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Review

Applications of Titanium Dioxide Nanostructure in Stomatology

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Abstract: Breakthroughs in the field of nanotechnology, especially in nanochemistry and nanofabrication technologies, have been attracting much attention, and various nanomaterials have recently been developed for biomedical applications. Among these nanomaterials, nanoscale titanium dioxide (nano-TiO_2) has been widely valued in stomatology due to the fact of its excellent biocompatibility, antibacterial activity, and photocatalytic activity as well as its potential use for applications such as dental implant surface modification, tissue engineering and regenerative medicine, drug delivery carrier, dental material additives, and oral tumor diagnosis and treatment. However, the biosafety of nano-TiO_2 is controversial and has become a key constraint in the development of nano-TiO_2 applications in stomatology. Therefore, in this review, we summarize recent research regarding the applications of nano-TiO_2 in stomatology, with an emphasis on its performance characteristics in different fields, and evaluations of the biological security of nano-TiO_2 applications. In addition, we discuss the challenges, prospects, and future research directions regarding applications of nano-TiO_2 in stomatology that are significant and worthy of further exploration.

Keywords: titanium dioxide; nanostructure; dental implant surface modification; antibacterial; dental material additives

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1. Introduction

The oral cavity is susceptible to a variety of biological, physical, chemical, and mechanical stimulations due to the fact of its dynamic and open characteristics. The hard and soft tissues of the oral cavity create an ideal environment for microbial growth and biofilm formation, making it prone to various oral diseases such as tooth and dental pulp diseases, tooth loss, periodontal disease, oral mucosal disease, tumor, and trauma. Therefore, there is a need to find a type of material that can meet the requirements for treating various oral diseases.

Recently, biomedical applications of nanomaterials have received considerable attention from researchers. Nanoscale titanium dioxide (nano-TiO_2) has been widely used in environmental protection, cosmetics, antibacterial agents, and composite nanofillers [1,2]; due to the fact of its unique size and high specific surface area, nano-TiO_2 has more stable physical and chemical properties compared to titanium dioxide. In addition, nano-TiO_2 has great application potential in biomedical fields [3,4] due to the fact of its good antibacterial activity, favorable biocompatibility, and unique photocatalytic activity [5].

Nano-TiO_2 nanostructures include titanium dioxide nanoparticles (TiO_2-NPs) and titanium dioxide nanotubes (TNTs). In nature, TiO_2-NPs mainly exist in the form of rutile, anatase, and brookite. Rutile is a stable phase, whereas anatase and brookite are metastable phases [6]. Anatase has the highest photocatalytic activity [7–9]. TNTs are

one-dimensional hollow structures. Preparation methods mainly include template synthesis [10], anodic oxidation [11], and hydrothermal synthesis [12]. Two different TiO_2 structures can produce reactive oxygen species to induce oxidative stress and destroy the cell walls of bacteria, thus exerting antibacterial activity and having strong mechanical properties in stomatology [13–16]. The most noteworthy are TNTs, which are considered to be ideal candidate materials for promoting the clinical therapeutic effects of medical implants among the various nanomorphological modifications of oral titanium (Ti) implants due to the fact of their enhanced biological activity and ability to achieve local drug elution [17,18].

The oral cavity's physiological function and pathological changes are closely related to the health of other parts of the body. Therefore, higher safety requirements should be put forward for materials used in the oral cavity. Before any material can be used in the mouth, its biosafety and stability in human tissue must be fully understood. Currently, the biological toxicity of nano-TiO_2 is considered to be related to its primary particle size, shape, agglomeration size, and other factors [19]. For example, the smaller the size of NPs, the more toxic they are thought to be [20,21]; needle- and short rod-shaped particles induce more cell damage than spherical- and long rod-shaped particles [22]. However, the existing experimental results and evidence do not specifically prove that nano-TiO_2 has serious effects on human tissue. Nano-TiO_2 has many advantages, acting as an oral cavity biomedical material and having huge application potential in stomatology (shown in Figure 1). Therefore, the application of nano-TiO_2 in stomatology deserves more in-depth research.

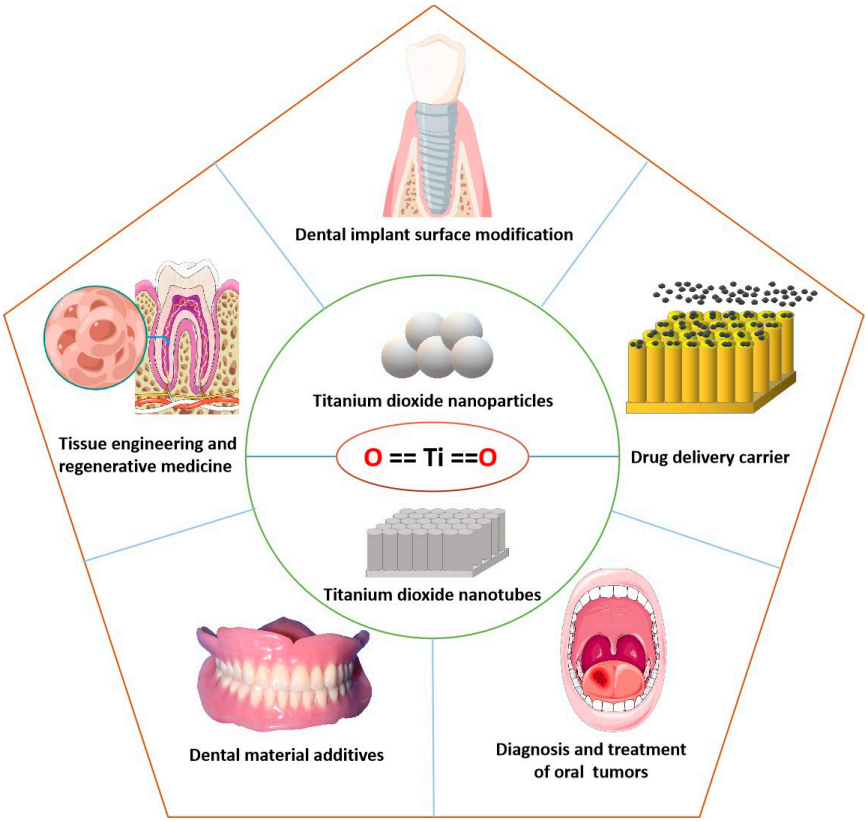

Figure 1. Common forms of nano-TiO_2 and its application in stomatology (the figure was drawn using Figdraw, and part of picture material is cited from https://smart.servier.com/ (accessed on 13 May 2022)).

In this review, we describe the characteristics and research status of applications of nano-TiO_2 according to the different research fields of oral disease treatment, we evaluate the toxicological effects of its applications, and we analyze the prospects and challenges

of its applications in stomatology. Our study should provide a basis for wider and safer applications of nano-TiO_2 in the field of stomatology in the future.

2. Surface Modification of Dental Implants

Ti and its alloys have good corrosion resistance, mechanical strength, and biocompatibility, making them ideal materials for dental implants [23–33]. However, the lack of biological activity on the surface of natural Ti implants makes them highly prone to bacterial infections [32,34,35] and often causes insufficient bone tissue integration [14]. These issues limit the application of Ti in dental implants. A bacterial infection usually occurs within the first two weeks after implantation [36]. Bacteria adhere to and grow on the implant surface to form a biofilm, which hinders the role of the immune system [37] and is resistant to antibiotics. In addition, the physical, chemical, and biological properties of the implant surface affect the proliferation, adhesion, growth, and differentiation of cells which, in turn, affect the osseous integration of the implant with surrounding tissues [38–42]. Therefore, the surfaces of implants should be modified appropriately to enhance antibacterial activity, to inhibit the formation of biofilms, and to avoid the occurrence of peri-implant infections [25,43], while at the same time guiding the biological behavior of cells, improving bone integration, and improving the success rate of implant surgery.

Nano-TiO_2 is one of the most studied metal oxides with antibacterial activity. It exhibits good bactericidal action against various Gram-positive and Gram-negative bacteria and fungi (e.g., *Escherichia coli* [15,16], *Staphylococcus aureus* [14,44,45], *Streptococcus mutans* [46], *Streptococcus sanguis* [47], and *Candida albicans* [48,49]) and, therefore, has potential for treating various oral infectious diseases [45,50] such as dental caries, periodontitis, dental pulp infection, and peri-implant inflammation [51]. Furthermore, TNTs can mimic the nanomorphology of the outer cell membranes of osteoblasts around implants, increasing the interaction between implant surfaces and neighboring cells, thereby enhancing osseointegration between native tissues and implant interfaces [52]. Therefore, nano-TiO_2 is an ideal structure for implant surface coating [53]. At present, methods for preparing nano-TiO_2 structural coatings on the surface of Ti and its alloy implants include an anodization technique [47,48], micro-arc oxidation [54], the sol-gel process [16], vapor deposition [44,55], pulse laser deposition [56], atomic layer deposition [37], and other methods.

On the surface of implants, nano-TiO_2 exhibits a good bacterial killing effect due to the fact of its small size and strong oxidation capacity; it can be combined with other antibacterial metals (such as silver [16,57]) [46,51] to achieve synergistic antibacterial effects [14,57], and it can be combined with antibiotics to combat drug-resistant strains [58]. Furthermore, Zhang et al. prepared neutrophils containing photocatalytic TiO_2-NPs in vivo, which fully mobilized the host's defense mechanism and achieved an effective and powerful therapeutic response to pathogenic bacterial infection with low drug resistance and low virulence [59]. In addition to the enhanced antibacterial effect, an implant surfaces modified by nano-TiO_2 also promoted the adhesion, proliferation, and growth of various mesenchymal stem cells (MSCs) [54,60], improving biocompatibility and bone integration [54,61].

To date, there have been several beneficial research results in the application of nano-TiO_2 to implant surface modification. For example, after preparing TNTs on the surface of Ti implants by an anodization technique, Huang et al. obtained implant surfaces with enhanced hydrophilicity and MSC differentiation and a higher percentage of bone–implant contact (BIC), which showed great potential for clinical applications [62]. Baoe et al. first loaded TNTs with simvastatin (Sim), a drug that can promote bone formation, and then coated the nanotubes (NTs) with a thermosensitive chitosan/glycerin/hydroxypropyl methylcellulose hydrogel (CGHH) coating to control the release of simvastatin. As compared with the Sim@NT and NT groups, the Sim@CGHH group showed higher alkaline phosphatase (ALP) activity, which was conducive to the osteogenic differentiation of MC3T3-E1 cells, and the number of E. coli colonies was also lower (as shown in Figure 2) [63]. Yong et al. prepared a FAgHA-TiO_2 (FagHA/TNT) nanocomposite double-layer coating on the surfaces of implants. The coating could simultaneously provide the

advantages of both TiO_2 and FagHA, and it had excellent antibacterial performance and cellular compatibility. Moreover, the anchoring effect of TNTs also increased the bonding strength of the coating by >17 MPa_2 and the corrosion resistance by nearly two orders of magnitude [42]. Although nano-TiO_2 in Ti implant surfaces has not been clinically applied due to the weak mechanical strength between it and Ti implants [64], in vitro studies have shown that nano-TiO_2 can provide good surface topography to improve the clinical performance of dental implants. In the future, nano-TiO_2 is expected to provide a promising surface modification strategy for improving the antimicrobial activity and biocompatibility of Ti implants with bone tissue.

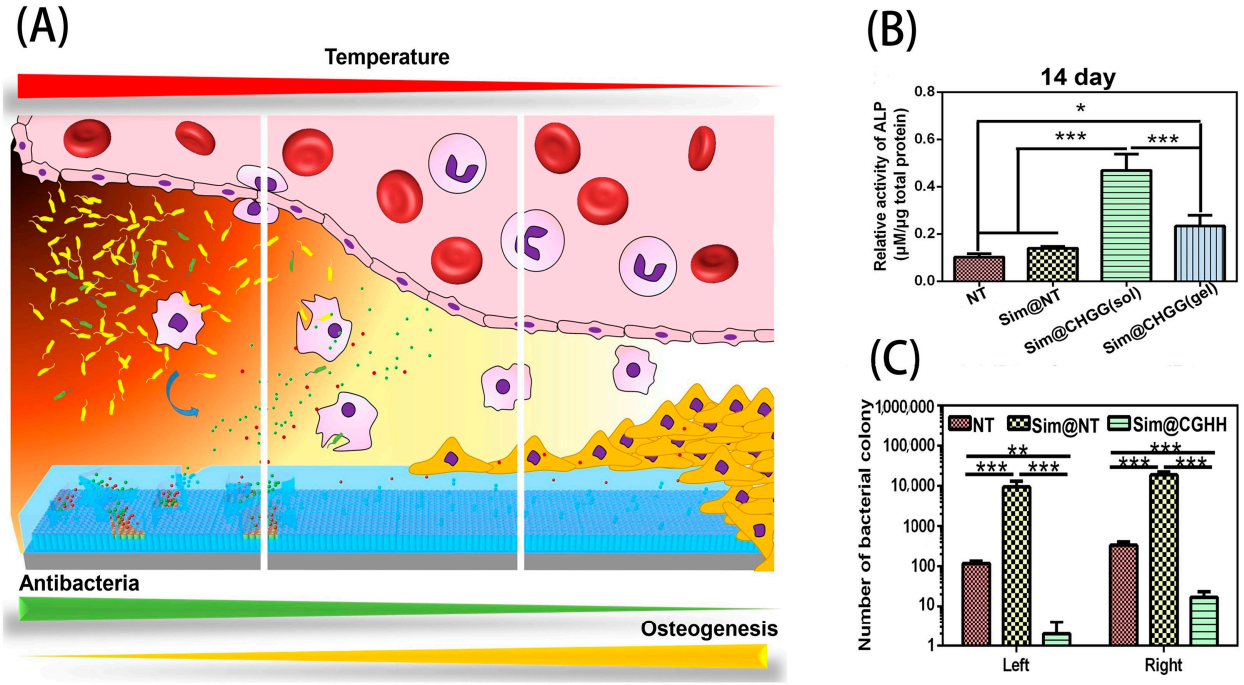

Figure 2. (**A**) The constructed coating. At a normal body temperature (37 °C), the hydrogel is in a sol state, which controls the continuous release of simvastatin and promotes long-term osteogenic differentiation. When the temperature rises to 40 °C, the hydrogel changes from sol to gel, releasing Gly to stimulate macrophages to polarize into a proinflammatory M1 phenotype to kill bacteria. (**B**) The results of the ALP activity of MC3T3-E1 after 14 days of culture. (**C**) *E. coli* colony count. Reprinted from Reference [63]; Copyright 2022, with permission from Elsevier. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

3. Applications in Tissue Engineering and Regenerative Medicine (TERM)

Recently, the field of tissue engineering and regenerative medicine in dentistry has shown great potential in the treatment of craniofacial and tooth defects caused by trauma, tumor, or other diseases. The field aims to research and develop biosubstitutes to repair damaged tissue structures and functions using elements such as biocompatible scaffolds, stem cells, and growth factors [65]. Scaffolds are an important part of research in this area, because they can provide the optimal aperture range for the specific cells that stem cells produce, mimic the extracellular matrix, and provide the appropriate culture medium for cell growth. Studies have shown that the mechanical properties and biological activity of commonly used bone tissue engineering scaffold materializers (bioceramics, polymers, etc.) can be improved by adding nano-TiO_2 [66,67] and can promote an increase in the production of mineralized matrix, making scaffolds with better biocompatibility and biological activity [67–69].

Although there have been many breakthroughs in the application of TERM in the oral cavity, it is difficult to achieve satisfactory bone integration after implantation due to

the inherent biological inertia, stress shielding effects, and limited space for bone inward growth of Ti implants commonly used in clinics today [70,71]. Therefore, promoting the regeneration and integration of bone defects around oral implants remains an urgent problem to be solved. In view of this situation, existing implants should be properly modified to promote the development of regenerative medicine in the oral cavity and better benefit patients with oral diseases.

Nanomaterials play a significant role in craniofacial and dental tissue engineering. Among them, TNTs exhibit excellent biological activity, which can improve the biological behavior of osteoblasts [72,73], human periodontal ligament stem cells (PDLSCs) [69], human bone-marrow-derived mesenchymal stem cells (BMSCs) [51,54], and adipose-derived stem cells (ADSCs) [60,74], thereby promoting bone integration directly. In addition, they can facilitate the adhesion and proliferation of fibroblasts [72,75], human gingival epithelial cells (HGECs), and human gingival fibroblasts (HGFs) [76], making the soft tissue around an implant form a protective tissue barrier for potential bone integration. Therefore, nano-TiO_2 can be directly incorporated into tissue engineering scaffolds to improve the mechanical properties of scaffolds and can also be applied to Ti implant coatings to provide effective surface modification [62,77]. For example, Roberta et al. prepared TNTs on implant surfaces and further modified them with polyelectrolyte multilayers (PEMs) based on Tanfloc (a cationic tannin derivative) and glycosaminoglycans (heparin and hyaluronic acid), increasing the rate of osteogenic differentiation and bone mineral deposition of ADSCs [78].

The osteogenic potential of TNTs is also reflected in their antioxidant properties [79]. Human osteogenesis is inhibited under oxidative stress [80], while nanotubes can effectively attenuate the negative effects of oxidative damage on osteogenesis via the synergistic effect of ITG $\alpha 5\beta 1$ and the activation of Wnt signaling [81]. The size of TNTs affects the biological behavior of stem cells. Shen and Seunghan's study showed that large TNTs were more conducive to the proliferation and differentiation of osteoblasts [82,83]. In addition, Yu's study showed that small TNTs were beneficial to the adhesion and proliferation of osteoblasts in a normal microenvironment, while large TNTs increased osteogenic differentiation. After H_2O_2 treatment (simulating oxidative stress), only large TNTs showed the cellular behavior of increasing osteoblast adhesion, survival, and differentiation (as shown in Figure 3) [81], indicating that large TNTs were more suitable for preventing oxidative damage [84]. These finding have implications for bone integration on implant surfaces in people with systemic diseases (diabetes, osteoporosis, etc.).

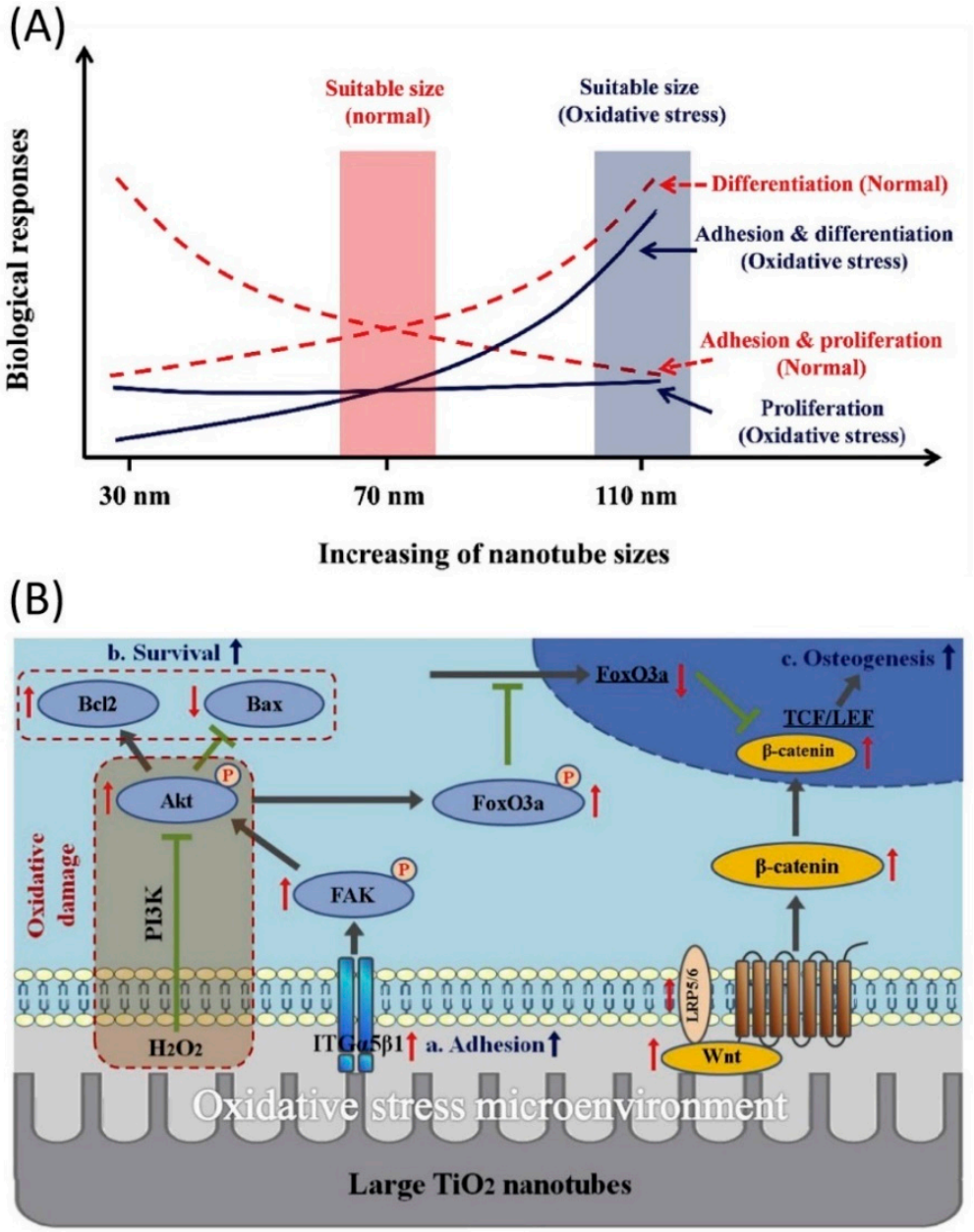

Figure 3. (**A**) Cell behavior in response to TNTs of different sizes in different microenvironments; (**B**) protective effect of large TNTs on ROS injury. Reprinted from Reference [81]; Copyright 2022, with permission from Elsevier. (a. The high expression of ITG α5β1 on TNT_{110} substrates promoted the early adhesion of osteo-blasts; b. The up-regulation of Bcl2 and down-regulation of Bax improved cell survival; c. High expression of p-FoxO3a and β-catenin proteins promoted the osteogenic differentiation).

4. Carrier for Drug Delivery

Targeted drug delivery and local drug delivery are considered to be the most forward-looking strategies to address the inherent limitations of traditional drug delivery [85]. The characteristics of oral diseases determine that treatment of them often requires local administration. The ideal oral local administration should provide sustainable and stable drug release, have a long-term therapeutic effect, and reduce the toxic side effects of drugs and medication frequency. Recently, advanced nanotechnology has produced various nanomaterials that are effective carriers of drugs and that are conducive to the efficient loading, targeted delivery, and controlled release of drugs. TNTs have become an ideal

substrate for drug delivery in stomatology [86,87] due to the fact of their higher drug loading capacity and slower drug release kinetics [88] as well as their excellent chemical inertia, mechanical robustness, and good biocompatibility.

Bacterial infection is the main reason for the failure of implant surgery. In order to prevent an infection around an implant after surgery, a drug sustained-release delivery system that can provide continuous release of antibacterial drugs at therapeutic concentrations over 4–6 weeks should be mounted on an implant surface [89]. Numerous studies have shown that TNT modification and antibiotic loading can significantly enhance the antibacterial ability and osteogenic activity of implants [90,91]. However, as a drug delivery system, TNTs have the disadvantage of uncontrollable drug release [92]. Researchers have found that covering the surfaces of the TNTs with a polymer layer is a promising way to solve the problem of their sudden release. Chitosan (CS) is a biopolymer with wide application potential. Coating the CS layer on porous TNT arrays can effectively control the release rate of drugs by controlling the thickness and degradation kinetics of the CS film [93–95]. Seyed et al. first prepared a completely regular titania nanotube (cRTNT) array on a titanium substrate, then prepared chitosan nanofiber (CH) and reduced graphene oxide (RGO) double-layer coatings on the nanotube, and finally loaded vancomycin (VM) into the system for experiments. The results showed that the system could improve the drug burst release and prolong the release time, as well as improve the osteogenic and antibacterial activity (as shown in Figure 4) [94]. This drug delivery system, which uses TNTs as carriers to prepare multifunctional surfaces through reasonable assembly of components with certain characteristics, has been used for loading and releasing a variety of antibiotics [17,92,96], indicating a promising direction for the development of advanced drug delivery systems.

In addition to CS, TNTs modified in other ways can also play an important role in drug delivery [97]. Baoe et al. found that the incorporation of AgNPs into TNTs showed valuable biological and time-dependent antibacterial properties. In the early stage, TNTs exhibited strong "release sterilization" activity that could prevent an initial infection after surgery. Then, they intelligently changed to exhibit "contact sterilization", thereby protecting implants from chronic infection, reducing the biosafety problems of AgNPs, and meeting various antibacterial requirements in different periods after biomaterial implantation [36]. Dong et al. prepared a pH-dependent AgNP-releasing implant through transplanting AgNPs onto the surface of an implant modified with TNTs via a low pH-sensitive acetal joint (TNT-Al-AgNPs). In the case of bacterial infection, the pH of the surface around the implant was reduced from 7.4 to 5.5 due to the bacterial metabolism and acid production, inducing the implant to release a higher dose of AgNPs than under physiological conditions, which increased the antibacterial efficiency of *Staphylococcus aureus* and *Enterobacter coli* by 12.7 times and 5.1 times, respectively, compared to that without infection, and it also enhanced the proliferation and differentiation of osteoblasts [98]. The photocatalytic activity of Nano-TiO_2 can only be triggered under ultraviolet (UV) irradiation, but UV has a limited penetration depth in tissue and can cause photodamage to biological tissues. Zhao designed a near-infrared (NIR) controlled drug delivery system with two hydrophilic structures using upconversion (UC) correlation strategies. The system triggered the photocatalytic activity of TiO_2-NTs through NIR and realized the controllable release of drugs; therefore, the hydrophobic monolayer on the surfaces of NTs could effectively reduce the toxicity of reactive oxygen species (ROS) on healthy skin cells, broadening the biological application of nano-TiO_2 [99]. These results indicate that TNTs can be used as a promising material for an oral medicine drug delivery system.

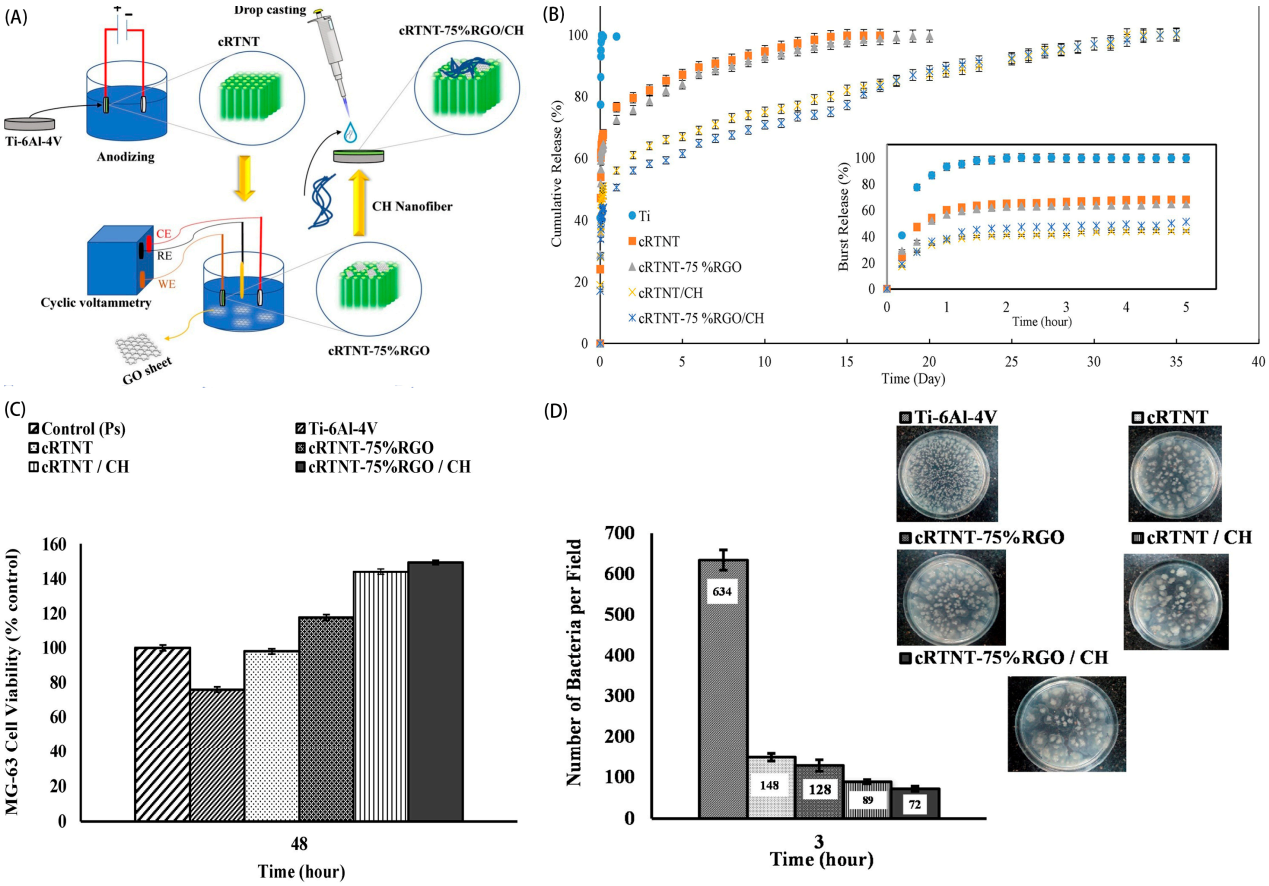

Figure 4. (**A**) Construction diagram of a nanofibrillated, chitosan-coated, highly ordered titania nanotube array/graphene nanocomposite; (**B**) release curves of vancomycin in different groups; (**C**) viability of MG63 cells in different groups; (**D**) colony count of Staphylococcus aureus in different groups. Reprinted from Reference [94]; Copyright 2022, with permission from Elsevier.

5. Additives in Dental Materials

TiO_2-NPs are ideal additives for enhancing the properties of polymer materials owing to their unique photocatalytic activity and chemical stability. As promising additives for dental materials, TiO_2-NPs mainly improve the antibacterial properties and mechanical strength of dental materials [100,101]. TiO_2-NPs have broad-spectrum antibacterial activity against microorganisms, with a noncontact bactericidal role [102], and they can be used as antibacterial fillers for dental composites [103]. Kuroiwa et al. applied a nano-TiO_2 coating on orthodontic resin to develop an orthodontic resin with antibacterial properties, and it achieved satisfactory results [104]. Moreover, the addition of TiO_2-NPs has been shown to improve the vinyl conversion degree of a resin [105] and to remarkably upgrade mechanical properties such as bending strength and hardness [106], thus enhancing the bond strength of the binder to teeth [107].

There have been many beneficial explorations of TiO_2-NPs as additives to enhance the antimicrobial properties and mechanical strength of dental materials. Two striking examples include poly(methyl methacrylate) (PMMA) and resin-modified glass ionomer cements. PMMA is one of the most widely used materials in the oral cavity, but its porous surface (conducive to microbial adhesion) and weak mechanical properties (leading to wear or fracture) are major problems in its application [108]. Adding TiO_2-NPs to PMMA can improve its mechanical stiffness, wear resistance, and fracture resistance, and it can reduce its roughness. The *C. Albicans* yeast colonization percentage of PMMA with 1% and 3% TiO_2-NPs decreased by 22% and 26%, respectively, after 48 h compared with PMMA without TiO_2-NPs [109,110]. Fully edentulous patients with 3D-printed dentures

showed significantly increased satisfaction in aesthetic, masticatory efficiency, and comfort, which maintained their improved characteristics after use for 18 months [111]. The weak mechanical strength and toughness of glass ionomer cement (GIC) are the main problems for permanent repair. The incorporation of TiO_2-NPs into GIC increased the particle size distribution and occupied the blank area between GIC particles to inhibit the propagation of cracks, thus enhancing the strength of the material [112]. The mechanical properties [113] and antibacterial properties [114] of the material were upgraded without affecting the bonding with enamel and dentin [115,116].

6. Assistance in the Diagnosis and Treatment of Oral Tumors

Oral cancer is a common malignant tumor of the head and neck, which is ranked as the sixth most common cancer in the whole body. Thus, simple, rapid, and accurate diagnostic tools are important for clinical diagnosis and treatment of tumors. Raman spectroscopy has been successfully used to detect tumor diseases in different parts of the body [117]. Nano-TiO_2 has attracted extensive attention in the development of surface-enhanced Raman scattering (SERS) substrates because of its easy growth and controllable nanostructure array [118]. Girish et al. constructed a catheter device with an SERS substrate consisting of foliated nano-TiO_2 modified using AgNPs. The SERS, composed of closely stacked adjacent foliated TiO_2 nanostructures and AgNPs, helped to form more "Raman" hot spots and could rapidly detect, classify, and grade normal, precancerous, and malignant tissues with high sensitivity and a high accuracy of 97.84%. The average detection time for each patient was only 25–30 min, which helped to improve the application effect of Raman spectroscopy in oral cancer detection [119].

At the early stage of malignant progression, circulating tumor cells (CTCs) can break away from original or metastatic tumors and then invade a distal site in different tissues of the body, which is the main route of cancer metastasis. Therefore, tumor progression can be determined by detecting CTCs, but CTCs are difficult to accurately detect and isolate as a result of their phenotypic heterogeneity and rarity [120]. Due to the fact of their large specific surface area, nanomaterials can enhance cell adhesion and, therefore, enhance the capture affinity and sensitivity of CTCs [121]. Nano-TiO_2 has great potential in efficiently and sensitively capturing CTCs [122]. The capture and release efficiencies of CTCs using a platform made of nano-TiO_2 were 92.9% and 89.9%, respectively, which was helpful for further diagnosis and treatment of tumors (the process of nano-TiO_2 modification and the capture and release of CTCs are shown in Figure 5) [123]. These studies show the potential of nano-TiO_2 applications in the diagnosis of oral tumors.

In addition to its diagnostic application for oral cancer, nano-TiO_2 can cause cytotoxicity and oxidative stress of cancer cells and can stimulate the production of ROS for cell killing; therefore, it has good anticancer activity [52]. TiO_2-NPs biologically modified by herbs show good anti-KB oral cancer cell performance and are also less toxic to normal cells [124,125]. In recent years, photodynamic therapy (PDT) based on photosensitizers that are activated to produce ROS after being irradiated with a specific wavelength of light to inhibit cancer cells has aroused great interest among scholars. However, due to the limited penetration depth of visible light, traditional PDT is limited to the treatment of superficial and flat lesions [126]. As a potential photosensitizer, TiO_2-NPs exhibit excellent UV-light induced cytotoxicity [127]. Upconversion nanoparticles (UCNs) have been embedded into TiO_2 matrix to improve the photocatalytic effect of TiO_2, showing great potential for improving the penetration depth limit of conventional PDT and for expanding the application of PDT to thick and solid advanced or recurrent head and neck cancers [128]. Currently, the use of nano-TiO_2 in the diagnosis and treatment of cancer has involved a number of cell and mouse experiments [129]; for example, a therapeutic diagnostic platform consisting of TiO_2-NPs doubled the survival rate of mice with multiple myeloma (MM), a malignant plasma cell disease of bone marrow origin [130]. In the future, more attention should be given to in vivo and clinical trials, and targeted research on oral cancer should be carried

out, striving for applications of this nanomaterial for oral cancer clinical treatment as soon as possible.

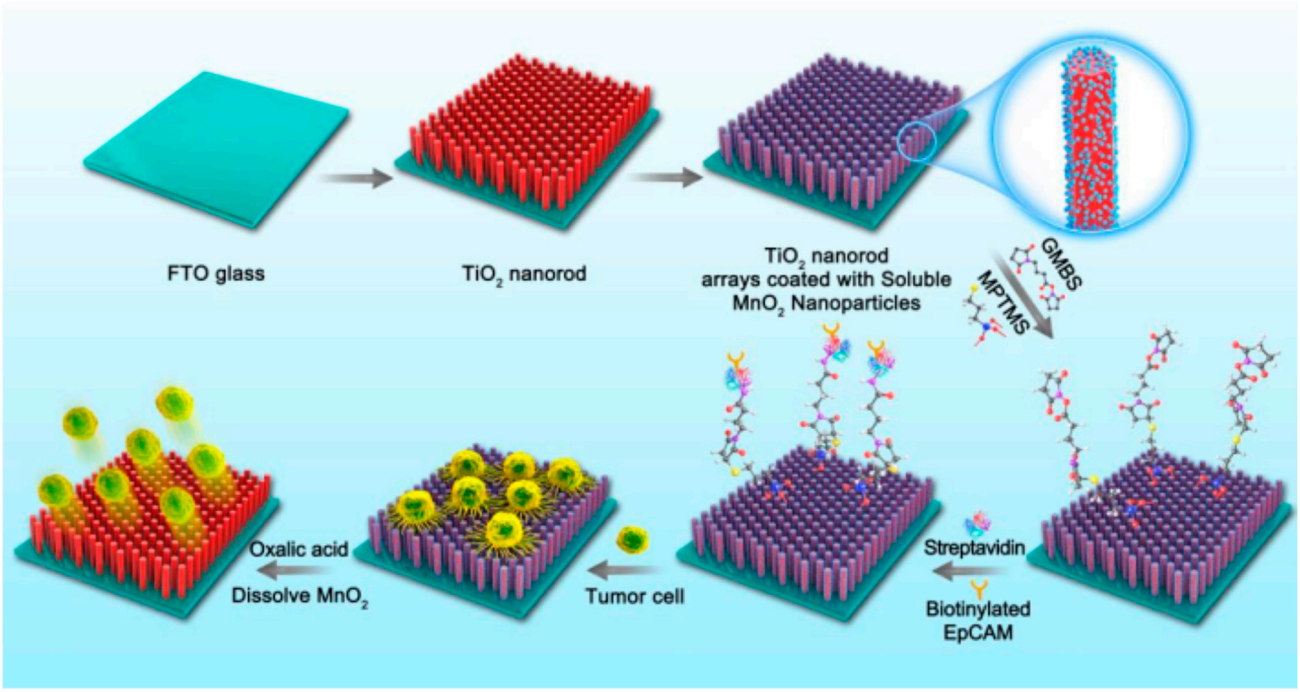

Figure 5. Modification of the substrate to capture and release CTCs. Reprinted with permission from Reference [123]; Copyright 2022, American Chemical Society.

7. Prospective Applications and Challenges of Nano-TiO_2 in Dentistry

Nano-TiO_2 has stable physicochemical properties, is inexpensive and easy to obtain, and has good biocompatibility; therefore, it is a research material that is considered to be significant in stomatology. The excellent antibacterial activity and biological activity of nano-TiO_2 provide a novel method for implant surface modification and tissue engineering. Its higher drug loading capacity and slower drug release kinetics make it a good carrier for oral drug delivery. Its strong antibacterial and mechanical properties make it a useful additive for dental materials. Moreover, its larger specific surface area can assist in the diagnosis of oral diseases.

Nevertheless, most studies on nano-TiO_2 are currently performed in vitro, and more information regarding the clinical outcomes of toxicity and biocompatibility is needed for careful evaluation before it is applied to clinical practice. At present, humans are mainly exposed to nano-TiO_2 through oral, inhalation, and skin contact; the oral route is the main type of exposure. In mouse experiments, after intragastric administration, TiO_2-NPs were absorbed by the gastrointestinal tract [131] and accumulated in the spleen and liver [132,133]. TiO_2-NPs have been shown to damage multiple organs of mice (intestine [134], liver [135], spleen [136], kidney [137], etc.) by inducing cell injury and changing the expression of inflammatory cytokines [138–141]. In addition, TiO_2-NPs have been reported to penetrate the placental barrier to induce developmental toxicity [142] and the blood–brain barrier (BBB) to induce neurotoxicity [22]. NPs deposited in the brain may induce oxidative stress imbalance, resulting in DNA damage and neurodegeneration, causing mice to exhibit significant behavioral deficits [143]. Intranasally administered TiO_2-NPs have been reported to accumulate in multiple organs (i.e., liver, spleen, kidney, brain, stomach, and heart) via pulmonary transport. High doses of TiO_2-NPs have been shown to cause or exacerbate some respiratory diseases [144,145], whereas long-term and low-concentration exposure (continuous exposure of A549 alveolar epithelial cells to 1–50 μg/mL TiO_2-NPs over 2 months) to TiO_2-NPs did not affect the cell viability of A549, but accumulation of TiO_2-NPs in the cells resulted in DNA damage, reduced cell prolifera-

tion rates, and caused an allergic response to methane methylsulfonate (MMS) [146]. After skin exposure, TiO_2-NPs were detectable in the stratum corneum layer of the epidermis and follicular epithelium but neither in the viable skin tissue nor in the internal organs (i.e., brain, liver, spleen, and kidney) [147]. There is no evidence of carcinogenicity, mutagenicity, or reproductive toxicity after skin exposure to nano-TiO_2 [148].

Due to the lack of reliable biosafety models, further studies on the biosafety of nano-TiO_2 are needed in the future. How to correctly and rationally use nano-TiO_2 is a challenge for researchers. Nevertheless, if we fully consider and prudently use nano-TiO_2 in the treatment of oral diseases, we believe it could significantly improve the therapeutic effect.

8. Conclusions

Nano-TiO_2 has low production costs, good physicochemical properties, and stable properties. Due to the fact of its photocatalytic sterilization and biocompatibility, it has great potential for the treatment of oral diseases. However, research on its application in oral disease treatment is still at the stage of cell and bacterial experiments in vitro and animal experiments in vivo, and currently there are no convincing clinical experimental results. There is still a long way to go before this nanomaterial can be applied in real-time clinical practice, and more investigative experiments are needed. In the future, while continuing to explore potential applications of nano-TiO_2 in stomatology, researchers also need to further explore methods to reduce its toxicity and to improve its mechanical stability and antibacterial effect. In addition, appropriate biological models need to be established as soon as possible for clinical research on the use of nano-TiO_2 to improve the oral health of the population.

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Abbreviations

Nanoscale titanium dioxide (nano-TiO_2), titanium dioxide nanoparticles (TiO_2-NPs), titanium dioxide nanotubes (TNTs), titanium (Ti), mesenchymal stem cells (MSCs), bone–implant contact (BIC), simvastatin (Sim), nanotubes (NTs), chitosan-glycerin-hydroxypropyl methyl cellulose hydrogel (CGHH), alkaline phosphatase (ALP), tissue engineering and regenerative medicine (TERM), periodontal ligament stem cells (PDLSCs), bone-marrow-derived mesenchymal stem cells (BMSCs), adipose-derived stem cells (ADSCs), human gingival epithelial cells (HGECs), human gingival fibroblasts (HGFs), polyelectrolyte multilayers (PEMs), chitosan (CS), regular titania nanotubes (cRTNTs), chitosan nanofibers (CHs), reduced graphene oxide (RGO), vancomycin (VM), ultraviolet (UV), near-infrared (NIR), upconversion (UC), reactive oxygen species (ROS), polymer poly(methyl methacrylate) (PMMA), glass ionomer cement (GIC), surface-enhanced Raman scattering (SERS), circulating tumor cells (CTCs), photodynamic therapy (PDT), upconversion nanoparticles (UCNs), multiple myeloma (MM), blood–brain barrier (BBB), and methane-methyl sulfonate (MMS).

References

1. Cuddy, M.F.; Poda, A.R.; Moser, R.D.; Weiss, C.A.; Cairns, C.; Steevens, J.A. A Weight-of-Evidence Approach to Identify Nanomaterials in Consumer Products: A Case Study of Nanoparticles in Commercial Sunscreens. *J. Expo. Sci. Environ. Epidemiol.* **2016**, *26*, 26–34. [CrossRef] [PubMed]
2. Weir, A.; Westerhoff, P.; Fabricius, L. Titanium Dioxide Nanoparticles in Food and Personal Care Products. *Environ. Sci. Technol. ES&T* **2012**, *46*, 2242–2250.
3. Ding, L.; Li, J.; Huang, R.; Liu, Z.; Li, C.; Yao, S.; Wang, J.; Qi, D.; Li, N.; Pi, J. Salvianolic Acid B Protects against Myocardial Damage Caused by Nanocarrier TiO_2; and Synergistic Anti-Breast Carcinoma Effect with Curcumin via Codelivery System of Folic Acid-Targeted and Polyethylene Glycol-Modified TiO_2 Nanoparticles. *Int. J. Nanomed.* **2016**, *11*, 5709–5727. [CrossRef]
4. Ai, J.W.; Liu, B.; Liu, W.D. Folic Acid-Tagged Titanium Dioxide Nanoparticles for Enhanced Anticancer Effect in Osteosarcoma Cells. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2017**, *76*, 1181–1187. [CrossRef]
5. Jia, L.; Qiu, J.; Du, L.; Li, Z.; Liu, H.; Ge, S. TiO_2 Nanorod Arrays as a Photocatalytic Coating Enhanced Antifungal and Antibacterial Efficiency of Ti Substrates. *Nanomedicine* **2017**, *12*, 761–776. [CrossRef] [PubMed]
6. Yang, F.; Liu, S.L.; Xu, Y.; Walker, S.G.; Cho, W.; Mironava, T.; Rafailovich, M. The Impact of TiO_2 Nanoparticle Exposure on Transmembrane Cholesterol Transport and Enhanced Bacterial Infectivity in Hela Cells. *Acta Biomater.* **2021**, *135*, 606–616. [CrossRef] [PubMed]
7. Zhang, J.; Zhou, P.; Liu, J.; Yu, J. New Understanding of the Difference of Photocatalytic Activity among Anatase, Rutile and Brookite TiO_2. *Phys. Chem. Chem. Phys.* **2014**, *16*, 20382–20386. [CrossRef]
8. Lee, W.S.; Park, Y.S.; Cho, Y.K. Significantly Enhanced Antibacterial Activity of TiO_2 Nanofibers with Hierarchical Nanostructures and Controlled Crystallinity. *Analyst* **2015**, *140*, 616–622. [CrossRef] [PubMed]
9. Dwivedi, C.; Dutta, V. Size Controlled Synthesis and Photocatalytic Activity of Anatase TiO_2 Hollow Microspheres. *Appl. Surf. Sci.* **2012**, *6*, 9584–9588. [CrossRef]
10. Xu, H.; Yu, W.; Zhang, J.; Zhou, Z.; Zhang, H.; Ge, H.; Wang, G.; Qin, Y. Rhodium Nanoparticles Confined in Titania Nanotubes for Efficient Hydrogen Evolution from Ammonia Borane. *J. Colloid. Interface Sci.* **2022**, *609*, 755–763. [CrossRef]
11. Santos, J.S.; Fereidooni, M.; Marquez, V.; Arumugam, M.; Tahir, M.; Praserthdam, S.; Praserthdam, P. Single-Step Fabrication of Highly Stable Amorphous TiO_2 Nanotubes Arrays (Am-Tnta) for Stimulating Gas-Phase Photoreduction of CO_2 to Methane. *Chemosphere* **2022**, *289*, 133170. [CrossRef] [PubMed]
12. Fan, L.; Liang, G.; Zhang, C.; Fan, L.; Yan, W.; Guo, Y.; Shuang, S.; Bi, Y.; Li, F.; Dong, C. Visible-Light-Driven Photoelectrochemical Sensing Platform Based on Bioi Nanoflowers/TiO_2 Nanotubes for Detection of Atrazine in Environmental Samples. *J. Hazard Mater.* **2021**, *409*, 124894. [CrossRef] [PubMed]
13. Saito, T.; Iwase, T.; Horie, J.; Morioka, T. Mode of Photocatalytic Bactericidal Action of Powdered Semiconductor TiO_2 on Mutans Streptococci. *J. Photochem. Photobiol. B* **1992**, *14*, 369–379. [CrossRef]
14. Yuan, Z.; Liu, P.; Hao, Y.; Ding, Y.; Cai, K. Construction of Ag-Incorporated Coating on Ti Substrates for Inhibited Bacterial Growth and Enhanced Osteoblast Response. *Colloids Surf. B Biointerfaces* **2018**, *171*, 597–605. [CrossRef]
15. Nesic, J.; Rtimi, S.; Laub, D.; Roglic, G.M.; Pulgarin, C.; Kiwi, J. New Evidence for TiO_2 Uniform Surfaces Leading to Complete Bacterial Reduction in the Dark: Critical Issues. *Colloids Surf. B Biointerfaces* **2014**, *123*, 593–599. [CrossRef] [PubMed]
16. Hou, X.; Ma, H.; Liu, F.; Deng, J.; Ai, Y.; Zhao, X.; Mao, D.; Li, D.; Liao, B. Synthesis of Ag Ion-Implanted TiO_2 Thin Films for Antibacterial Application and Photocatalytic Performance. *J. Hazard Mater.* **2015**, *299*, 59–66. [CrossRef] [PubMed]
17. Gulati, K.; Ramakrishnan, S.; Aw, M.S.; Atkins, G.J.; Findlay, D.M.; Losic, D. Biocompatible Polymer Coating of Titania Nanotube Arrays for Improved Drug Elution and Osteoblast Adhesion. *Acta Biomater.* **2012**, *8*, 449–456. [CrossRef]
18. Lai, M.; Jin, Z.; Su, Z. Surface Modification of TiO_2 Nanotubes with Osteogenic Growth Peptide to Enhance Osteoblast Differentiation. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2017**, *73*, 490–497. [CrossRef]
19. Lin, X.; Li, J.; Ma, S.; Liu, G.; Yang, K.; Tong, M.; Lin, D. Toxicity of TiO_2 Nanoparticles to Escherichia Coli: Effects of Particle Size, Crystal Phase and Water Chemistry. *PLoS ONE* **2014**, *9*, e110247. [CrossRef]
20. Hou, J.; Zhou, Y.; Wang, C.; Li, S.; Wang, X. Toxic Effects and Molecular Mechanism of Different Types of Silver Nanoparticles to the Aquatic Crustacean Daphnia Magna. *Environ. Sci. Technol.* **2017**, *51*, 12868–12878. [CrossRef]
21. Bruno, M.E.; Tasat, D.R.; Ramos, E.; Paparella, M.L.; Evelson, P.; Rebagliati, R.J.; Cabrini, R.L.; Guglielmotti, M.B.; Olmedo, D.G. Impact through Time of Different Sized Titanium Dioxide Particles on Biochemical and Histopathological Parameters. *J. Biomed. Mater. Res. A* **2014**, *102*, 1439–1448. [CrossRef] [PubMed]
22. Liu, X.; Sui, B.; Sun, J. Size- and Shape-Dependent Effects of Titanium Dioxide Nanoparticles on the Permeabilization of the Blood-Brain Barrier. *J. Mater. Chem. B* **2017**, *5*, 9558–9570. [CrossRef] [PubMed]
23. Zeng, Q.; Zhu, Y.; Yu, B.; Sun, Y.; Ding, X.; Xu, C.; Wu, Y.W.; Tang, Z.; Xu, F.J. Antimicrobial and Antifouling Polymeric Agents for Surface Functionalization of Medical Implants. *Biomacromolecules* **2018**, *19*, 2805–2811. [CrossRef] [PubMed]
24. Liu, Z.; Ma, S.; Duan, S.; Xuliang, D.; Sun, Y.; Zhang, X.; Xu, X.; Guan, B.; Wang, C.; Hu, M.; et al. Modification of Titanium Substrates with Chimeric Peptides Comprising Antimicrobial and Titanium-Binding Motifs Connected by Linkers to Inhibit Biofilm Formation. *ACS Appl. Mater. Interfaces* **2016**, *8*, 5124–5136. [CrossRef] [PubMed]
25. Rosenbaum, J.; Versace, D.L.; Abbad-Andallousi, S.; Pires, R.; Azevedo, C.; Cénédese, P.; Dubot, P. Antibacterial Properties of Nanostructured Cu-TiO_2 Surfaces for Dental Implants. *Biomater. Sci.* **2017**, *5*, 455–462. [CrossRef] [PubMed]

26. Li, Q.; Wang, Z. Involvement of Fak/P38 Signaling Pathways in Mediating the Enhanced Osteogenesis Induced by Nano-Graphene Oxide Modification on Titanium Implant Surface. *Int. J. Nanomed.* **2020**, *15*, 4659–4676. [CrossRef] [PubMed]
27. Huang, Q.; Elkhooly, T.A.; Liu, X.; Zhang, R.; Yang, X.; Shen, Z.; Feng, Q. Effects of Hierarchical Micro/Nano-Topographies on the Morphology, Proliferation and Differentiation of Osteoblast-Like Cells. *Colloids Surf. B Biointerfaces* **2016**, *145*, 37–45. [CrossRef] [PubMed]
28. Sobolev, A.; Valkov, A.; Kossenko, A.; Wolicki, I.; Zinigrad, M.; Borodianskiy, K. Bioactive Coating on Ti Alloy with High Osseointegration and Antibacterial Ag Nanoparticles. *ACS Appl. Mater. Interfaces* **2019**, *11*, 39534–39544. [CrossRef]
29. Li, Y.; Liu, Y.; Bai, H.; Li, R.; Shang, J.; Zhu, Z.; Zhu, L.; Zhu, C.; Che, Z.; Wang, J.; et al. Sustained Release of Vegf to Promote Angiogenesis and Osteointegration of Three-Dimensional Printed Biomimetic Titanium Alloy Implants. *Front. Bioeng. Biotechnol.* **2021**, *9*, 757767. [CrossRef]
30. Nan, J.; Zhijun, G.; Dan, S.; Yubao, L.; Yutao, Y.; Chen, C.; Li, Z.; Songsong, Z. Promoting Osseointegration of Ti Implants through Micro/Nanoscaled Hierarchical Ti Phosphate/Ti Oxide Hybrid Coating. *ACS Nano* **2018**, *12*, 7883–7891.
31. André, R.S.; Zamperini, C.A.; Mima, E.G.; Longo, V.M. Antimicrobial Activity of Tio2:Ag Nanocrystalline Heterostructures: Experimental and Theoretical Insights. *Chem. Phys.* **2015**, *459*, 87–95. [CrossRef]
32. Yu, Y.; Shen, X.; Liu, J.; Hu, Y.; Ran, Q.; Mu, C.; Cai, K. Regulation of Osteogenesis by Micro/Nano Hierarchical Titanium Surfaces through a Rock-Wnt5a Feedback Loop. *Colloids Surf. B Biointerfaces* **2018**, *170*, 1–10. [CrossRef] [PubMed]
33. Kapat, K.; Srivas, P.K.; Rameshbabu, A.P.; Maity, P.P.; Jana, S.; Dutta, J.; Majumdar, P.; Chakrabarti, D.; Dhara, S. Influence of Porosity and Pore-Size Distribution in Ti_6Al_4V Foam on Physicomechanical Properties, Osteogenesis, and Quantitative Validation of Bone Ingrowth by Micro-Computed Tomography. *ACS Appl. Mater. Interfaces* **2017**, *9*, 39235–392348. [CrossRef]
34. Bandyopadhyay, A.; Shivaram, A.; Tarafder, S.; Sahasrabudhe, H.; Banerjee, D.; Bose, S. In Vivo Response of Laser Processed Porous Titanium Implants for Load-Bearing Implants. *Ann. Biomed. Eng.* **2017**, *45*, 249–260. [CrossRef] [PubMed]
35. Sieniawski, J.; Ziaja, W. *Titanium Alloys—Advances in Properties Control*; IntechOpen: London, UK, 2013; Chapter 2.
36. Li, B.; Ma, J.; Wang, D.; Liu, X.; Li, H.; Zhou, L.; Liang, C.; Wang, H. Self-Adjusting Antibacterial Properties of Ag-Incorporated Nanotubes on Micro-Nanostructured Ti Surfaces. *Biomater. Sci.* **2019**, *7*, 4075–4087. [CrossRef] [PubMed]
37. Liu, L.; Bhatia, R.; Webster, T.J. Atomic Layer Deposition of Nano-TiO_2 Thin Films with Enhanced Biocompatibility and Antimicrobial Activity for Orthopedic Implants. *Int. J. Nanomed.* **2017**, *12*, 8711–8723. [CrossRef]
38. Cheng, M.; Qiao, Y.; Wang, Q.; Jin, G.; Qin, H.; Zhao, Y.; Peng, X.; Zhang, X.; Liu, X. Calcium Plasma Implanted Titanium Surface with Hierarchical Microstructure for Improving the Bone Formation. *ACS Appl. Mater. Interfaces* **2015**, *7*, 13053–130561. [CrossRef]
39. Zhang, W.; Wang, G.; Liu, Y.; Zhao, X.; Zou, D.; Zhu, C.; Jin, Y.; Huang, Q.; Sun, J.; Liu, X.; et al. The Synergistic Effect of Hierarchical Micro/Nano-Topography and Bioactive Ions for Enhanced Osseointegration. *Biomaterials* **2013**, *34*, 3184–3195. [CrossRef]
40. Cao, H.; Liu, X.; Meng, F.; Chu, P.K. Biological Actions of Silver Nanoparticles Embedded in Titanium Controlled by Micro-Galvanic Effects. *Biomaterials* **2011**, *32*, 693–705. [CrossRef]
41. Cheng, H.; Li, Y.; Huo, K.; Gao, B.; Xiong, W. Long-Lasting in Vivo and in Vitro Antibacterial Ability of Nanostructured Titania Coating Incorporated with Silver Nanoparticles. *J. Biomed. Mater. Res. A* **2014**, *102*, 3488–3499. [CrossRef]
42. Huang, Y.; Song, G.; Chang, X.; Wang, Z.; Zhang, X.; Han, S.; Su, Z.; Yang, H.; Yang, D.; Zhang, X. Nanostructured Ag(+)-Substituted Fluorhydroxyapatite-TiO_2 Coatings for Enhanced Bactericidal Effects and Osteoinductivity of Ti for Biomedical Applications. *Int. J. Nanomed.* **2018**, *13*, 2665–2684. [CrossRef] [PubMed]
43. Liu, R.; Tang, Y.; Zeng, L.; Zhao, Y.; Ma, Z.; Sun, Z.; Xiang, L.; Ren, L.; Yang, K. In Vitro and in Vivo Studies of Anti-Bacterial Copper-Bearing Titanium Alloy for Dental Application. *Dent. Mater.* **2018**, *34*, 1112–1126. [CrossRef] [PubMed]
44. Lopes, F.S.; Oliveira, J.R.; Milani, J.; Oliveira, L.D.; Machado, J.P.D.; Trava-Airoldi, V.J.; Lobo, A.O.; Marciano, F.R. Biomineralized Diamond-Like Carbon Films with Incorporated Titanium Dioxide Nanoparticles Improved Bioactivity Properties and Reduced Biofilm Formation. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2017**, *81*, 373–379. [CrossRef] [PubMed]
45. Gunputh, U.F.; Le, H.; Lawton, K.; Besinis, A.; Tredwin, C.; Handy, R.D. Antibacterial Properties of Silver Nanoparticles Grown in Situ and Anchored to Titanium Dioxide Nanotubes on Titanium Implant against Staphylococcus Aureus. *Nanotoxicology* **2020**, *14*, 97–110. [CrossRef]
46. Xu, Y.; Zhao, S.; Weng, Z.; Zhang, W.; Wan, X.; Cui, T.; Ye, J.; Liao, L.; Wang, X. Jelly-Inspired Injectable Guided Tissue Regeneration Strategy with Shape Auto-Matched and Dual-Light-Defined Antibacterial/Osteogenic Pattern Switch Properties. *ACS Appl. Mater. Interfaces* **2020**, *12*, 54497–54506. [CrossRef]
47. Besinis, A.; Hadi, S.D.; Le, H.R.; Tredwin, C.; Handy, R.D. Antibacterial Activity and Biofilm Inhibition by Surface Modified Titanium Alloy Medical Implants Following Application of Silver, Titanium Dioxide and Hydroxyapatite Nanocoatings. *Nanotoxicology* **2017**, *11*, 327–338. [CrossRef]
48. Roguska, A.; Belcarz, A.; Zalewska, J.; Hołdyński, M.; Andrzejczuk, M.; Pisarek, M.; Ginalska, G. Metal TiO_2 Nanotube Layers for the Treatment of Dental Implant Infections. *ACS Appl. Mater. Interfaces* **2018**, *10*, 17089–17099. [CrossRef]
49. Beltrán-Partida, E.; Valdez-Salas, B.; Curiel-Álvarez, M.; Castillo-Uribe, S.; Escamilla, A.; Nedev, N. Enhanced Antifungal Activity by Disinfected Titanium Dioxide Nanotubes Via Reduced Nano-Adhesion Bonds. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2017**, *76*, 59–65. [CrossRef]

50. Chernozem, R.V.; Surmeneva, M.A.; Krause, B.; Baumbach, T.; Ignatov, V.P.; Prymak, O.; Loza, K.; Epple, M.; Ennen-Roth, F.A.; Wittmar, M.; et al. Functionalization of Titania Nanotubes with Electrophoretically Deposited Silver and Calcium Phosphate Nanoparticles: Structure, Composition and Antibacterial Assay. *Mater. Sci. Eng. C. Mater. Biol. Appl.* **2019**, *97*, 420–430. [CrossRef]
51. Moon, K.S.; Park, Y.B.; Bae, J.M.; Choi, E.J.; Oh, S.H. Visible Light-Mediated Sustainable Antibacterial Activity and Osteogenic Functionality of Au and Pt Multi-Coated TiO_2 Nanotubes. *Materials* **2021**, *14*, 5976. [CrossRef]
52. Ahamed, M.; Khan, M.A.M.; Akhtar, M.J.; Alhadlaq, H.A.; Alshamsan, A. Ag-Doping Regulates the Cytotoxicity of TiO_2 Nanoparticles Via Oxidative Stress in Human Cancer Cells. *Sci. Rep.* **2017**, *7*, 17662. [CrossRef] [PubMed]
53. Xu, Z.; Jiang, X. Rapid Fabrication of TiO_2 Coatings with Nanoporous Composite Structure and Evaluation of Application in Artificial Implants—Sciencedirect. *Surf. Coat. Technol.* **2020**, *381*, 125094. [CrossRef]
54. Li, Y.; Wang, W.; Liu, H.; Lei, J.; Zhang, J.; Zhou, H.; Qi, M. Formation and in Vitro/in Vivo Performance of "Cortex-Like" Micro/Nano-Structured TiO_2 Coatings on Titanium by Micro-Arc Oxidation. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2018**, *87*, 90–103. [CrossRef]
55. Amin, M.S.; Randeniya, L.K.; Bendavid, A.; Martin, P.J.; Preston, E.W. Amorphous Carbonated Apatite Formation on Diamond-Like Carbon Containing Titanium Oxide. *Diam. Relat. Mater.* **2009**, *18*, 1139–1144. [CrossRef]
56. Amin, M.S.; Randeniya, L.K.; Bendavid, A.; Martin, P.J.; Preston, E.W. Biomimetic Apatite Growth from Simulated Body Fluid on Various Oxide Containing Dlc Thin Films. *Diam. Relat. Mater.* **2011**, *21*, 42–49. [CrossRef]
57. Esfandiari, N.; Simchi, A.; Bagheri, R. Size Tuning of Ag-Decorated Tio_2 Nanotube Arrays for Improved Bactericidal Capacity of Orthopedic Implants. *J. Biomed. Mater. Res. A* **2014**, *102*, 2625–2635. [CrossRef]
58. Ahmed, F.Y.; Aly, U.F.; Abd El-Baky, R.M.; Waly, N.G. Comparative Study of Antibacterial Effects of Titanium Dioxide Nanoparticles Alone and in Combination with Antibiotics on Mdr Pseudomonas Aeruginosa Strains. *Int. J. Nanomed.* **2020**, *15*, 3393–3404.
59. Zhang, P.; Zhao, Q.; Shi, M.; Yin, C.; Zhao, Z.; Shen, K.; Qiu, Y.; Xiao, Y.; Zhao, Y.; Yang, X.; et al. Fe3O4@Tio(2)-Laden Neutrophils Activate Innate Immunity Via Photosensitive Reactive Oxygen Species Release. *Nano. Lett.* **2020**, *20*, 261–271. [CrossRef]
60. Dias-Netipanyj, M.F.; Cowden, K.; Sopchenski, L.; Cogo, S.C.; Elifio-Esposito, S.; Popat, K.; Soares, P. Effect of Crystalline Phases of Titania Nanotube Arrays on Adipose Derived Stem Cell Adhesion and Proliferation. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2019**, *103*, 109850. [CrossRef]
61. Wachesk, C.C.; Seabra, S.H.; Dos Santos, T.A.T.; Trava-Airoldi, V.J.; Lobo, A.O.; Marciano, F.R. In Vivo Biocompatibility of Diamond-Like Carbon Films Containing TiO_2 Nanoparticles for Biomedical Applications. *J. Mater. Sci. Mater. Med.* **2021**, *32*, 117. [CrossRef]
62. Huang, J.; Zhang, X.; Yan, W.; Chen, Z.; Shuai, X.; Wang, A.; Wang, Y. Nanotubular Topography Enhances the Bioactivity of Titanium Implants. *Nanomedicine* **2017**, *13*, 1913–1923. [CrossRef] [PubMed]
63. Li, B.; Zhang, L.; Wang, D.; Peng, F.; Zhao, X.; Liang, C.; Li, H.; Wang, H. Thermosensitive -Hydrogel-Coated Titania Nanotubes with Controlled Drug Release and Immunoregulatory Characteristics for Orthopedic Applications. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2021**, *122*, 111878. [CrossRef] [PubMed]
64. Li, T.; Gulati, K.; Wang, N.; Zhang, Z.; Ivanovski, S. Understanding and Augmenting the Stability of Therapeutic Nanotubes on Anodized Titanium Implants. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2018**, *88*, 182–195. [CrossRef] [PubMed]
65. Yelick, P.C.; Sharpe, P.T. Tooth Bioengineering and Regenerative Dentistry. *J. Dent. Res.* **2019**, *98*, 1173–1182. [CrossRef]
66. Khoshroo, K.; Jafarzadeh Kashi, T.S.; Moztarzadeh, F.; Tahriri, M.; Jazayeri, H.W.; Tayebi, L. Development of 3d Pcl Microsphere/TiO_2 Nanotube Composite Scaffolds for Bone Tissue Engineering. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2017**, *70*, 586–598. [CrossRef]
67. Rasoulianboroujeni, M.; Fahimipour, F.; Shah, P.; Khoshroo, K.; Tahriri, M.; Eslami, H.; Yadegari, A.; Dashtimoghadam, E.; Tayebi, L. Development of 3d-Printed Plga/TiO_2 Nanocomposite Scaffolds for Bone Tissue Engineering Applications. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2019**, *96*, 105–113. [CrossRef] [PubMed]
68. Rasoulianboroujeni, M.; Yazdimamaghani, M.; Khoshkenar, P.; Pothineni, V.R.; Kim, K.M.; Murray, T.A.; Rajadas, J.; Mills, D.K.; Vashaee, D.; Moharamzadeh, K.; et al. From Solvent-Free Microspheres to Bioactive Gradient Scaffolds. *Nanomedicine* **2017**, *13*, 1157–1169. [CrossRef]
69. Li, Z.; Qiu, J.; Du, Q.L.; Jia, L.; Liu, H.; Ge, S. TiO_2 Nanorod Arrays Modified Ti Substrates Promote the Adhesion, Proliferation and Osteogenic Differentiation of Human Periodontal Ligament Stem Cells. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2017**, *76*, 684–691. [CrossRef]
70. Chang, B.; Song, W.; Han, T.; Yan, J.; Li, F.; Zhao, L.; Kou, H.; Zhang, Y. Influence of Pore Size of Porous Titanium Fabricated by Vacuum Diffusion Bonding of Titanium Meshes on Cell Penetration and Bone Ingrowth. *Acta Biomater.* **2016**, *33*, 311–321. [CrossRef]
71. Chen, Z.; Yan, X.; Yin, S.; Liu, L.; Liu, X.; Zhao, G.; Ma, W.; Qi, W.; Ren, Z.; Liao, H.; et al. Influence of the Pore Size and Porosity of Selective Laser Melted Ti_6Al_4V Eli Porous Scaffold on Cell Proliferation, Osteogenesis and Bone Ingrowth. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2020**, *106*, 110289. [CrossRef]
72. Gulati, K.; Moon, H.J.; Li, T.; Sudheesh Kumar, P.T.; Ivanovski, S. Titania Nanopores with Dual Micro-/Nano-Topography for Selective Cellular Bioactivity. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2018**, *91*, 624–630. [CrossRef] [PubMed]
73. Chen, B.; You, Y.; Ma, A.; Song, Y.; Jiao, J.; Song, L.; Shi, E.; Zhong, X.; Li, Y.; Li, C. Zn-Incorporated TiO_2 Nanotube Surface Improves Osteogenesis Ability through Influencing Immunomodulatory Function of Macrophages. *Int. J. Nanomed.* **2020**, *15*, 2095–2118. [CrossRef] [PubMed]

74. Dias-Netipanyj, M.F.; Sopchenski, L.; Gradowski, T.; Elifio-Esposito, S.; Popat, K.C.; Soares, P. Crystallinity of TiO_2 Nanotubes and Its Effects on Fibroblast Viability, Adhesion, and Proliferation. *J. Mater. Sci. Mater. Med.* **2020**, *31*, 94. [CrossRef] [PubMed]
75. Li, K.; Liu, S.; Xue, Y.; Zhang, L.; Han, Y. A Superparamagnetic Fe_3O_4-TiO_2 Composite Coating on Titanium by Micro-Arc Oxidation for Percutaneous Implants. *J. Mater. Chem. B* **2019**, *7*, 5265–5276. [CrossRef]
76. Xu, R.; Hu, X.; Yu, X.; Wan, S.; Wu, F.; Ouyang, J.; Deng, F. 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. *Int. J. Nanomed.* **2018**, *13*, 5045–5057. [CrossRef]
77. Zhao, X.; You, L.; Wang, T.; Zhang, X.; Li, Z.; Ding, L.; Li, J.; Xiao, C.; Han, F.; Li, B. Enhanced Osseointegration of Titanium Implants by Surface Modification with Silicon-Doped Titania Nanotubes. *Int. J. Nanomed.* **2020**, *15*, 8583–8594. [CrossRef]
78. Sabino, R.M.; Mondini, G.; Kipper, M.J.; Martins, A.F.; Popat, K.C. Tanfloc/Heparin Polyelectrolyte Multilayers Improve Osteogenic Differentiation of Adipose-Derived Stem Cells on Titania Nanotube Surfaces. *Carbohydr. Polym.* **2021**, *251*, 117079. [CrossRef]
79. Yang, J.; Zhang, H.; Chan, S.M.; Li, R.; Wu, Y.; Cai, M.; Wang, A.; Wang, Y. TiO_2 Nanotubes Alleviate Diabetes-Induced Osteogenetic Inhibition. *Int. J. Nanomed.* **2020**, *15*, 3523–3537. [CrossRef]
80. Nishimura, K.; Shindo, S.; Movila, A.; Kayal, R.; Abdullah, A.; Savitri, I.J.; Ikeda, A.; Yamaguchi, Y.; Howait, M.; Al-Dharrab, A.; et al. Trap-Positive Osteoclast Precursors Mediate Ros/No-Dependent Bactericidal Activity via Tlr4. *Free Radic. Biol. Med.* **2016**, *97*, 330–341. [CrossRef]
81. Yu, Y.; Shen, X.; Luo, Z.; Hu, Y.; Li, M.; Ma, P.; Ran, Q.; Dai, L.; He, Y.; Cai, K. Osteogenesis Potential of Different Titania Nanotubes in Oxidative Stress Microenvironment. *Biomaterials* **2018**, *167*, 44–57. [CrossRef]
82. Shen, X.; Ma, P.; Hu, Y.; Xu, G.; Zhou, J.; Cai, K. Mesenchymal Stem Cell Growth Behavior on Micro/Nano Hierarchical Surfaces of Titanium Substrates. *Colloids Surf. B Biointerfaces* **2015**, *127*, 221–232. [CrossRef] [PubMed]
83. Oh, S.; Brammer, K.S.; Li, Y.S.; Teng, D.; Engler, A.J.; Chien, S.; Jin, S. Stem Cell Fate Dictated Solely by Altered Nanotube Dimension. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 2130–2135. [CrossRef] [PubMed]
84. Shen, X.; Yu, Y.; Ma, P.; Luo, Z.; Hu, Y.; Li, M.; He, Y.; Zhang, Y.; Peng, Z.; Song, G.; et al. Titania Nanotubes Promote Osteogenesis Via Mediating Crosstalk between Macrophages and Mscs under Oxidative Stress. *Colloids Surfaces B Biointerfaces* **2019**, *180*, 39–48. [CrossRef] [PubMed]
85. He, P.; Zhang, H.; Li, Y.; Ren, M.; Xiang, J.; Zhang, Z.; Ji, P.; Yang, S. 1α,25-Dihydroxyvitamin D3-Loaded Hierarchical Titanium Scaffold Enhanced Early Osseointegration. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2020**, *109*, 110551. [CrossRef] [PubMed]
86. Piszczek, P.; Lewandowska, Z.; Radtke, A.; Jędrzejewski, T.; Kozak, W.; Sadowska, B.; Szubka, M.; Talik, E.; Fiori, F. Biocompatibility of Titania Nanotube Coatings Enriched with Silver Nanograins by Chemical Vapor Deposition. *Nanomaterials* **2017**, *7*, 274. [CrossRef] [PubMed]
87. Mansoorianfar, M.; Khataee, A.; Riahi, Z.; Shahin, K.; Asadnia, M.; Razmjou, A.; Hojjati-Najafabadi, A.; Mei, C.; Orooji, Y.; Li, D. Scalable Fabrication of Tunable Titanium Nanotubes Via Sonoelectrochemical Process for Biomedical Applications. *Ultrason. Sonochem.* **2020**, *64*, 104783. [CrossRef]
88. Hasanzadeh Kafshgari, M.; Kah, D.; Mazare, A.; Nguyen, N.T.; Distaso, M.; Peukert, W.; Goldmann, W.H.; Schmuki, P.; Fabry, B. Anodic Titanium Dioxide Nanotubes for Magnetically Guided Therapeutic Delivery. *Sci. Rep.* **2019**, *9*, 13439. [CrossRef]
89. Shen, S.C.; Letchmanan, K.; Chow, P.S.; Tan, R.B.H. Antibiotic Elution and Mechanical Property of TiO_2 Nanotubes Functionalized Pmma-Based Bone Cements. *J. Mech. Behav. Biomed. Mater.* **2019**, *91*, 91–98. [CrossRef]
90. Lin, W.T.; Tan, H.L.; Duan, Z.L.; Yue, B.; Ma, R.; He, G.; Tang, T.T. Inhibited Bacterial Biofilm Formation and Improved Osteogenic Activity on Gentamicin-Loaded Titania Nanotubes with Various Diameters. *Int. J. Nanomed.* **2014**, *9*, 1215–1230.
91. Kumeria, T.; Mon, H.; Aw, M.S.; Gulati, K.; Santos, A.; Griesser, H.J.; Losic, D. Advanced Biopolymer-Coated Drug-Releasing Titania Nanotubes (Tnts) Implants with Simultaneously Enhanced Osteoblast Adhesion and Antibacterial Properties. *Colloids Surf. B Biointerfaces* **2015**, *130*, 255–263. [CrossRef]
92. Feng, W.; Geng, Z.; Li, Z.; Cui, Z.; Zhu, S.; Liang, Y.; Liu, Y.; Wang, R.; Yang, X. Controlled Release Behaviour and Antibacterial Effects of Antibiotic-Loaded Titania Nanotubes. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2016**, *62*, 105–112. [CrossRef] [PubMed]
93. Aw, M.S. Controlling Drug Release from Titania Nanotube Arrays Using Polymer Nanocarriers and Biopolymer Coating. *J. Biomater. Nanobiotechnol.* **2012**, *2*, 477–484. [CrossRef]
94. Rahnamaee, S.Y.; 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. [CrossRef] [PubMed]
95. Hashemi, A.; Ezati, M.; Mohammadnejad, J.; Houshmand, B.; Faghihi, S. Chitosan Coating of TiO_2 Nanotube Arrays for Improved Metformin Release and Osteoblast Differentiation. *Int. J. Nanomed.* **2020**, *15*, 4471–4481. [CrossRef] [PubMed]
96. Niu, X.; Sun, L.; Zhang, X.; Sun, Y.; Wang, J. Fabrication and Antibacterial Properties of Cefuroxime-Loaded TiO_2 Nanotubes. *Appl. Microbiol. Biotechnol.* **2020**, *104*, 2947–2955. [CrossRef]
97. Torres, C.C.; Campos, C.H.; Diáz, C.; Jiménez, V.A.; Vidal, F.; Guzmán, L.; Alderete, J.B. Pamam-Grafted TiO_2 Nanotubes as Novel Versatile Materials for Drug Delivery Applications. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2016**, *65*, 164–171. [CrossRef]
98. Dong, Y.; Ye, H.; Liu, Y.; Xu, L.; Wu, Z.; Hu, X.; Ma, J.; Pathak, J.L.; Liu, J.; Wu, G. Ph Dependent Silver Nanoparticles Releasing Titanium Implant: A Novel Therapeutic Approach to Control Peri-Implant Infection. *Colloids Surf. B Biointerfaces* **2017**, *158*, 127–136. [CrossRef]

99. Zhao, J.; Xu, J.; Jian, X.; Xu, J.; Gao, Z.; Song, Y.Y. Nir Light-Driven Photocatalysis on Amphiphilic TiO_2 Nanotubes for Controllable Drug Release. *ACS Appl. Mater. Interfaces* **2020**, *12*, 23606–23616. [CrossRef]
100. Chuang, Y.C.; Yu, Y.; Wei, M.T.; Chang, C.C.; Ricotta, V.; Feng, K.C.; Wang, L.; Bherwani, A.K.; Ou-Yang, H.D.; Simon, M.; et al. Regulating Substrate Mechanics to Achieve Odontogenic Differentiation for Dental Pulp Stem Cells on TiO_2 Filled and Unfilled Polyisoprene. *Acta Biomater.* **2019**, *89*, 6072. [CrossRef]
101. Sun, J.; Forster, A.M.; Johnson, P.M.; Eidelman, N.; Quinn, G.; Schumacher, G.; Zhang, X.; Wu, W.L. Improving Performance of Dental Resins by Adding Titanium Dioxide Nanoparticles. *Dent. Mater.* **2011**, *27*, 972–982. [CrossRef]
102. Kubacka, A.; Diez, M.S.; Rojo, D.; Bargiela, R.; Ciordia, S.; Zapico, I.; Albar, J.P.; Barbas, C.; Martins dos Santos, V.A.; Fernández-García, M.; et al. Understanding the Antimicrobial Mechanism of Tio_2-Based Nanocomposite Films in a Pathogenic Bacterium. *Sci. Rep.* **2014**, *4*, 4134. [CrossRef] [PubMed]
103. Garcia, I.M.; Souza, V.S.; Hellriegel, C.; Scholten, J.D.; Collares, F.M. Ionic Liquid-Stabilized Titania Quantum Dots Applied in Adhesive Resin. *J. Dent. Res.* **2019**, *98*, 682–688. [CrossRef] [PubMed]
104. Kuroiwa, A.; Nomura, Y.; Ochiai, T.; Sudo, T.; Nomoto, R.; Hayakawa, T.; Kanzaki, H.; Nakamura, Y.; Hanada, N. Antibacterial, Hydrophilic Effect and Mechanical Properties of Orthodontic Resin Coated with Uv-Responsive Photocatalyst. *Materials* **2018**, *11*, 889. [CrossRef]
105. Guimarães, G.M.F.; Bronze-Uhle, E.S.; Lisboa-Filho, P.N.; Fugolin, A.P.P.; Borges, A.F.S.; Gonzaga, C.C.; Pfeifer, C.S.; Furuse., A.Y. Effect of the Addition of Functionalized TiO_2 Nanotubes and Nanoparticles on Properties of Experimental Resin Composites. *Dent. Mater.* **2020**, *36*, 1544–1556. [CrossRef] [PubMed]
106. Pires, L.A.; de Azevedo Silva, L.J.; Ferrairo, B.M.; Erbereli, R.; Lovo, J.F.P.; Ponce Gomes, O.; Rubo, J.H.; Lisboa-Filho, P.N.; Griggs, J.A.; Fortulan, C.A.; et al. Effects of Zno/TiO_2 Nanoparticle and TiO_2 Nanotube Additions to Dense Polycrystalline Hydroxyapatite Bioceramic from Bovine Bones. *Dent. Mater.* **2020**, *36*, e38–e46. [CrossRef] [PubMed]
107. Sun, J.; Petersen, E.J.; Watson, S.S.; Sims, C.M.; Kassman, A.; Frukhtbeyn, S.; Skrtic, D.; Ok, M.T.; Jacobs, D.S.; Reipa, V.; et al. Biophysical Characterization of Functionalized Titania Nanoparticles and Their Application in Dental Adhesives. *Acta Biomater.* **2017**, *53*, 585–597. [CrossRef]
108. Vojdani, M.; Bagheri, R.; Khaledi, A. Effects of Aluminum Oxide Addition on the Flexural Strength, Surface Hardness, and Roughness of Heat-Polymerized Acrylic Resin. *J. Dent. Sci.* **2012**, *7*, 238–244. [CrossRef]
109. Cascione, M.; De Matteis, V.; Pellegrino, P.; Albanese, G.; De Giorgi, M.L.; Paladini, F.; Corsalini, M.; Rinaldi, R. Improvement of Pmma Dental Matrix Performance by Addition of Titanium Dioxide Nanoparticles and Clay Nanotubes. *Nanomaterials* **2021**, *11*, 2027. [CrossRef]
110. Totu, E.E.; Nechifor, A.C.; Nechifor, G.; Aboul-Enein, H.Y.; Cristache, C.M. Poly(methyl methacrylate) with TiO_2 Nanoparticles Inclusion for Stereolitographic Complete Denture Manufacturing—The Future in Dental Care for Elderly Edentulous Patients? *J. Dent.* **2017**, *59*, 68–77. [CrossRef]
111. Cristache, C.M.; Totu, E.E.; Iorgulescu, G.; Pantazi, A.; Dorobantu, D.; Nechifor, A.C.; Isildak, I.; Burlibasa, M.; Nechifor, G.; Enachescu, M. Eighteen Months Follow-Up with Patient-Centered Outcomes Assessment of Complete Dentures Manufactured Using a Hybrid Nanocomposite and Additive Cad/Cam Protocol. *J. Clin. Med.* **2020**, *9*, 324. [CrossRef]
112. Laiteerapong, A.; Reichl, F.X.; Hickel, R.; Högg, C. Effect of Eluates from Zirconia-Modified Glass Ionomer Cements on DNA Double-Stranded Breaks in Human Gingival Fibroblast Cells. *Dent. Mater.* **2019**, *35*, 444–449. [CrossRef] [PubMed]
113. Ibrahim, M.A.; Meera Priyadarshini, B.; Neo, J.; Fawzy, A.S. Characterization of Chitosan/TiO_2 Nano-Powder Modified Glass-Ionomer Cement for Restorative Dental Applications. *J. Esthet. Restor. Dent.* **2017**, *29*, 146–156. [CrossRef] [PubMed]
114. Elsaka, S.E.; Hamouda, I.M.; Swain, M.V. Titanium Dioxide Nanoparticles Addition to a Conventional Glass-Ionomer Restorative: Influence on Physical and Antibacterial Properties. *J. Dent.* **2011**, *39*, 589–598. [CrossRef] [PubMed]
115. Garcia-Contreras, R.; Scougall-Vilchis, R.J.; Contreras-Bulnes, R.; Sakagami, H.; Morales-Luckie, R.A.; Nakajima, H. Mechanical, Antibacterial and Bond Strength Properties of Nano-Titanium-Enriched Glass Ionomer Cement. *J. Appl. Oral Sci.* **2015**, *23*, 321–328. [CrossRef] [PubMed]
116. Jowkar, Z.; Fattah, Z.; Ghanbarian, S.; Shafiei, F. The Effects of Silver, Zinc Oxide, and Titanium Dioxide Nanoparticles Used as Dentin Pretreatments on the Microshear Bond Strength of a Conventional Glass Ionomer Cement to Dentin. *Int. J. Nanomed.* **2020**, *15*, 4755–4762. [CrossRef]
117. Xue, L.; Yan, B.; Li, Y.; Tan, Y.; Luo, X.; Wang, M. Surface-Enhanced Raman Spectroscopy of Blood Serum Based on Gold Nanoparticles for Tumor Stages Detection and Histologic Grades Classification of Oral Squamous Cell Carcinoma. *Int. J. Nanomed.* **2018**, *13*, 4977–4986. [CrossRef]
118. Girish, C.M.; Iyer, S.; Thankappan, K.; Rani, V.V.D.; Gowd, G.S.; Menon, D.; Nair, S.; Koyakutty, M. Rapid Detection of Oral Cancer Using Ag-TiO_2 Nanostructured Surface-Enhanced Raman Spectroscopic Substrates. *J. Mater. Chem. B* **2014**, *2*, 989–998. [CrossRef]
119. Chundayil Madathil, G.; Iyer, S.; Thankappan, K.; Gowd, G.S.; Nair, S.; Koyakutty, M. A Novel Surface Enhanced Raman Catheter for Rapid Detection, Classification, and Grading of Oral Cancer. *Adv. Healthc. Mater.* **2019**, *8*, e1801557. [CrossRef]
120. Sun, N.; Liu, M.; Wang, J.; Wang, Z.; Li, X.; Jiang, B.; Pei, R. Chitosan Nanofibers for Specific Capture and Nondestructive Release of Ctcs Assisted by Pcbma Brushes. *Small* **2016**, *12*, 5090–5097. [CrossRef]
121. Xiao, Y.; Wang, M.; Lin, L.; Du, L.; Shen, M.; Shi, X. Specific Capture and Release of Circulating Tumor Cells Using a Multifunctional Nanofiber-Integrated Microfluidic Chip. *Nanomedicine* **2019**, *14*, 183–199. [CrossRef]

122. Sun, N.; Li, X.; Wang, Z.; Zhang, R.; Wang, J.; Wang, K.; Pei, R. A Multiscale TiO_2 Nanorod Array for Ultrasensitive Capture of Circulating Tumor Cells. *ACS Appl. Mater. Interfaces* **2016**, *8*, 12638–12643. [CrossRef] [PubMed]
123. Li, R.; Chen, F.F.; Liu, H.Q.; Wang, Z.X.; Zhang, Z.T.; Wang, Y.; Cui, H.; Liu, W.; Zhao, X.Z.; Sun, Z.J.; et al. Efficient Capture and High Activity Release of Circulating Tumor Cells by Using TiO_2 Nanorod Arrays Coated with Soluble Mno(2) Nanoparticles. *ACS Appl. Mater. Interfaces.* **2018**, *10*, 16327–16334. [CrossRef]
124. Maheswari, P.; Harish, S.; Ponnusamy, S.; Muthamizhchelvan, C. A Novel Strategy of Nanosized Herbal Plectranthus Amboinicus, Phyllanthus Niruri and Euphorbia Hirta Treated TiO_2 Nanoparticles for Antibacterial and Anticancer Activities. *Bioprocess. Biosyst. Eng.* **2021**, *44*, 1593–1616. [CrossRef] [PubMed]
125. Maheswari, P.; Harish, S.; Navaneethan, M.; Muthamizhchelvan, C.; Ponnusamy, S.; Hayakawa, Y. Bio-Modified TiO_2 Nanoparticles with Withania Somnifera, Eclipta Prostrata and Glycyrrhiza Glabra for Anticancer and Antibacterial Applications. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2020**, *108*, 110457. [CrossRef] [PubMed]
126. Xu, Q.C.; Zhang, Y.; Tan, M.J.; Liu, Y.; Yuan, S.; Choong, C.; Tan, N.S.; Tan, T.T. Anti-Cangptl4 Ab-Conjugated N-Tio(2)/Nayf(4):Yb,Tm Nanocomposite for near Infrared-Triggered Drug Release and Enhanced Targeted Cancer Cell Ablation. *Adv. Healthc. Mater.* **2012**, *1*, 470–474. [CrossRef]
127. Hou, Z.; Zhang, Y.; Deng, K.; Chen, Y.; Li, X.; Deng, X.; Cheng, Z.; Lian, H.; Li, C.; Lin, J. Uv-Emitting Upconversion-Based TiO_2 Photosensitizing Nanoplatform: Near-Infrared Light Mediated in Vivo Photodynamic Therapy via Mitochondria-Involved Apoptosis Pathway. *ACS Nano.* **2015**, *9*, 2584–2599. [CrossRef]
128. Lucky, S.S.; Idris, N.M.; Huang, K.; Kim, J.; Li, Z.; Thong, P.S.; Xu, R.; Soo, K.C.; Zhang, Y. In Vivo Biocompatibility, Biodistribution and Therapeutic Efficiency of Titania Coated Upconversion Nanoparticles for Photodynamic Therapy of Solid Oral Cancers. *Theranostics* **2016**, *6*, 1844–1865. [CrossRef]
129. Yurt, F.; Ince, M.; Colak, S.G.; Ocakoglu, K.; Er, O.; Soylu, H.M.; Gunduz, C.; Avci, C.B.; Kurt, C.C. Investigation of in Vitro Pdt Activities of Zinc Phthalocyanine Immobilised TiO_2 Nanoparticles. *Int. J. Pharm.* **2017**, *524*, 467–474. [CrossRef]
130. Tang, R.; Zheleznyak, A.; Mixdorf, M.; Ghai, A.; Prior, J.; Black, K.C.L.; Shokeen, M.; Reed, N.; Biswas, P.; Achilefu, S. Osteotropic Radiolabeled Nanophotosensitizer for Imaging and Treating Multiple Myeloma. *ACS Nano.* **2020**, *14*, 4255–4264. [CrossRef]
131. Riedle, S.; Wills, J.W.; Miniter, M.; Otter, D.E.; Singh, H.; Brown, A.P.; Micklethwaite, S.; Rees, P.; Jugdaohsingh, R.; Roy, N.C.; et al. A Murine Oral-Exposure Model for Nano- and Micro-Particulates: Demonstrating Human Relevance with Food-Grade Titanium Dioxide. *Small* **2020**, *16*, e2000486. [CrossRef]
132. da Silva, A.B.; Miniter, M.; Thom, W.; Hewitt, R.E.; Wills, J.; Jugdaohsingh, R.; Powell, J.J. Gastrointestinal Absorption and Toxicity of Nanoparticles and Microparticles: Myth, Reality and Pitfalls Explored through Titanium Dioxide. *Curr. Opin. Toxicol.* **2020**, *19*, 112–120. [CrossRef] [PubMed]
133. Janer, G.; Mas del Molino, E.; Fernández-Rosas, E.; Fernández, A.; Vázquez-Campos, S. Cell Uptake and Oral Absorption of Titanium Dioxide Nanoparticles. *Toxicol. Lett.* **2014**, *228*, 103–110. [CrossRef] [PubMed]
134. Cao, X.; Han, Y.; Gu, M.; Du, H.; Song, M.; Zhu, X.; Ma, H.; Pan, C.; Wang, W.; Zhao, E.; 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*, e2001858. [CrossRef] [PubMed]
135. Zhao, Y.; Tang, Y.; Liu, S.; Jia, T.; Zhou, D.; Xu, H. Foodborne TiO_2 Nanoparticles Induced More Severe Hepatotoxicity in Fructose-Induced Metabolic Syndrome Mice Via Exacerbating Oxidative Stress-Mediated Intestinal Barrier Damage. *Foods* **2021**, *10*, 986. [CrossRef] [PubMed]
136. Li, N.; Duan, Y.; Hong, M.; Zheng, L.; Fei, M.; Zhao, X.; Wang, J.; Cui, Y.; Liu, H.; Cai, J.; et al. Spleen Injury and Apoptotic Pathway in Mice Caused by Titanium Dioxide Nanoparticules. *Toxicol. Lett.* **2010**, *195*, 161–168. [CrossRef]
137. Gui, S.; Zhang, Z.; Zheng, L.; Cui, Y.; Liu, X.; Li, N.; Sang, X.; Sun, Q.; Gao, G.; Cheng, Z.; et al. Molecular Mechanism of Kidney Injury of Mice Caused by Exposure to Titanium Dioxide Nanoparticles. *J. Hazard. Mater.* **2011**, *195*, 365–370. [CrossRef]
138. Chen, Z.; Han, S.; Zhou, D.; Zhou, S.; Jia, G. Effects of Oral Exposure to Titanium Dioxide Nanoparticles on Gut Microbiota and Gut-Associated Metabolism in Vivo. *Nanoscale* **2019**, *11*, 22398–22412. [CrossRef]
139. Ruiz, P.A.; Morón, B.; Becker, H.M.; Lang, S.; Atrott, K.; Spalinger, M.R.; Scharl, M.; Wojtal, K.A.; Fischbeck-Terhalle, A.; Frey-Wagner, I.; et al. Titanium Dioxide Nanoparticles Exacerbate Dss-Induced Colitis: Role of the Nlrp3 Inflammasome. *Gut* **2017**, *66*, 1216–1224. [CrossRef]
140. Chen, Z.; Zhou, D.; Han, S.; Zhou, S.; Jia, G. Hepatotoxicity and the Role of the Gut-Liver Axis in Rats after Oral Administration of Titanium Dioxide Nanoparticles. *Part. Fibre Toxicol.* **2019**, *16*, 48. [CrossRef]
141. Sang, X.; Fei, M.; Sheng, L.; Zhao, X.; Yu, X.; Hong, J.; Ze, Y.; Gui, S.; Sun, Q.; Ze, X.; et al. Immunomodulatory Effects in the Spleen-Injured Mice Following Exposure to Titanium Dioxide Nanoparticles. *J. Biomed. Mater. Res. A* **2014**, *102*, 3562–3572. [CrossRef]
142. Lee, J.; Jeong, J.S.; Kim, S.Y.; Park, M.K.; Choi, S.D.; Kim, U.J.; Park, K.; Jeong, E.J.; Nam, S.Y.; Yu, W.J. Titanium Dioxide Nanoparticles Oral Exposure to Pregnant Rats and Its Distribution. *Part. Fibre Toxicol.* **2019**, *16*, 31. [CrossRef] [PubMed]
143. Aijie, C.; Huimin, L.; Jia, L.; Lingling, O.; Limin, W.; Junrong, W.; Xuan, L.; Xue, H.; Longquan, S. Central Neurotoxicity Induced by the Instillation of Zno and TiO_2 Nanoparticles through the Taste Nerve Pathway. *Nanomedicine* **2017**, *12*, 2453–2470. [CrossRef] [PubMed]

144. Abdulnasser Harfoush, S.; Hannig, M.; Le, D.D.; Heck, S.; Leitner, M.; Omlor, A.J.; Tavernaro, I.; Kraegeloh, A.; Kautenburger, R.; Kickelbick, G.; et al. High-Dose Intranasal Application of Titanium Dioxide Nanoparticles Induces the Systemic Uptakes and Allergic Airway Inflammation in Asthmatic Mice. *Respir. Res.* **2020**, *21*, 168. [CrossRef] [PubMed]
145. Lim, J.O.; Lee, S.J.; Kim, W.I.; Pak, S.W.; Moon, C.; Shin, I.S.; Heo, J.D.; Ko, J.W.; Kim, J.C. Titanium Dioxide Nanoparticles Exacerbate Allergic Airway Inflammation via Txnip Upregulation in a Mouse Model of Asthma. *Int. J. Mol. Sci.* **2021**, *22*, 9924. [CrossRef] [PubMed]
146. Armand, L.; Tarantini, A.; Beal, D.; Biola-Clier, M.; Bobyk, L.; Sorieul, S.; Pernet-Gallay, K.; Marie-Desvergne, C.; Lynch, I.; Herlin-Boime, N.; et al. Long-Term Exposure of A549 Cells to Titanium Dioxide Nanoparticles Induces DNA Damage and Sensitizes Cells towards Genotoxic Agents. *Nanotoxicology* **2016**, *10*, 913–923. [CrossRef] [PubMed]
147. Adachi, K.; Yamada, N.; Yoshida, Y.; Yamamoto, O. Subchronic Exposure of Titanium Dioxide Nanoparticles to Hairless Rat Skin. *Exp. Dermatol.* **2013**, *22*, 278–283. [CrossRef]
148. Chaudhry, Q. Opinion of the Scientific Committee on Consumer Safety (Sccs)—Revision of the Opinion on the Safety of the Use of Titanium Dioxide, Nano Form, in Cosmetic Products. *Regul. Toxicol. Pharmacol.* **2015**, *73*, 669–670.