoparticles on the strength and surface properties of PMMA denture base material: an in vitro study. *Inter Biomater*. 2022;2022(1):5856545. doi:10.1155/2022/5856545
176. Cierech M, Szerszeń M, Wojnarowicz J, Łojkowski W, Kostrzewa-Janicka J, Mierzwińska-Nastalska E. Preparation and characterisation of poly (methyl metacrylate)-titanium dioxide nanocomposites for denture bases. *Polymers*. 2020;12(11):2655. doi:10.3390/polym12112655
177. Darwish G, Huang S, Knoernschild K, et al. Improving polymethyl methacrylate resin using a novel titanium dioxide coating. *J Prosthodontic*. 2019;28(9):1011–1017. doi:10.1111/jopr.13032
178. Yadfout A, Asri Y, Merzouk N, Regragui A. Denture base resin coated with titanium dioxide (TiO₂): a systematic review. *Inter J Nanomed*. 2023;18:6941–6953. doi:10.2147/IJN.S425702
179. Gad MM, Abualsaud R. Behavior of PMMA denture base materials containing titanium dioxide nanoparticles: a literature review. *Inter J Biomater*. 2019;2019:6190610. doi:10.1155/2019/6190610
180. de Boa PWM, de Sousa Santos K, da Silva Souza AM, da Silva-Júnior AA, Borges BCD. Impact of nanostructured additives in tooth bleaching agents on enhancing color change and reducing side effects: a scoping review. *Clin Oral Invest*. 2025;29(1):70. doi:10.1007/s00784-025-06148-0
181. Guo B, Tao Y, Yang T, et al. Biomaterials based on advanced oxidation processes in tooth whitening: fundamentals, progress, and models. *J Mater Chem B*. 2024;12(38):9459–9477. doi:10.1039/D4TB01311E
182. Cheng Y-L, Su C, Zhong B-J, Yu H. Bleaching effectiveness of hydrogen peroxide containing titanium dioxide: a systematic review and meta-analysis. *J Dentist*. 2025;156:105692. doi:10.1016/j.jdent.2025.105692
183. Martín J, Vildósola P, Bersezio C, et al. Effectiveness of 6% hydrogen peroxide concentration for tooth bleaching—A double-blind, randomized clinical trial. *J Dentist*. 2015;43(8):965–972. doi:10.1016/j.jdent.2015.05.011
184. Bortolatto JF, Pretel H, Floros MC, et al. Low concentration H₂O₂/TiO₂ in office Bleaching. *J Dental Res*. 2014;93(7_suppl):66S–71S. doi:10.1177/0022034514537466
185. Ghadimi E, Eimar H, Marelli B, et al. Trace elements can influence the physical properties of tooth enamel. *SpringerPlus*. 2013;2(1):499. doi:10.1186/2193-1801-2-499
186. Eimar H, Marelli B, Nazhat SN, et al. The role of enamel crystallography on tooth shade. *J Dentist*. 2011;39:e3–e10. doi:10.1016/j.jdent.2011.11.008
187. Huang J, Best SM, Bonfield W, Buckland T. Development and characterization of titanium-containing hydroxyapatite for medical applications. *Acta Biomaterialia*. 2010;6(1):241–249. doi:10.1016/j.actbio.2009.06.032
188. Kury M, Esteban Florez FL, Tabchoury CPM, Cavalli V. Effects of experimental in-office bleaching gels incorporated with co-doped titanium dioxide nanoparticles on dental enamel physical properties. *Odontology*. 2025;113(1):318–330. doi:10.1007/s10266-024-00976-4
189. Rifane TO, Nascimento IS, Santos SCAV, Mesquita LR, de Paula DM, Feitosa VP. Peroxide-free titanium dioxide nanoparticle-based photocatalytic bleaching: in vitro study on bovine teeth. *BioMed Res Inter*. 2025;2025(1):9311501. doi:10.1155/bmri/9311501
190. Ali M. What function of nanoparticles is the primary factor for their hyper-toxicity? *Adv Colloid Interface Science*. 2023;314:102881. doi:10.1016/j.cis.2023.102881
191. Boutillier S, Fourmentin S, Laperche B. History of titanium dioxide regulation as a food additive: a review. *Environ Chem Letters*. 2022;20(2):1017–1033. doi:10.1007/s10311-021-01360-2
192. Gojznikar J, Zdravković B, Vidak M, Leskošek B, Ferik P. TiO₂ nanoparticles and their effects on eukaryotic cells: a double-edged sword. *Inter J Mol Sci*. 2022;23(20):12353. doi:10.3390/ijms232012353
193. Li L, Sun W, Yu J, Lei W, Zeng H, Shi B. Effects of titanium dioxide microparticles and nanoparticles on cytoskeletal organization, cell adhesion, migration, and proliferation in human gingival fibroblasts in the presence of lipopolysaccharide. *J Periodont Res*. 2022;57(3):644–659. doi:10.1111/jre.12993
194. Chang X, Zhang Y, Tang M, Wang B. Health effects of exposure to nano-TiO₂: a meta-analysis of experimental studies. *Nanoscale Res Letters*. 2013;8(1):51. doi:10.1186/1556-276X-8-51
195. Abbasi-Oshaghi E, Mirzaei F, Pourjafar M. NLRP3 inflammasome, oxidative stress, and apoptosis induced in the intestine and liver of rats treated with titanium dioxide nanoparticles: in vivo and in vitro study. *Inter J Nanomed*. 2019;14:1919–1936. doi:10.2147/IJN.S192382
196. Brand W, Peters RJB, Braakhuis HM, Maślankiewicz L, Oomen AG. Possible effects of titanium dioxide particles on human liver, intestinal tissue, spleen and kidney after oral exposure. *Nanotoxicology*. 2020;14(7):985–1007. doi:10.1080/17435390.2020.1778809
197. Sang X, Li B, Ze Y, et al. Toxicological mechanisms of nanosized titanium dioxide-induced spleen injury in mice after repeated peroral application. *J Agricul Food Chem*. 2013;61(23):5590–5599. doi:10.1021/jf3035989

198. Gui S, Li B, Zhao X, et al. Renal injury and Nrf2 modulation in mouse kidney following chronic exposure to TiO₂ nanoparticles. *J Agric Food Chem.* 2013;61(37):8959–8968. doi:10.1021/jf402387e
199. Sheng L, Wang X, Sang X, et al. Cardiac oxidative damage in mice following exposure to nanoparticulate titanium dioxide. *J Biomed Mater Res Part A.* 2013;101(11):3238–3246. doi:10.1002/jbm.a.34634
200. Cao X, Han Y, Gu M, et al. Foodborne titanium dioxide nanoparticles induce stronger adverse effects in obese mice than non-obese mice: gut microbiota dysbiosis, colonic inflammation, and proteome alterations. *Small.* 2020;16(36):2001858. doi:10.1002/sml.202001858
201. Gao G, Ze Y, Li B, et al. Ovarian dysfunction and gene-expressed characteristics of female mice caused by long-term exposure to titanium dioxide nanoparticles. *J Hazard Mater.* 2012;243:19–27. doi:10.1016/j.jhazmat.2012.08.049
202. Shukla RK, Sharma V, Pandey AK, Singh S, Sultana S, Dhawan A. ROS-mediated genotoxicity induced by titanium dioxide nanoparticles in human epidermal cells. *Toxicol Vitro.* 2011;25(1):231–241. doi:10.1016/j.tiv.2010.11.008
203. Dar GI, Saeed M, Wu A. Toxicity of TiO₂ nanoparticles. *TiO₂ Nanoparticles.* 2020;67–103.
204. Song B, Liu J, Feng X, Wei L, Shao L. A review on potential neurotoxicity of titanium dioxide nanoparticles. *Nanoscale Res Letters.* 2015;10(1):342. doi:10.1186/s11671-015-1042-9
205. Baranowska-Wójcik E, Szwajgier D, Oleszczuk P, Winiarska-Mieczan A. Effects of titanium dioxide nanoparticles exposure on human health—a review. *Biologic Trace Element Res.* 2020;193(1):118–129. doi:10.1007/s12011-019-01706-6
206. Mou J, Lin T, Huang F, Chen H, Shi J. Black titania-based theranostic nanopatform for single NIR laser induced dual-modal imaging-guided PTT/PDT. *Biomaterials.* 2016;84:13–24. doi:10.1016/j.biomaterials.2016.01.009
207. Kononenko V, Drobne D. In vitro cytotoxicity evaluation of the magnéli phase titanium suboxides (Ti_xO_{2x-1}) on A549 human lung cells. *Inter J Mol Sci.* 2019;20(1):196. doi:10.3390/ijms20010196
208. Prokopiuk V, Yefimova S, Onishchenko A, et al. Assessing the cytotoxicity of TiO_{2-x} nanoparticles with a different Ti³⁺(Ti²⁺)/Ti⁴⁺ ratio. *Biological Trace Element Research.* 2023;201(6):3117–3130. doi:10.1007/s12011-022-03403-3
209. Ren W, Yan Y, Zeng L, et al. A near infrared light triggered hydrogenated black TiO₂ for cancer photothermal therapy. *Adv Healthcare Mater.* 2015;4(10):1526–1536. doi:10.1002/adhm.201500273
210. Liang S, Deng X, Xu G, et al. A novel Pt–TiO₂ heterostructure with oxygen-deficient layer as bilaterally enhanced sonosensitizer for synergistic chemo-sonodynamic cancer therapy. *Adv Funct Mater.* 2020;30(13):1908598. doi:10.1002/adfm.201908598
211. Shen J, Karges J, Xiong K, Chen Y, Ji L, Chao H. Cancer cell membrane camouflaged iridium complexes functionalized black-titanium nanoparticles for hierarchical-targeted synergistic NIR-II photothermal and sonodynamic therapy. *Biomaterials.* 2021;275:120979. doi:10.1016/j.biomaterials.2021.120979
212. Saxena M, Loza-Rosas SA, Gaur K, Sharma S, Pérez Otero SC, Tinoco AD. Exploring titanium(IV) chemical proximity to iron(III) to elucidate a function for Ti(IV) in the human body. *Coord Chem Rev.* 2018;363:109–125. doi:10.1016/j.ccr.2018.03.006
213. Laisney J, Chevallet M, Fauquant C, et al. Ligand-promoted surface solubilization of TiO₂ nanoparticles by the enterobactin siderophore in biological medium. *Biomolecules.* 2022;12(10):1516. doi:10.3390/biom12101516
214. Zheng X, Zhang F, Wang K, et al. Smart biosensors and intelligent devices for salivary biomarker detection. *TrAC Trends Analy Chem.* 2021;140:116281. doi:10.1016/j.trac.2021.116281
215. Takakura Y, Takahashi Y. Strategies for persistent retention of macromolecules and nanoparticles in the blood circulation. *J Controlled Release.* 2022;350:486–493. doi:10.1016/j.jconrel.2022.05.063
216. Rodrigues CF, Fernandes N, de Melo-Diogo D, Correia IJ, Moreira AF. Cell-derived vesicles for nanoparticles coating: biomimetic approaches for enhanced blood circulation and cancer therapy. *Adv Healthcare Mater.* 2022;11(23):2201214. doi:10.1002/adhm.202201214
217. Wang Q, Liang Q, Dou J, et al. Breaking through the basement membrane barrier to improve nanotherapeutic delivery to tumours. *Nat Nanotechnol.* 2023. doi:10.1038/s41565-023-01498-w

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