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Review Article

Antimicrobial Efficacy of Metal-Doped Titanium Dioxide Nanoparticles: A Comprehensive Review

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ABSTRACT

Titanium dioxide nanoparticles, or TiO_2 NPs, have shown potential in the fight against a range of diseases, including bacteria, viruses, fungi and parasites. Doping metals with nanoparticles modify their size and magnetic characteristics by decreasing the energy band gap and mixing spins and electrical charges. Furthermore, it has been shown that owing to their higher surface-to-volume ratio and improved ability to interact with bacterial cells, smaller metal-doped nanoparticles have better antibacterial action. Due in large part to their production, TiO_3-NPs have outstanding antifungal and antibacterial capabilities. The major mechanism of TiO_3-NPs' antibacterial activity is their potent oxidizing capacity, which produces superoxide and hydroxyl anion radicals. *Pseudomonas aeruginosa, Staphylococcus aureus* and *Escherichia coli* are just a few of the pathogens against which TiO_2 NPs have been shown to have antibacterial ability. Review topics will include the most recent discoveries in the sectors of water treatment, agriculture and medicine as well as the synthesis of TiO_3- nanoparticles and their antimicrobial actions. TiO_2 NPs as antibacterial agents: prospects and challenges will also be highlighted in the review.

Keywords: Titanium dioxide, Nanoparticles, Metal-doped titanium dioxide, Anti-microbial activity, Multidrug-resistant pathogens, Mechanisms.

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INTRODUCTION

Antimicrobial Resistance (AMR) undermines the effectiveness of currently available antibiotics; it poses a serious threat to both human health and the global health community. It is critically important to develop new tactics and effective antimicrobial agents in this constantly changing fight against harmful bacteria. One of the most promising alternatives is titanium dioxide nanoparticles (TiO_2 NPs) doped with metal; their exceptional antibacterial activity against a variety of microorganisms has drawn attention to them. This thorough analysis explores the intriguing world of these nanoparticles, elucidating their modes of action, demonstrating their effectiveness against a range of infections and critically evaluating their potential in the fight against AMR.[1] Because of its photocatalytic activity, pure titanium dioxide has been shown to have innate antibacterial qualities. When Ultraviolet (UV) light interacts with TiO_2 Nanoparticles (NPs), it produces Reactive Oxygen Species (ROS) such as Hydroxyl radicals (OH-) and superoxide anions (O_2-), which are potent antibacterial agents that damage and eventually kill micro, organisms by damaging their membranes, DNA and cell walls. However, the main limitation of pristine TiO_2 NPs is that it require UV light to activate, which limits their use in a lot of practical situations.[2] The increasing incidence of microbial attacks in various industries, including food, pharmaceuticals, textiles, water purification and food packaging, prompts a continuous quest for novel antimicrobial compounds. Interest in the production of inorganic antimicrobial chemicals has developed due to the increased bacterial resistance to specific antibiotics and the toxicity of certain organic antimicrobials agents to human health. Because of their broad-spectrum antibacterial properties, metal as well as several combinations of metal oxides have garnered a lot of attention among these substances. However, because of their superior qualities resulting from a high surface area-to-volume ratio, nanoscale materials are broadly acceptable. Antimicrobial nanoparticles have demonstrated better and unique activities from their bulk properties.[3] Additionally, the greater surface area that nanoparticles have in touch with bacteria amplifies their antibacterial properties.[4]

It has been demonstrated that TiO_2 nanoparticles exhibit exceptional antifungal and antibacterial properties against different pathogens, like viruses, fungi, also Gram-positive and Gram-negative bacteria.[5] Numerous investigations have demonstrated the increased antibacterial activity of TiO_2 nanoparticles via metal doping, including co-doping with nitrogen and silver and the creation of unique hollow TiO_2 nanospheres with antibacterial qualities.[6] TiO_2 may be categorized as amorphous or crystalline depending on its crystallinity.[7]

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Three polymorphs of Titanium dioxide (TiO_2) are known to be available: rutile, brookite and anatase. Because anatase has a higher photocatalytic activity than rutile and brookite, it is the one that is most frequently used for photocatalytic applications.[8] While rutile has the smallest band gap (~3.0 eV), it often exhibits photocatalytic activity that is up to ten times lower than that of anatase. Even though pure brookite polymorphs may have more photocatalytic activity than the other two polymorphs, using them in heterogeneous photocatalysis is a difficult challenge because of their intricate production process. When compared to individual polymorphs, mixed phases of TiO_2 showed considerably better photocatalytic activity.[9]

TiO_2 has been extensively researched for its capacity to function as a photocatalyst, producing The light-induced inactivation of microorganisms caused by Reactive Oxygen Species (ROS).[10] TiO_2 is the most effective photocatalyst among the many types. It has been shown that numerous organic contaminants may be efficiently degraded by photocatalytic disinfection using TiO_2. Because of its commercial availability and chemical stability, TiO_2 has been utilized extensively in photocatalysis.[11] Because of the randomly arranged particles, the amorphous form of titanium dioxide (TiO_2), sometimes referred to as anatase, has an uneven shape and typically develops around 350ºC. Between 500 and 800ºC, anatase and brookite permanently change into the stable rutile polymorph. Compared to rutile and brookite, anatase exhibits the highest degree of photosensitivity of the three polymorphs.[12-14]

Definition and properties of Titanium Dioxide (TiO_2)

Titanium dioxide (TiO_2) Nanoparticles (NPs) have drawn a great deal of attention due to their unique characteristics and uses, especially in the biomedical industry. Although a lot of research has been done on chemically manufactured TiO_2 NPs, microbial production has a number of benefits over it, such as lower toxicity, biocompatibility and environmental friendliness. By biotransformation titanium precursors and using their metabolites, biomolecules such as enzymes as stabilizing and capping agents, microorganisms including bacteria, fungus and algae create TiO_2 NPs.[15] One major drawback is the effectiveness and efficiency of these microbially generated TiO_2 NPs as a nano-photocatalyst or antibacterial agent.[16] This is because different microbial proteins that are capped on the microbially generated TiO_2 NPs (which have previously been shown in the literature) prevent the TiO_2 NPs from doing their intended function. There is less contact between pathogens and TiO_2 NPs or between pollutants and TiO_2 NPs as a consequence of the biomolecule masking the active sites of TiO_2 NPs during their antibacterial activity and photocatalytic impact. Furthermore, bigger biological macromolecules-up to several kilodaltons in size-are capped on the microbially produced TiO_2 NPs, increasing the total size of the particles. Because biological macromolecules are larger than TiO_2 NPs, the pathogens cannot be destroyed photocatalytically by them, which significantly reduces their entry into the pathogens. These TiO_2 NPs produced by microbiology are not as effective as TiO_2 NPs produced chemically or physically as antimicrobial agents or nano-photocatalysts.[16]

Depending on the synthesis technique used, Titanium dioxide (TiO_2) Nanoparticles (NPs) may have different sizes. TiO_2 NPs produced by microbial synthesis may have diameters ranging from 10-30 nm to over 100 nm, while NPs produced by chemical synthesis can have sizes between 10 and 100 nm.[15] TiO_2 nanoparticles may be produced using different kind of methods, including the sol-gel method,, solvothermal method, immediate synthesis method, simple mixing method, method, microwave-assisted synthesis and precipitation method, according to the results from the cited publication.[17] In general, the synthesis technique may affect the size of TiO_2 NPs, but other elements including surface chemistry and crystalline structure are also very important in defining their characteristics and uses.

Experimental techniques for metal-doped TiO_2, SOL-GEL TiO_2 by using different metal nanoparticles

It is seen that metal-doped titanium dioxide nanoparticles increase antibacterial effectiveness.[18-20] TiO_2's photocatalytic activity is increased by doping it with different elements because new energy levels arise near to the conduction band. The heterogeneous process of photocatalysis using titanium dioxide depends critically on the catalyst's surface.[21] During the synthesis process, metal ions are added to the TiO_2 lattice to create metal-doped Titanium dioxide (TiO_2) Nanoparticles (NPs). Zn and Cd are examples of non-transition metals, while transition metals like Fe, Cu and Ni may be the dopants.[22] TiO_2 NPs may be doped to increase their photocatalytic activity, stability and adjustable bandgap characteristics, which will increase their efficiency in breaking down pollutants and producing hydrogen.[9] There are numerous approaches to synthesize metal-doped TiO_2 NPs, also solvothermal, sol-gel and hydrothermal approaches. The environmentally benign and biocompatible method of microbial synthesis has also been used to create metal-doped TiO_2 NPs.[23] However, TiO_2's antibacterial activity may be improved by doping it with metals like Silver (Ag), Nickel (Ni), Copper (Cu), Manganese (Mn) and Sulfur (S), particularly when exposed to visible light. Under visible light, Ag-doped TiO^2 nanoparticles exhibited increased antibacterial activity against *Staphylococcus aureus*. TiO_2 NPs doped with Ni, Cu, Mn and S have also demonstrated antibacterial activity against various bacterial species. Table 1 show TiO_2-materials doped with metals has antibacterial properties against a variety of microorganisms. Moreover, it has been discovered that adding metal-doped TiO_2 nanoparticles to elastomers improves the photoinactivation effectiveness of visible light for surface cleaning. These results imply that metal-doped TiO_2 nanoparticles may find usage in a variety of applications as powerful antibacterial agents.

Experimental techniques for metal-doped TiO_2, sol-gel TiO_2/Ni synthesis and antibacterial testing

Sol-gel TiO_2/Ni synthesis and antibacterial testing

According to Haque *et al*. (2023) the compound's synthesis has concluded. For the procedure TiO_2 nanoparticles were produced via sol-gel using titanium isopropoxide as the titania precursor. A homogeneous 1:1 (v/v) mixture of water and 2-proponal was combined with a solution of titanium isopropoxide (0.1 M) in 2-proponal (25 mL), added drop by drop and constantly stirred. Turbidity in the solution would emerge as a consequence, indicating the hydrolysis of titanium isopropoxide. Following the full addition, the mixture was shaken for the whole night before being filtered and repeatedly cleaned with water. In order to dope TiO_2 particles with nickel, a solution including water and 2-proponal was mixed with a known concentration of $NiCl_2$ (0.1-0.8%) before being added to the titanium isopropoxide solution. First, the undoped TiO_2 and Ni-TiO_2 were both dried for 2-3 hr at 100 C. After the dry residue was manually ground in an agate mortar, it was heated to various temperatures-300, 400 and 500°C-for 4 hr. Figure 1 demonstrate the sol-gel method's synthesis of metal-doped TiO_2/Ag.[28] Figure 1 show the Synthesis of metal-doped TiO_2/Ni by sol-gel method.

Characterization of TiO_2/Ni

Using a range of analytical methods, the structural, morphological and elemental properties of TiO_2/Ni nanocomposites prepared by the sol-gel process are examined. Numerous techniques, including as X-ray Diffraction (XRD), Scanning Electron Microscopy (SEM), energy dispersive X-ray Spectroscopy (EDX), Fourier Transform Infrared Spectroscopy (FTIR), etc., are often used to study TiO_2/Ni nanocomposites.[29] SEM, XRD and UV-vis spectroscopy were among the traditional analytical techniques used to characterize the generated catalysts. To study the particle morphology, a Hitachi S-5000 FEG scanning electron microscope running at 20 kV was used. Using Cu Kα radiation (h=1.5418 ù) from a Rigaku Miniflex II device running at 30 kV and 15 mA, X-ray Diffraction (XRD) was used to structurally characterize the undoped TiO_2 and Ni-TiO_2 nanoparticles in the 20-80° range. Using a Shimadzu UV-vis spectrophotometer (Model 1601), the UV-Vis spectra in the 300-800 nm range was obtained at room temperature [28]

Antibacterial Effects

Staphylococcus aureus is strongly inhibited by Ni-doped TiO_2 nanoparticles. The antibacterial activity was measured using the well diffusion method. After being prepared, cleaned and put into a petri plate, Mueller-Hinton agar (Hi-Media) was used. After allowing the medium to solidify, the aseptic placement of the prepared inoculum onto the plate occurred. Using a cotton swab or an L-shaped glass spreader that had been sterilized, the inoculum was applied. A sterilized test tube was used to create a well with a 6 mm diameter, which was then filled with a 2.5 L suspension of various diluted products to be tested. At 28 degrees, the plates were incubated for three days. The zone of inhibition diameter (mm) is used to represent the activity. Figure 2 shows how different concentrations of the Ni dopant TiO_2 affected antibacterial activity. With an increase in dopant concentration, the zone of inhibition widened. However, it was shown that agglomeration caused the zone of inhibition to narrow at a concentration of 2%.[30]

Experimental techniques for metal-doped TiO_2, sol-gel TiO_2/Ag synthesis and antibacterial testing

Nanoparticles composed of Ag-TiO_2 were synthesized through a range of diverse methodologies as described in the investigations conducted by Fan *et al*.,[31] de Oliveira *et al*.,[18] Wani *et al*. and Ren *et al*.[32] Fan and colleagues conducted a synthesis of a composite material that consisted of Polyamino Acid (PAA) and TiO_2/Ag nanoparticles via *in situ* melting polycondensation.[33] Ag-doped TiO_2 nanoparticles were synthesized by de Oliveira *et al*. using the sol-gel process followed by Ag doping. Wani *et al*. looked into the use of ion beam irradiation to create N and Ag-modified nanocrystalline TiO_2. Ren *et al*.'s attempt to create PPDO-coated Ag loading TiO_2 nanoparticles was unsuccessful. These studies used a variety of approaches, including ion beam irradiation, sol-gel process and *in situ* melting polycondensation, to create Ag-TiO_2 nanoparticles with different compositions and

Table 1: TiO_2-materials doped with metals have antibacterial properties against a variety of microorganisms.

Metal Dopant	Bacteria Tested	Inhibition Zone (mm) or MIC	References
Ag	*Staphylococcus. aureus, Escherichia coli.*	10-20 mm; MIC=0.05 mg/mL.	24
Cu	*Bacillus subtilis, Pseudomonas aeruginosa.*	15-20 mm; MIC=0.1-0.5 mg/mL.	25
Zn	*Staphylocccus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa.*	10-20 mm; MIC=0.1-0.5 mg/mL.	26
Cr	*Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa.*	10.5-19.25 mm; MIC=31.25 ug/mL.	[27]

characteristics. Figure 3 show TiO_2, sol-gel TiO_2/Ag synthesis. The synthesis of Ag-TiO_2 nanocomposites can be accomplished through a modified sol-gel technique, wherein the incorporation of silver ions takes place in the course of the preparation and undergoes reduction to generate Ag nanoparticles on the surface of TiO_2.[34,35]

Using a nickel filter, powder X-ray Diffraction (XRD) spectra of anode Cu-WL 1 radiation with a wavelength of 1.5406 nm were acquired from PAN Analytical in order to assess the crystalline structure of the photocatalysts. The voltage was 40 kV and the current was 40 milliamperes. The average crystallite size of anatase was determined by using the Scherrer equation in combination with Full Width at Half Maximum (FWHM) data from the chosen peak. The surface area and porosity of the material were determined using the Micrometrics Gemini VII surface area analyzer. The nitrogen adsorption/desorption isotherms were monitored two or three times to get repeatable results. The data came from the surface/volume mesopore study of BJH. By using the Frenkel-Halsey-Hill isotherm equation, the micropores' volume may be calculated. For duration of 2 hr, every sample was degassed at 300ºC. A Transmission Electron Microscope (TEM) equipped with JEOL/JEM 2100 and running at 200 kV was used to measure the catalyst's size. Using a Scanning Electron Microscope (SEM), the catalyst's form and underlying elemental composition were examined.[36] The researchers are Imandi Manga Raju, Siva Rao Tirukkovalluri and Sankara Rao Miditana.

The following reaction rate kinetic constants were determined using the pseudo-first-order kinetic model:

$$\ln (/0) = - kt.$$ [37]

Where,

t is the irradiation time,

k is kinetic constant (min-1) and,

C is the concentration of the MB (mg/L).

Antibacterial action of amorphous and crystalline titanium doped with silver

In compliance with reference methods of the Clinical and Laboratory Standards Institute (CLSI) for the determination of MICs of aerobic bacteria by broth microdilution, the antibacterial activity of amorphous and crystalline TiO_2:Ag0, TiO_2a: Ag0, TiO_2:Ag0/Ag+, TiO_2:Ag0/Ag+ and TiO_2:Ag0/Ag0 nanospheres was evaluated using Minimal Inhibitory Concentration (MIC) and Minimal Bactericidal Concentration (MBC) values. The lowest concentration of silver on a microplate that prevented bacterial growth was known as the Minimum Inhibitory Concentration (MIC) and it was determined after 16-19 hr of incubation at 37ºC. The lowest extract concentration that was found in MBC eliminated 99.9% of the germs.[38] Two important microbiological indicators that indicate how well antimicrobial medications work against bacteria are the Minimum Bactericidal Concentration (MBC) and least Inhibitory Concentration (MIC) values. Lower MIC and MBC values, which indicate the lowest doses at which 99.9% of bacteria are killed and bacterial growth is inhibited, respectively, indicate better antibacterial efficacy. The Figure 4 show graphical statics of Antibacterial Action of Ni/TiO_2 against *Staphylococcus*. Mueller Hinton Broth (MHB) and Mueller Hinton Agar (MHA) were utilized as the bacterial growth media throughout the experiment. 200 ml was dispensed each spot for testing and the antimicrobial agent stock solution was diluted by published methods. The Figure 4 show graphical statics of Antibacterial Action of Ni/TiO_2 against *Staphylococcus*. A 0.5 McFarland standard containing around 1-2×10^8 Colony-Forming Units per milliliter (CFU/mL) was altered to generate the inoculum. To get the intended final inoculum concentration of 10^4 CFU per spot, this standard was then diluted at a ratio of 1:10 in sterile saline. Spots devoid of

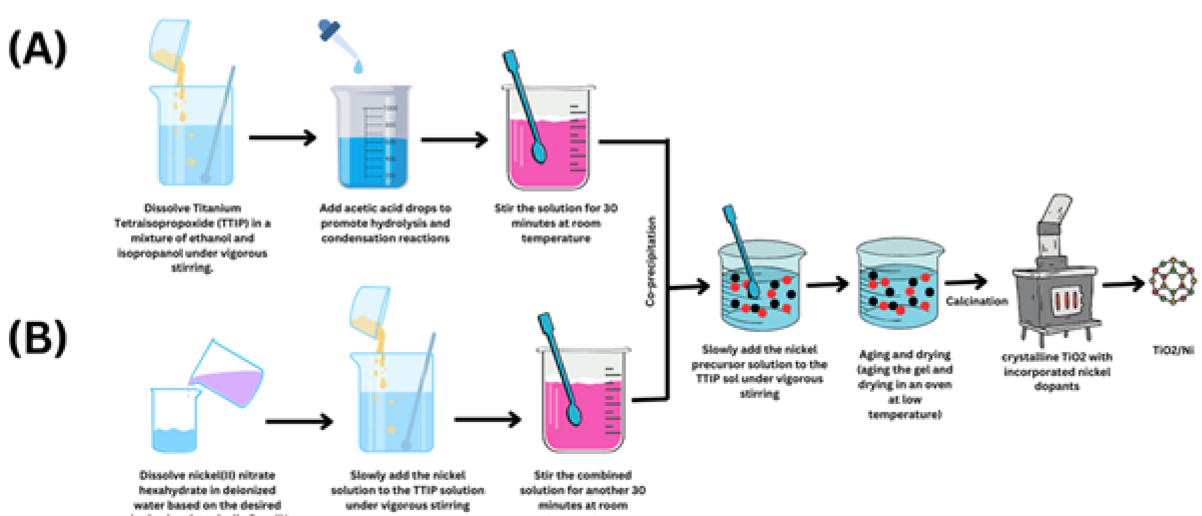

Figure 1: Synthesis of metal-doped TiO_2/Ni by sol-gel method.

nanoparticles containing medium and cultures were included as controls to guarantee precise evaluation of the antimicrobial agent's ability to impede bacterial growth and kill it.[35]

Nanoparticles of doped titanium dioxide (TiO_3-NPS)

TiO_3-NPs, or nanoparticles of doped titanium dioxide, have drawn a lot of interest because of their special qualities and possible uses. The physicochemical characteristics of titanium dioxide nanoparticles vary from those of their fine particle analogs, potentially modifying their bioactivity Because of their stability and photocatalytic qualities, TiO_2 NPs are extensively employed in many different sectors, including solar cells, water treatment and catalytic processes. Inhalation is the main way that people are exposed to TiO_2 NPs at work, however, consumer goods like sunscreen and makeup may also expose people to these particles.[39]

TiO_2 NPs may move from the lung and gastrointestinal tract to systemic organs, according to studies, which raises questions regarding possible health repercussions.[40]

Additionally, studies have concentrated on creating nitrogen-doped titanium dioxide nanoparticles, which exhibit greater absorbance in the visible spectrum than plain ones.[41] There are many ways to synthesize titanium dioxide nanoparticles, one of which is green synthesis, which uses plant extracts and is safe for the environment and non-toxic. Applications in wastewater treatment and antibacterial activity have also been investigated for the microbial production of titanium dioxide nanoparticles.[15]

Various Uses of Doped-TiO_3 in Biomedicine

Numerous applications for doped-TiO_2 nanoparticles exist in biomedicine. They have been investigated as possible temperature nanoprobes, between the doped nanoparticles' thermally sensitive radiative transitions, the fluorescence intensity ratio establishes the sensors' relative sensitivity.[42] Doped or undoped TiO_2 nanoparticles have shown significant use in enhancing chemical, biological and physical behavior. They have been used to improve several facets of the environment, agriculture and health, such as enhancing nanomedicine, eliminating pollutants from the environment and enhancing agricultural qualities.[43] Potential optical nanothermometers using Nd^{3+} doped TiO_2 nanocrystals have been studied. Temperature is determined by the fluorescence intensity ratio of emissions at various wavelengths.[44] The Figure 5 shows various applications of Various Uses of Doped-TiO_3 in Biomedicine.

Additionally, doped-TiO_2 nanoparticles have been used to produce novel biocompatible materials with distinct physical-chemical characteristics, such as coatings of magnetite nanoparticles with noble metals.[45] Nitrogen-doped nanoparticles have demonstrated enhanced actions that include cytotoxic, antifungal, antioxidant, antidiabetic and inhibit protein kinase when compared to undoped TiO_2 nanoparticles. As such, they represent a strong contender for biomedical applications.[46]

Current research on the use of doped-TiO_3 in biomedical applications is centered on its utilization in ferroelectrics and luminous phosphors, among other functional materials. One well-known example is the development of a Mn- and Yb-doped Ba TiO_3-(Na_0.5Bi_0.5) TiO_3 ferroelectric relaxor material; the Mn doping results in better dielectric characteristics. This work suggests that Mn dopant functions as an acceptor, enhancing electrical resistivity in the vicinity of the Curie temperature and decreasing oxygen vacancies, which enhances insulation resistance.[47]

A further investigation delves into the creation and description of (Ba, Sr) TiO_3 phosphors doped with Eu^{3+} and Dy^{3+}, demonstrating that these dopants provide adjustable photoluminescence characteristics. The emission intensities of the phosphors change when Sr^{2+} is substituted for Ba^{2+}, causing a phase shift from tetragonal to cubic structures.[48]

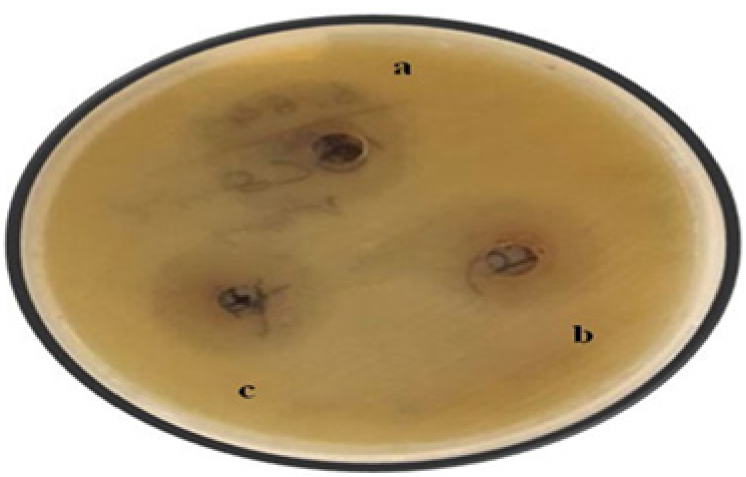

Figure 2: Antibacterial effect of (a) 1% Ni/TiO_2 (b) 1.5% Ni/TiO_2 and (c) 2% Ni/TiO_2 against *Staphylococcus aureus*. The figure is taken from.[30]

It is further shown that the structural, electrical and optical characteristics of the resultant materials may be studied by doping Y at the Ba and Ti sites of $BaTiO_2$.[49] Rare-earth element doping (Pr^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Ho^{3+}, Er^{3}⁎ and Yb^{3+}) in lead-free ferroelectric $Bi_1/_2Na_1/_2TiO_3$ materials has also been investigated to get adjustable photoluminescent characteristics.[50]

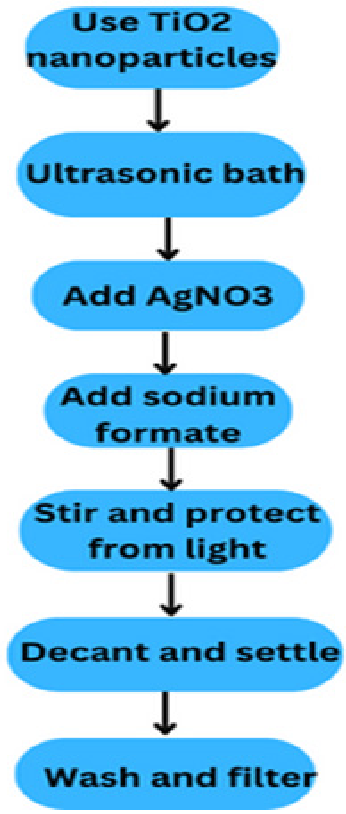

Figure 3: TiO_2, sol-gel TiO_2/Ag synthesis.

Doped-TiO_2-Based Antimicrobial Activities

Doped TiO_2 nanoparticles have shown antimicrobial efficacy against a variety of bacteria under a range of lighting conditions. Under visible light, methicillin-resistant and susceptible *Staphylococcus aureus* was more effectively inhibited by Ag-doped TiO_2 nanoparticles.[18] Table 2 shows possible mechanisms and Doped Materials.

Escherichia coli and *B. subtilis* are two examples of the Gram-positive and Gram-negative bacteria that the ZnO-doped TiO_2 nanocomposites shown increased antibacterial activity against.[51] Furthermore, yttrium-doped TiO_2 nanostructures showed exceptional antibacterial properties against *E. coli*.[52] One can decrease electron-hole recombination, boost resistance to microorganisms and dope TiO_2 with various ions or compounds to expand photocatalytic activity to visible light.[29] Under visible light, it has been shown that metal-doped TiO_2, e.g., TiO_2/Ni, TiO_2/Cu and TiO_2/Mn/S, inhibits a variety of bacteria, including *B. coagulans, K. pneumonia, E. coli* and *S. aureus*.[53]

Doped-TIO_2'S antimicrobial activity mechanisms

Doped-TiO_2 has antibacterial action via a variety of methods. TiO_2 may be doped with various ions or chemicals and compounded with polymers to increase its photocatalytic activity and range to visible light, hence improving its antibacterial effectiveness.[18] ZnO-doped TiO_2, one kind of etal-doped TiO_2, has shown improved antibacterial activity against a range of microbes., such as *Escherichia coli* and *Staphylococcus aureus*.[29] Figure 6 illustrates the Mechanism of actions of doped-TiO_2. Doped-TiO_2 has antibacterial properties because light exposure produces Reactive Oxygen Species (ROS), which may harm the cell membranes of bacteria and prevent bacterial development.[51] To ensure the uniformity and control over mass distribution of

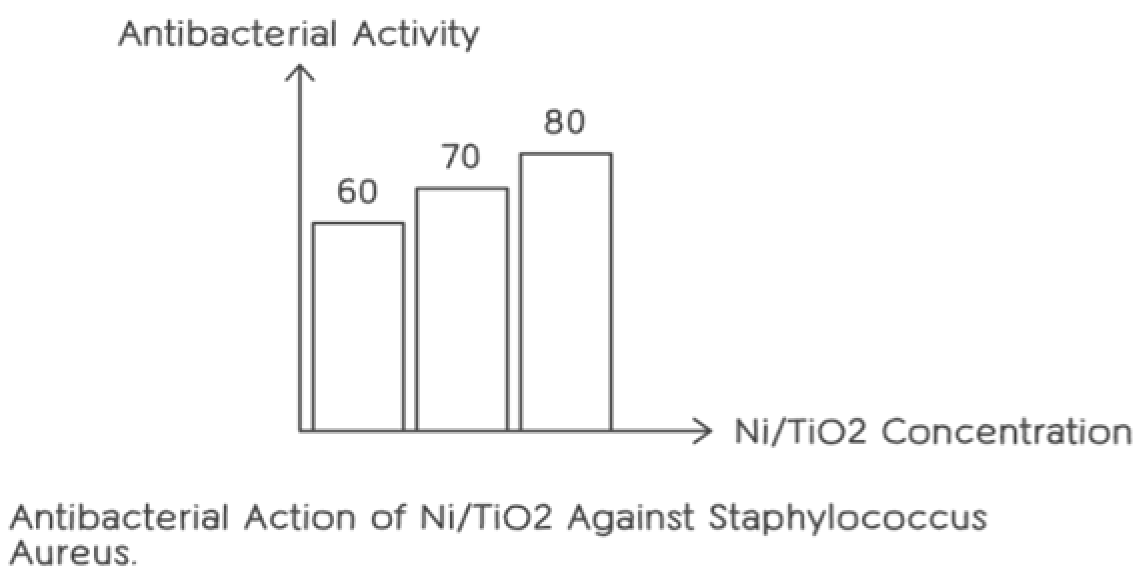

Figure 4: Antibacterial Action of Ni/TiO_2 against Staphylococcus.

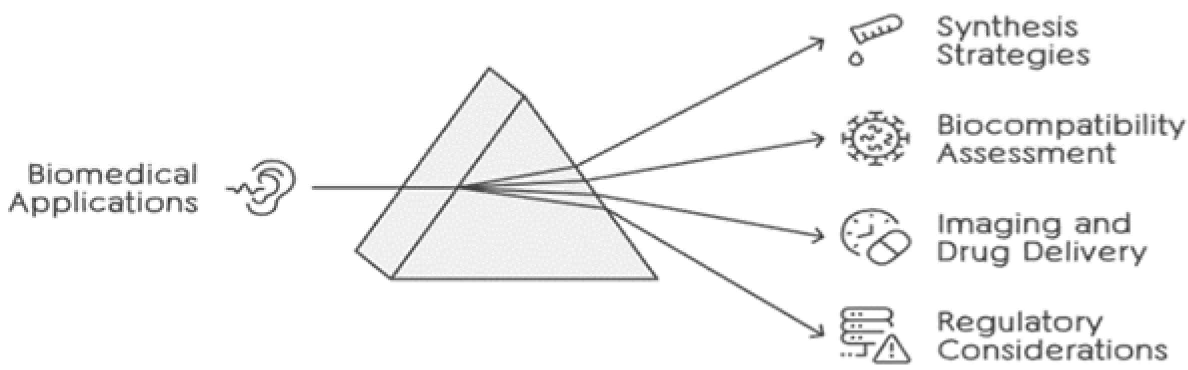

Figure 5: Various Uses of Doped-TiO_3 in Biomedicine.

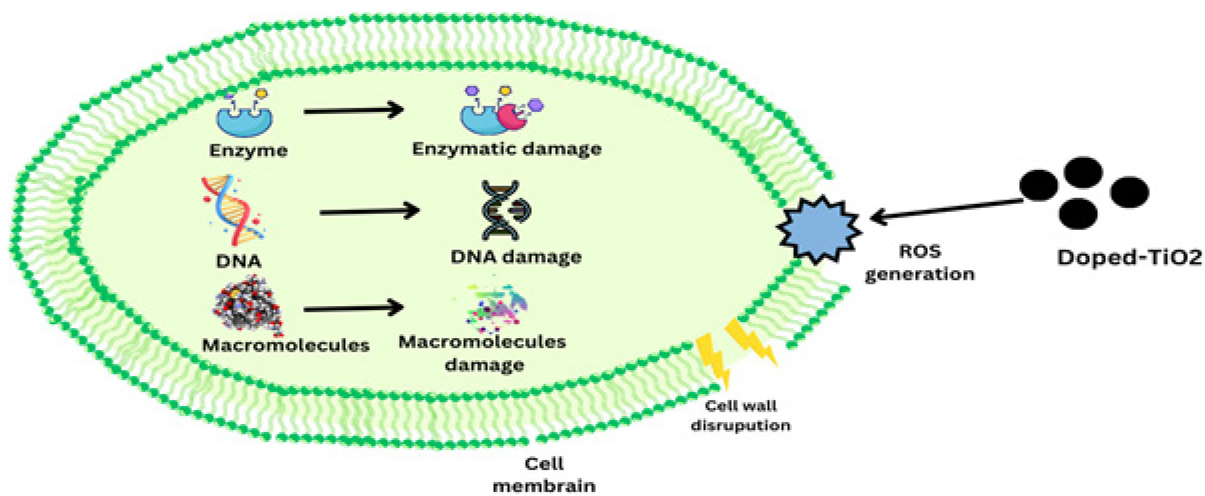

Figure 6: Mechanism of actions of doped-TiO_2.

doped TiO_2 nanoparticles, the sol-gel production process is often used. TiO_2 has strong antibacterial properties because of the synergistic effects of photocatalysis and the targeted activities of dopant compounds. Doped-TiO_2 produces Reactive Oxygen Species (ROS) such as superoxide anions and hydroxyl radicals when exposed to light. These ROS led to oxidative stress in microbial cells, which harms proteins, lipids and DNA and finally causes cell death. Dopants such as zinc and copper also contribute extra antibacterial mechanisms. For example, copper ions may physically harm cell membranes and interfere with cellular metabolic processes. Doped-TiO_2 is a very powerful substance that can effectively fight a variety of bacteria, viruses and fungi due to the combined effects of these methods.[58]

ROS generation

Numerous studies place a strong emphasis on the generation of Reactive Oxygen Species (ROS). A promising method for LDs-mediated photodynamic treatment was created by Wang *et al.* using a photosensitizer-based system that preferentially accumulates into Lipid Droplets (LDs) and produces ROS upon light activation.[59] Palladium (Pd) nanocrystals with various crystalline forms were examined for their cytotoxicity by Wu *et al.* They discovered that facet-dependent ROS production, which is facilitated by Pd nanocrystals, is a critical component of cytotoxicity.[60] A potential therapeutic approach has been presented by Ling *et al.*'s development of a biomimetic nanosheet material that can create ROS via a cascade of intracellular biological events and provide H_2O_2 in an acidic environment.[61]

Photoexcitation

Photon energy higher than or equal to the doped TiO_2's modified bandgap are absorbed by the substance. In the Valence Band (VB), a positive hole (h+) remains because an electron (e-) is promoted to the Conduction Band (CB).

The formula is as follows:

$$TiO_2 + h\nu \rightarrow TiO_2(e^- CB + h^+ VB).$$[62]

Dynamics of Charge Carriers

Dopants add trap sites that catch holes or electrons, preventing their recombination and boosting the effectiveness of following processes that generate ROS.[63]

Table 2: Mechanism of actions of doped-TiO_2 and possible mechanisms.

Doped Materials	Nanoparticles	Size (nm)	Synthesis Methods	Coating Materials	Organisms	Conc. of Nanoparticles (µg/mL)	ZOI (mm)	MIC (µg/mL)	MBC (µg/mL)	Mechanisms	References
Ag/TiO_2	Silver/ Titanium Dioxide	10-20	Sol-gel	None	*E. coli*	50	15	25	50	Cell membrane disruption, ROS generation.	54
Cu/TiO_2	Copper/ Titanium Dioxide	5-15	Hydrothermal	Chitosan	*S. aureus*	100	18	50	100	DNA damage, protein denaturation.	55
Zn/TiO_2	Zinc/Titanium Dioxide	20-30	Co-precipitation	PEG	*B. subtilis*	25	12	10	20	Lipid peroxidation, oxidative stress.	56
Fe/TiO_2	Iron/Titanium Dioxide	8-15	Solvothermal	Silica	*P. aeruginosa*	75	20	30	60	Membrane damage, enzyme inhibition.	57

ROS Formation

Holes react when they come into contact with hydroxide ions or adsorbed water molecules.

$$TiO_2\ (h+VB)+H_2O \rightarrow TiO_2+OH+H+$$

$$TiO_2\ (h+VB)+OH- \rightarrow TiO_2+\bullet OH$$

Electron reactions: Electrons cut down on molecules of dissolved oxygen.

$$TiO_2\ (e\text{-}CB)+O_2 \rightarrow TiO_2+\bullet O_2\text{-}.$$ [62,64]

CONCLUSION

Metal-doped titanium dioxide nanoparticles have demonstrated amazing potential as an antibacterial agent against a range of illnesses. Doping metals on top of nanoparticles can change their size and magnetic characteristics by mixing spins and electrical charges to reduce the energy band gap. Additionally, it has been demonstrated that because of their larger surface-to-volume ratio and enhanced ability to interact with bacterial cells, smaller metal-doped nanoparticles exhibit stronger antibacterial action. TiO_2 NPs have remarkable antifungal and antibacterial properties. Their primary mode of action against bacteria is attributed to their strong oxidizing ability, which generates radicals such as superoxide and hydroxyl anion. TiO_2 NPs doped with metals, namely silver, nickel, copper, manganese and sulfur, have shown increased antibacterial activity against several kinds of bacteria. Sol-gel, solvothermal and hydrothermal techniques are some of the ways that may be used to synthesize metal-doped TiO_2 NPs. It is possible to assess the antibacterial activity of metal-doped TiO_2 NPs utilizing methods like the well diffusion technique. All things considered, metal-doped titanium dioxide nanoparticles have the potential to be an effective antibacterial agent in a variety of fields, such as medicine, agriculture and water treatment.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

UV: Ultraviolet ROS: Reactive Oxygen Species; **OH:** Hydroxyl radicals; **O_2:** Superoxide anions; **MIC:** Minimal Inhibitory Concentration; **MBC:** Minimal Bactericidal Concentration; **CFU/mL:** Colony-Forming Units per milliliter; **CLSI:** Clinical and Laboratory Standards Institute; **MHB:** Mueller Hinton Broth

MHA: Mueller Hinton Agar; **TEM:** Transmission Electron Microscope; **SEM:** Scanning Electron Microscope; **BJH:** Brunauer, Emmett, and Teller; **FHH:** Frenkel-Halsey-Hill.

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