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Titanium Nanoparticles in Theranostics: A Multifunctional Platform for Targeted Therapy and Advanced Diagnostics

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Abstract

Aim: To assess the theranostic potential of titanium nanoparticles (TiNPs), especially titanium dioxide nanoclusters, by assessing their distinct physicochemical characteristics and uses in biomedical domains as gene transport, immunotherapy, antimicrobial therapy, cancer, and biosensing.

Methods: The multifunctional properties of TiNPs were reviewed, with particular attention paid to their wide surface area, photo-reactivity, biocompatibility, and simplicity of surface modification. They were evaluated for use in drug delivery, photothermal and photodynamic therapy, biosensing, immunotherapy, gene therapy, antibacterial and antiviral activity, imaging (MRI, CT, fluorescence, optical, and photoacoustic imaging), and immunotherapy.

Result and Discussion: TiNPs have been demonstrated to improve imaging accuracy and sensitivity while facilitating real-time therapy monitoring. Through targeted administration, they decreased systemic toxicity and increased therapeutic efficacy in oncology. Their production of reactive oxygen species (ROS) promotes their antiviral, antibacterial, and biofilm-inhibitory properties. TiNPs also make it easier to distribute checkpoint inhibitors for immunotherapy and to deliver genes through targeted uptake and electrostatic interactions. They also have high-resolution molecular imaging capabilities and perform better in biosensing and diagnostics.

Conclusion: By integrating therapeutic and diagnostic properties on one platform, titanium-based nanostructures demonstrate notable theranostic potential. The development of next-generation targeted medicines and diagnostics, better treatment results, and customized therapies are all made possible by their multifunctional nature.

Keywords Titanium nanoparticles, Gene therapy, Immunotherapy, Diagnostics, Reactive Oxygen Species a(ROS)

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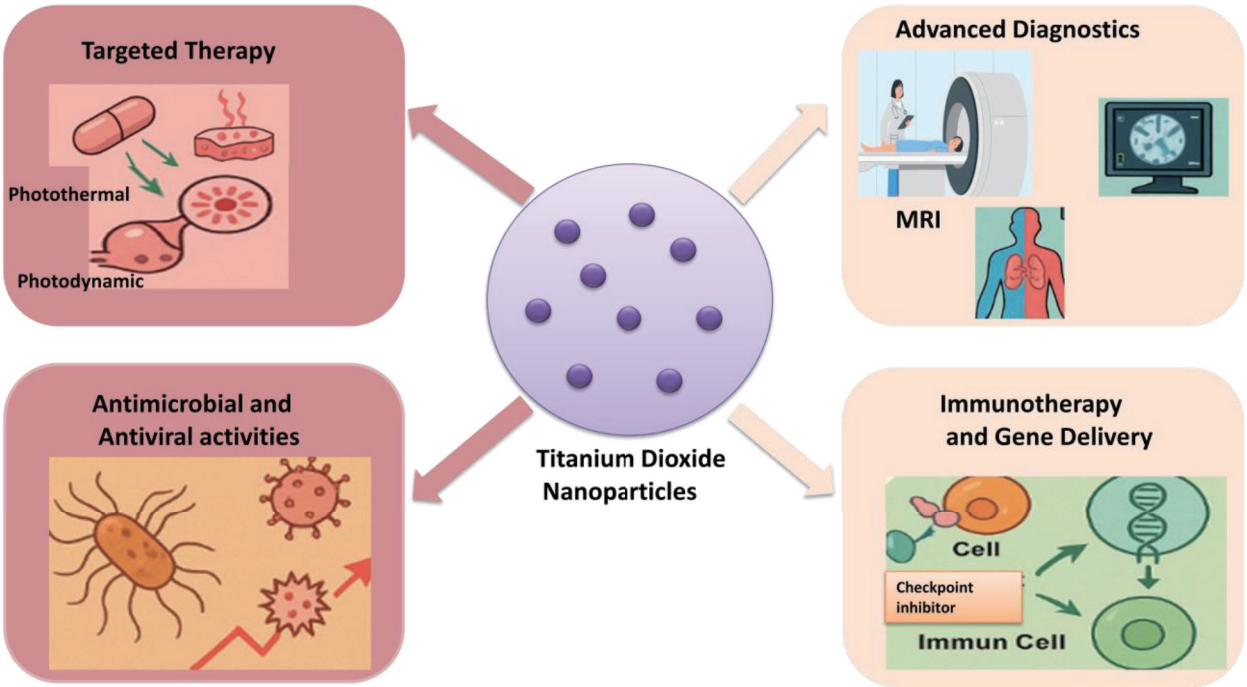
Graphical Abstract



1. Introduction

Since the beginning of the twentieth century, nanotechnology has been an acknowledged research area. Numerous revolutionary advancements have been made in the field of nanotechnology since Nobel laureate Richard P. Feynman introduced the concept in his well-known 1959 lecture, "There's Plenty of Room at the Bottom". Materials of numerous varieties were created at the nanoscale level by nanotechnology[1]. According to Laurent nanoparticles (NPs) are a broad class of materials that contain particulate compounds with at least one dimension smaller than 100 nm[1]. These materials can be 0D, 1D, 2D, or 3D, depending on their general shape. The significance of these materials became apparent when scientists established that a substance's size can affect its physiochemical traits such as its optical capabilities[2]. TiO2 has been extensively researched and proven to be helpful in the development of self-healing and anti-corrosive coatings. The smart flexible polymeric layer on the surface of the nanoparticles has been shown to strengthen their dispersion in an epoxy-based matrix and act as a self-healing coating. Furthermore, the employed polymeric gels showed "smart" behavior in the presence of water and corrosive agents, enabling segmental mobility to fix the damaged areas. Despite the encouraging findings of the technique, there is a study vacuum concerning the quantitative assessment of corrosion and self-healing efficiency. Feasibility studies that have been evaluated qualitatively have been the main focus of this approach[3]. Research on additional uses of TiO2 nanoparticles, especially in nanobiotechnology and nanomedicine, has risen significantly since Fujishima and Honda's crucial discovery of ultraviolet (UV) light-mediated water splitting on the surface of TiO2[4]. Nanoparticles are grouped according to their size, shape, and place of origin. It is possible to categorize the original NPs as manufactured or natural. Physics, chemistry, biology, medicine, and materials science are all interwoven within the multidisciplinary field of nanoscience. Liposomes, dendrimers, carbon-based, and metal-based NPs are among the several shapes and sizes that they can have[5].As the metastable anatase phase has a lower surface energy than the equilibrium rutile phase, nanoparticles of titanium dioxide are more likely to develop there. Because of its photocatalytic sterilizing capabilities, the surface of ultrafine titanium dioxide in the anatase structure can be used as an additive to produce construction materials, such as self-cleaning windows and antifogging coatings[6]. According to reports, lead, mercury, and tin heavy metal nanoparticles are so robust and inflexible that it is difficult to degrade them, which can have substantial adverse effects on the environment. These particles exhibit physical, chemical, and biological characteristics that differ from those of individual atoms because they behave completely differently at

the atomic, ionic, and molecular of their respective bulk matters[7]. Materials classified as nanomaterials have at least one dimension less than 100 nm (1 nm = 10-9 m). The compounds demonstrate absolutely ideal characteristics as their dimensions become smaller. For example, the graphene nanomaterial becomes extremely conductive as its size decreases.

2. Methods of synthesis of TiNP

2.1. Physical and chemical method for synthesis of titanium dioxide nanoparticles

For the synthesis of TiNP nanoparticles, a variety of chemical synthesis methods are used, which involve sol-gel, solvo-thermal also known as hydrothermal methods. The synthesis of TiNPs by a chemical technique is widespread because it is simple and enables control over the size and form of the NPs. However, there are shortcomings, such as high energy costs, high temperature and pressure, ecotoxicity, and environmental sustainability. Furthermore, this restricts their mass production and their uses in a number of industries[8].

2.1.1. The Sol-gel technique

Nanoparticles of tin oxide, tungsten oxide, zinc oxide, and titanium dioxide are commonly synthesizedusing the sol-gel process. Hydrolysis, polycondensation, aging, drying, and thermal degradation are the five primary lines of this process. A solvent (alcohol, water, or a solvent containing a hydroxyl bond) and an initiator (metal alkoxide) are needed for the hydrolysis stage. The goal is to extract the metal from the alkoxide and reunite it with the -OH bond at this point. The M-O-M bond is created during polycondensation, which releases the M-OH molecule from the solvent. Then it is allowed to mature. Various gel forms are included based on the kind of drying, including freeze-drying, thermal drying, supercritical drying, and calcination, which yields the finalproduct[9]. The sol-gel technique for titanium dioxide nanoparticles is based on a titanium (IV) alkoxide initiator hydrolyzing and then condensing. For the Ti-O-Ti chain to be obtained, hydrolysis with a modest amount of water is preferred. In general, titanium tetraisopropoxide serves as the initiator. Temperature influences both the solution's viscosity and the solidification rate constant. The Lifshitz-Slyozov-Wagner model shows that the average TiO2's radius expands with time. Titanium dioxide is produced using the sol-gel process as anatase[9].

2.1.2. Hydro/solvothermal method

Solvothermal and hydrothermal are two processes that are nearly identical. The hydrothermal method uses an aqueous solution of the material to crystallize it at a high temperature and high vapor pressure. It is often presented as crystal synthesis or crystal formation from substances that are insoluble at standard pressures (less than 1 atm) and temperatures (100°C). The procedure is conducted in autoclaves with regulated pressure and temperature. It permits the usage of temperatures higher than water's boiling point. Since the temperature can be raised considerably, high boiling point solvents may be utilized, the solvothermal process has more control over the characteristics of TiO2 than the hydrothermal approach, and it uses a non-aqueous solvent[10].

2.2. Biological method for synthesis of titanium nanoparticles

The environmental toxicity of chemical methods for producing Titanium nanoparticles has been established, and the high temperature and pressure required for the synthesis limit the amount of TiNP that can be produced in huge quantities. Thereby, considering green nanotechnology uses reducing agents obtained from biological sources and may be used to synthesize numerous metallic compounds, it has been investigated as an alternative and ecologically sustainable method for the manufacture of TiNPs, shown in fig.1. Utilizing plants, their waste products, fruit extract, and microbes in the synthesis also reduces the need for costly and hazardous chemicals.

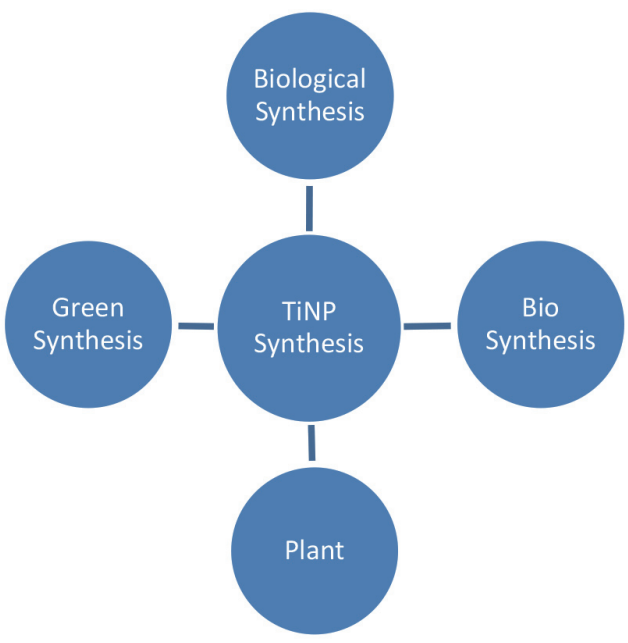


Figure 1: Methods of synthesis of titanium nanoparticles.

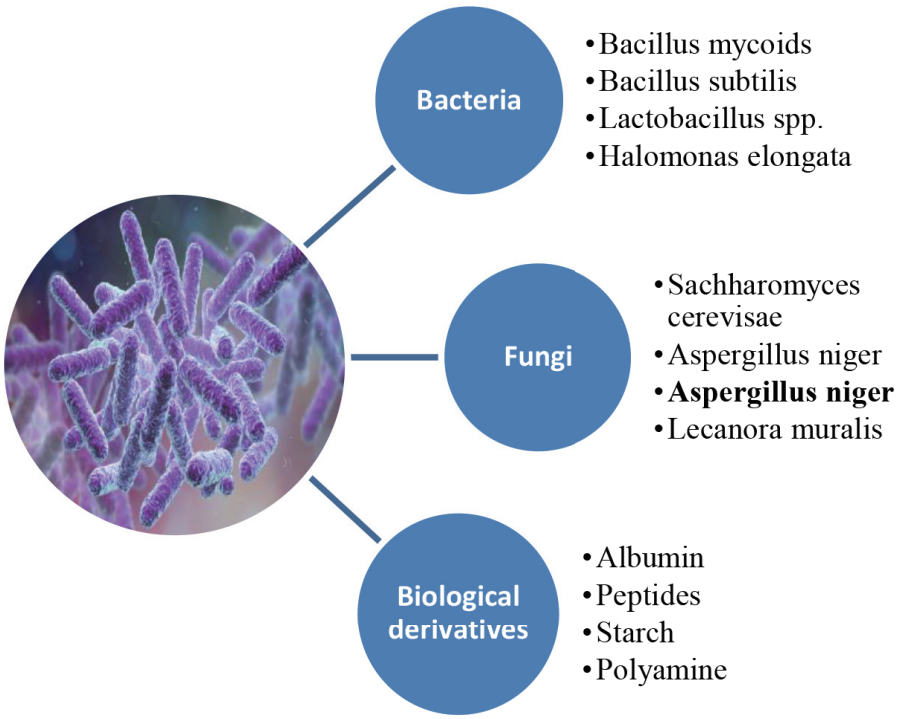


Figure 2: Biological synthesis of TiNP as a green method with the help of different bacterial, fungal and biological derivative compound

Additionally, TiNPs can be produced on a mass scale at a reasonable cost using this method as shown in fig.2. Green synthesis methods are therefore necessary for synthesizing stable, suitable-sized, and dispersible NPs requiring little energy usage[8].

2.2.1. Direct oxidation method

The metal titanium is oxidized by oxidants. TiO2 nanorods usually are synthesized via the direct oxidation process. The dissolution precipitation mechanism is responsible for this process. For example, crystallized TiO2 nanotubes are produced when the anodized titanium plate is heated to 500 ° C for six hours in an oxygen environment. It has also been observed that TiO2 nanorods develop when titanium metal is directly oxidized with hydrogen peroxide[11].

2.2.2.Physical and Chemical vapour deposition method

By condensing a vaporized material, vapor deposition techniques can produce a solid phase material. Coatings are usually applied using this approach in order to alter the mechanical, electrical, thermal, optical, corrosion, and wear resistance of various substrates[12].

2.2.3. Synthesis from green plant extract

Considering its advantages in terms of feasibility and safety, plant extract isusually the most important factor in the synthesis of titanium dioxide nanoparticles. Plants and its various parts—the stem, leaves, latex, flowers, seeds, and rootsare the source of nanoparticles of many different sizes and shapes. The majority of research has been concentrated on plant parts like leaves, seeds, and flowers. They have gained popularity mostly because of their extraordinary ability to reduce metal ions. Accessibility of plants and safety during handling are additional benefits. Based on plants bioactive compounds that serve as reducing and stabilizing agents comprise polysaccharides, alkaloids, diterpenoids, salicylic acids, lactones, glycosides, amino acids, steroids, and even more. Aluminum, iron, zinc, manganese, copper, titanium, and cobalt nanoparticles are all being satisfactorily synthesized using green chemistry. Due to its many advantages, including expenditures fewer toxic effects, environmental friendliness, and enhanced applications, green synthesis is gaining traction over chemicaltechniques[13].

3. Techniques for characterization of TiNP

3.1. STEM technique

Scanning Transmission Electron Microscopy (STEM) was used to examine the composites' morphology at 200 kV using an H-7650 120 kV Automatic Microscope

(Hitachi, Japan). An SU-8230 operating at 30 kV was additionally utilized for the SEM examination. A few µL of diluted ethanol suspension was dropped onto the nickel grid to create the samples.

3.2. FT-IR Technique

A Bruker Tensor II spectrometer (from KBr pellets) was implemented to record Fourier Transform Infrared (FT-IR) spectra in transmission mode (Bruker Optics, Billerica, MA, USA). UV-570 JASCO Spectrophotometer (Jasco International Co, Ltd., Tokyo, Japan) was used to record the UV–Vis absorption spectra. Using CuKα1 radiation (λ = 1.5406 Å), X-ray powder diffraction (XRD) findings were carried out on a Bruker D8 Advance diffractometer (Billerica, MA, USA)[14].

3.3. XRD Technique

The structure and phase formation of the sample were examined using the TiO2 NPs' X-ray diffraction (XRD) pattern. A well-crystallized anatase profile for TiO2 NPs was seen and the outcome demonstrated that the structure was tetragonal, which is in good agreement with SEM and TEM examination[15].A RigakuMiniflex X-ray diffractometer with Cu Kα (1.5406Aº) radiation scanning throughout 2θ from 10º to 90º was used to obtain the powder X-ray diffraction (XRD) pattern. The Tescan scanning electron microscope with Vega3sem software was implemented to view the sample's surface morphology. The HORIBA XGT5200 Energy Dispersive X-ray Fluorescence analyzer (ED-XRF) was used to identify the samples' elemental compositions[16].

4. Biomedical properties of titanium nanoclusters

TiNPs possess special antibacterial, optical, electrical, and photocatalytic qualities, as shown in fig.3. Serious cutaneous, mucosal, and systemic fungal infections are known to be caused by Candida species. TiNPs exhibited strong antifungal action against Candida albicans in both their rutile and anatase forms. There was a dose- and time-dependent lowering of cell viability. Additionally, TiO2 NPs influence the shape of cells. Photocatalytic paints created with the anatase form of TiO2 shown antifungal effects against A. niger due to their strong photocatalytic activity.

4.1. Biocompatibility and non-toxicity of TiNP

The low toxicity of titanium dioxide contributes to its widespread availability. A number of studies using titanium in various nanoparticle and microparticle sizes and crystal forms have been performed to evaluate hematotoxicity, skin, lung, and immune system effects. Regardless of being a very common ingredient in many cosmetic formulations, particularly sunscreens, powders, and eyeshadows, titania's

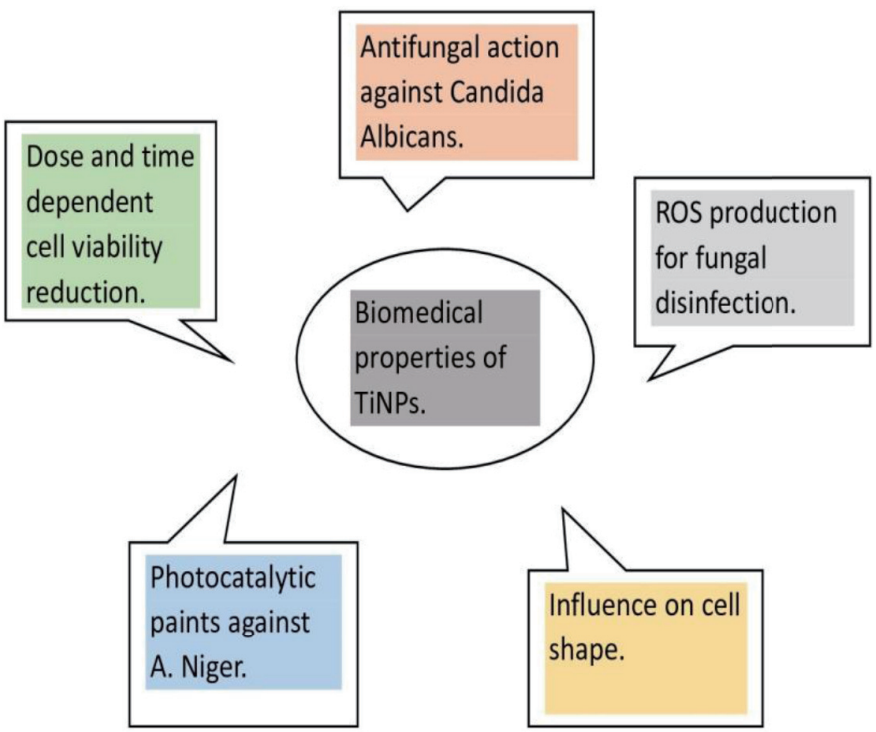


Figure 3: Unveiling the multifaceted biomedical properties of TiNPs

size and crystal shapes (rutile and anatase) seemed to affect how safe it is to use. Two problems were identified up by the in vitro and in vivo investigations conducted into the toxicity of TiNPs to the skin: skin toxicity and systemic toxicity associated to skin penetration. Following subchronic dermal exposure, Wu et al. investigated the toxicity and penetration of TiNPs in the skin of pigs and hairless mice[17].

The researchers came to the conclusion that, mostly because of its deeper tissue dispersion, nanosized titanium may be harmful to human health following prolonged, chronic cutaneous exposure. In a different study, Crosera et al. used both intact and needle-abraded human skin to examine the penetration of TiNPs on Franz cells over 24 hours and assess the cytotoxicity on Ha Ca T keratinocytes.The analysis showed that TiNPs could only be detected in the epidermal layer, whereas their concentration in the dermal layer was below the detection limit.

Only after continued exposure did a minor cytotoxic effect on human Ha Ca T keratinocytes indicated a possible risk associated with TiNPs[18]. The results indicate that the formation of reactive oxygen species (ROS) produced during UVA irradiation cause TiNPs to be phototoxic to human skin keratinocytes. It is noteworthy that anatase demonstrated more phototoxicity than the rutile form of nano-TiO2[19]. Multiple studies have investigated any potential hazards brought about by inhaling TiO2, described in table.1. Titania-related adverse effects were primarily discovered in the toxicology study, along with several studies that might have shown serious "overload." One study by Lee et al. can be used as an illustration[20].

4.2. Antibacterial and anticancer properties of titanium nanoclusters

TiO2 nanoparticles' capability for generating Reactive Oxygen Species (ROS) has been correlated to their antibacterial and photocatalytic properties as shown in table.2[21]. The deposition of bioproducts onto the surface of TiO2 can significantly increase ROS production, which in ultimately leads to increased biological and photocatalytic activity. They also function as an effective anticancer drug since they have their propensity to produce a significant quantity of reactive oxygen species in cancer cells[22].There have been reports about multiple wild mushrooms having probableanticancer and antioxidant qualities. In particular, edible mushrooms have an abundance of bioactive compounds with distinct and varied bioactivities, such as antibacterial, anti-inflammatory, antioxidant, antitumor, and anticancer effects[23]. An attempt was made to use F. fomentarius extracts, which were obtained from an angiosperm host in the natural forest of the Kashmir valley, India, as reducing agents for the synthesis of TiO2 and AgNPs in light of these reports. As per recent anti-inflammatory, antioxidant reports, this wild mushroom consists of cytotoxic, antibacterial,, antinociceptive, and antidiabetic properties[24,25].

Table 1. Biocompatibility and non-toxicity of titanium nanoparticles.

Aspects	Details
General Safety	TiO2 is widely used due to low toxicity; common in sunscreens, powders and eyeshadow.
Crystal form influence	Safety is influenced by size and crystal form (anatase vs. rutile).
Skin toxicity studies	Subchronic dermal exposure in pigs and mice showed that deeper tissue penetration can lead to systemic toxicity. Titanium nanoparticles penetrated only the epidermal layer, not the dermis. Minor cytotoxicity observed with prolonged exposure
Phototoxicity	Under UVA, Titanium nanoparticles produce ROS- phototoxic to human keratinocytes (HaCaT cells); anatase is more phototoxic than rutile.
Inhalation toxicity	Studies indicated respiratory concerns and “overload” toxic effect upon inhalation.

Table 2. Antibacterial and anticancer properties of titanium nanoparticles

Property	Details
Mechanism	Antibacterial and anticancer effects attributed to ROS generation.
Enhanced ROS	Surface deposition of bioproducts increases ROS and photocatalytic activity.
Anticancer application	High ROS in cancer cells enables titanium dioxide nanoparticles to act as anticancer agents.
Bioactivity of Mushroom extracts	These extracts show cytotoxic, antibacterial, anti-inflammatory, antioxidant, antitumor, and antidiabetic activities.

5. Diagnostic applications of Titanium nanoclusters

Studies on titanium dioxide (titanium(IV)oxide, titania, TiO2) nanoparticles—which come under the category of metallic NPs—are presented in this study. Notably, the driving force behind this work was the assessment of currently used TiO2 functionalization techniques together with the biological and medicinal effects of these NPs. TiO2 was first produced in massive quantities in the early 1900s as a non-toxic alternative to white paint dye[26]. These days, the TiO2 molecule is used in many everyday goods as a colorant in white plastics, an excipient in the pharmaceutical industry, a sunscreen manufacture in the cosmetics industry, and an affordable, nontoxic food pigment that has been approved by the appropriate European Union authorities for the safety of food additives as summarized in fig.4[27].

Despite the paucity of knowledge concerning potential interactions between nanotechnology tools and biological tissues or cells, developments in nanotechnology suggest novel strategies to cure many human ailments. As an example, contrast agents comprise gold nanoparticles for X-rays, magnetic nanoparticles for MRIs, and hybrid nanoparticles (iron oxide and gold) for both MRIs and CT scans[29].

The most frequently used nanoparticles in these new cancer treatment techniques are zinc oxide (ZnO) and titanium dioxide (TiO2) nanoparticles. Although the micro-sized particles of these metal oxides are thought to be safe for humans and animals, the nanoparticles of these metal oxides are thought to be toxic. The physical and electrochemical characteristics of these nanoparticles, however, make them suitable for use in photodynamic and sonodynamic processes[30].

5.1. Imaging techniques: MRI, CT and Fluorescence

5.1.1.MRI

Poly (lactic-co-glycolic acid) nanoparticles were developed for enhancing the bioavailability of curcumin, and the intracellular transport was successful, according to reports. Titanium dioxide (TiO2) is a semiconductor nanoparticle that is widely used as an ingredient in paints, food coloring, cosmetics, and toothpaste. It has a wide range of diagnostic and therapeutic applications considering its nontoxic nature and high chemical stability in the biological system; it is biocompatible with less or no toxicity in vitro and in vivo; reports confirmed the reducing toxic effects when functionalized with other nontoxic molecules[31].

5.1.2. CT

CT is one of the most reliable and extensively used diagnostic technologies in hospital due to varying

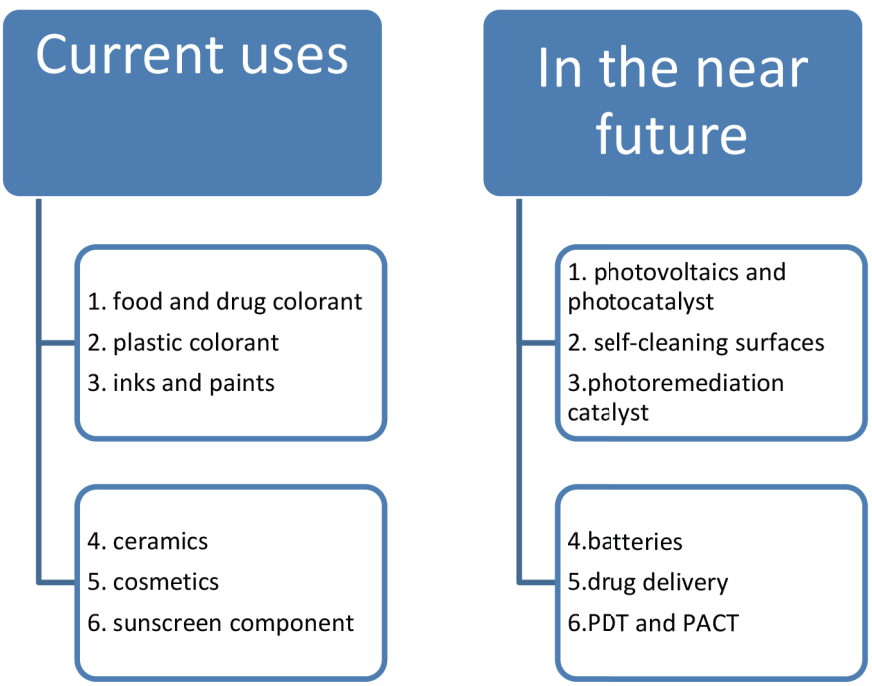


Figure 4: Current applications and potential future use of TiO2.PDT, photodynamic therapy, PACT, antimicrobial photodynamic therapy; DSSC[dye-sensitized solar cell[28].

X-ray absorption of tissue and lesion. The CT scanners temporal and spatial resolutions are getting improved due to its growing number of detectors and quicker rotation speed. In order to boost visibility in the administered area of the body, clinical contrast agents for CT contrast enhancement are based on iodinated molecules and compounds with a high X-ray absorption coefficient. It makes the use of nanoparticles for enhancing visibility of scanned area[32].

5.1.3. Fluorescence

With qualities like improved brightness (defined as absorbance times quantum yield), inertness to their microenvironment, and a more even distribution (unless targeted imaging of specific domains is desired, of course), the availability of nanomaterials for imaging purposes has led to the introduction of a variety of imaging techniques. Unlike molecular probes, nanoparticles (NPs) frequently do not trigger cytotoxicity and do not experience unexpected sequestration or nonspecific binding by cellular biomacromolecules[33].

5.2. Biosensors: Detection of biomarkers, DNA or pathogens

5.2.1. TiNP in detection of biomarkers

For confirmation of the impact of occupational exposure to TiNPs on human health and investigate biomarkers for biological monitoring, epidemiological analysis is performed. The occupational population's safety assessment is also very important for nano safety. In accordance to the current investigation, variations in the profile of blood metabolites may result from occupational exposure to TiNPs. Liquoric acid is one of eight distinct metabolites that may be employed as indicators of occupational exposure to TiNPs. These putative biomarkers' sensitivity and specificity were demonstrated statistically. Metabolomics was thought to be beneficial method for finding nano-biomarkers, which would help investigate biological monitoring markers for nanomaterial exposure at work[34].Concern has been aroused about the deleterious consequences of occupational exposure to TiNPs. Nevertheless, epidemiological research has been scarce thus far[35]. As a result of its high stability, anticorrosion, and photocatalytic qualities, TiNPs are much sought after by nanotechnology. Mammals exposed to TiNPs using various routes have shown harmful effects. For instance, research has shown that TiNPs have the ability to enter nuclei and disrupt DNA activities. TiNPs may also result in genotoxicity, enzyme inhibition, reactive oxygen species generation, and changes to blood biomarkers[36].

5.2.2. TiNP in detection of DNA

TiO2 nanoparticles (NPs) are frequently employed in the production of photoelectrodes for PEC DNA biosensors as well as other PEC uses, including photocatalysis and photovoltaic devices. Because of their high photocatalytic activity, chemical stability, morphological and crystallinity tunability, ideal valence and conduction band levels for initiating a variety of electrochemical reactions, water insolubility, non-toxicity, and low manufacturing cost, TiNPs are perfect for PEC-based applications[37].Because of their high conductivity and affordability, titanium dioxide nanostructures in a variety of shapes make an interesting material for electrode modification in electrochemical biosensors. TiO2 nanostructures seem to enhance mass and electron transport at the electrode surface, particularly in carbon-based electrodes[38].Since TiO2-based semiconductor metal-oxide materials have garnered a lot of curiosity because of their affordability and versatility in manufacture, TiO2 has been used as the substrate on the sensing surface[39].A large number of biosensors that depend on traditional three-electrode electrochemical detection techniques, such as cyclic voltammetry, exhibit subpar detection limitations. As a result, more research has been carried out on microelectronic devices that can shorten detection times and increase sensitivity[40].

5.2.3. TiNP in detection of pathogens

Several molecular techniques, including the reverse transcription-polymerase chain reaction (RT-PCR), which is still the gold standard for pathogen identification, are frequently used in the detection of viruses and bacteria.Isolation, culture, and biochemical analysis are typically essential for the traditional detection techniques of these infections[41]. Additionally, antibodies and immunoglobulin necessary for identification have been identified by serological tests such as the Enzyme-Linked Immunosorbent Assay (ELISA)[42].One of the most widespread metal oxides for sensing applications is titanium dioxide (TiO2) nanoparticles (NPs), which have excellent properties like high chemical resistance, large specific surface area, high catalytic efficiency, high electrical conductivity, and physical strength. They can additionally improve the interaction between biomolecules and electrode surfaces[43][44].Since TiO2-based semiconductor metal-oxide materials gained a lot of attention because of their affordability and versatility in production, TiO2 was utilized as the

substrate on the sensing surface. TiO2 nanoparticles' biocompatibility in biosensor development offers improved electron-transfer kinetics and improved sensing performance. For metal-oxide nanostructures, it has been suggested that the target DNA can readily modify the semiconducting conductance in order to improve sensitivity and the surface-to-volume ratio[45].

5.3. Role of TiNP in diagnostic kits and platforms

Titanium dioxide nanoparticles in their anatase phase have been shown to suppress the H9N2 avian influenza virus in a study by Cui et al. interestingly, the inhibitory activity of the nanoparticles activated in the presence of UV radiation was higher than that of the ones that were not exposed.Copper doped titanium dioxide (Cu+2/TiO2) nanoparticles with higher photocatalytic activity were examined for antiviral activity in follow-up research by Jiang et al. In contrast to their titanium dioxide counterparts, the data indicated a greater degree of antiviral activity. When the UV intensity is 0.5 mW/cm2, the amount of H9N2 is 0.1 mL, and the UV illumination time is 2.5 h, it has been proved that the inactivating rate on H9N2 viruses may reach 100%. In a different study, 100 titanium dioxide nanoparticles which were electrostatically bound to DNA (v3′) and pointed towards the 3′ end of the viral (H3N2) DNA's non-encoding region effectively prevented virus replication. Additional research indicated that the DNA-tagged titanium dioxide nanoparticles had comparable efficacy against the H5N1 and H1N1 viruses[46].

6. Therapeutic applications of Titanium Nanoclusters

6.1. Drug delivery: encapsulation of drugs-controlled release mechanism

Approaches, formulations, technologies, and systems that facilitate the entrance and movement of medicinal chemicals within the body to provide the intended therapeutic effect are collectively referred to as drug delivery (DD). Drugs are usually administered orally (tablets), parenterally (injection), transmucosally, and inhaled in conventional or systemic DD (SDD) administration. In these cases, the drugs are distributed throughout the body rather than just to the specific site of interest, necessitating the use of rational DD systems. Two concepts based on localized drug delivery (LDDS) and targeting DD systems have emerged as the most promising strategies.

Numerous issues and restrictions, including poor biodistribution, lack of selectivity, adverse effects, toxicity, and drug solubility, are present with this common pharmacological administration route [47].

Silver (Ag)/titanium dioxide (TiO2)/polyethylene glycol (PEG), titanium dioxide (TiO2)/polyethylene glycol (PEG), and silver (Ag)/titanium dioxide (TiO2)/chitosan (Ct's) are the three nanocomposites that are being synthesized and characterized in this study using the laser ablation method. These mixtures serve as vehicles for the anticancer drug 5-fluorouracil (5Fu). A number of characterization methods were used, including transmission electron microscopy, UV-visible, X-ray diffraction analysis, and Fourier transform infrared spectroscopy[47]. Titania (TiO2) nanoparticles, also known as titanium dioxide, are well-liked among the different types of inorganic nanoparticles because of their distinctive photoresponsive qualities, simplicity of scaling up, non-immunogenicity, and structural stability . Because of its effective optical absorption, affordability, and chemical stability, titanium dioxide is primarily investigated in the fields of photocatalysis, photodegradation, photovoltaics, etc. [48]. An electron (e) and hole (h+) pair are created when ultraviolet (UV) light is excited, and the valence electrons are excited to the conduction band. This creates active free radicals (OH and O2) that efficiently break down organic substances on the outer layer of the TiO2 particle, giving rise to a theoretical basis for light-triggered release of drugs. It's important to note that TiO2 has been shown to have a strong anticancer impact because it produces active free radicals when exposed to UV light [49].

6.2. Photothermal and photodynamic therapy

6.2.1. In photodynamic therapy

The three primary components of photodynamic treatment (PDT) are an oxygen molecule, a light source, and a photosensitizer (PS). Living tissues and cells can be exposed to a benign photosensitizer, such as a macromolecular compound55, organic material at the nanoscale56, or an inorganic particle57. The absorbing of photon from a visible- light source excites these PSs, which then impart energies to the oxygen molecule to generate reactive oxygen species (ROS) and singlet oxygen (1O2). 58,59 PDT offers greater benefits than traditional theranostics for cancer, including a better safety record, minimum invasiveness, cost effectiveness, and high localization with few to no side effects[50].

6.2.2. In photothermal therapy

NP-based photo-thermal therapy (PTT) holds promise as a novel approach for successfully treating cancer cells without significant drawbacks or adverse effects. Because of their unique physicochemical characteristics, NPs are particularly effective at transforming the energy of photons of laser beams into heat and causing hyperthermia in cancerous tissues. Numerous nanostructures, including carbon nanotubes, silver nanoparticles, and gold nanoparticles, have so far been effectively created to cause tumor tissues to become extremely hot. Titanium dioxide (TiO2) nanoparticles are a good contender with particular properties for the Treatment of cancers[51].TiO2 has garnered increasing attention in recent years. It is often regarded as physiologically inert and finds application in the cosmetics and pharmaceutical industries. In addition to having remarkable qualities such a high refractive index, photocatalytic capabilities, and magnetic properties, it is biocompatible. The spontaneous development of a layer of oxide over the surface of titanium is the cause of these TiO2 properties. TiO2 is an efficient catalyzer for the treatment of malignant tumors and has the ability to eliminate bacteria, viruses, fungus, and cancer cells. TiO2 NPs are used in biomedical applications such as PDT, delivery of drugs, cell image processing, biosensors for biological assays, and genetic engineering[52].

6.3. Treatment of cancer, infection and other diseases

In Smith et al.'s work, titanium dioxide nanoparticles have been investigated as a way to improve radiation therapy and computed tomography imaging (CT). Ionizing radiation is used in radiation therapy to target tumors and disrupt their DNA, which kills the tumor cells. Although it hasn't been fully explored yet, dual-mode contrast between images and improvement therapy is another application for nanoparticles. Since iodine is frequently employed as a CT image contrast agent, it can be utilized to track iodine uptake in tumors.

Another anticancer mechanism of TiO2 NPs is the production of reactive oxygen species (ROS). In the study by Fujiwara et al. (2015), inflammatory cytokines (Macrophage Inflammatory Protein-1α (MIP-1α) and High Mobility Group Protein-1 (HMGB1)) were produced by both cancer cells and noncancerous tissues. These cytokines caused oxidative stress and activated macrophages, which in turn activated HMGB1; these macrophages, in turn, secreted HMGB1, which in turn caused the activation of caspase-3 and apoptosis.TiO2 nanoparticles were administered intratumorally in a form of gel plug to prevent the unintended toxicity that could result from the diffusion of nanoparticles, which the study found caused apoptosis and inhibited the growth of remaining cells if HMGB1 had not been released.

7. Theranostic applications of titanium nanoclusters

A combination of the words "therapeutic" and "diagnostic," the term "theranostic" describes a medical strategy that utilizes both diagnosis and therapy, frequently with the use of radiopharmaceuticals, to more precisely target and treat illnesses. Titanium nanoparticles' theranostic uses combine therapeutic and diagnostic properties, providing significant promise for both medical diagnosis and therapy as shown in fig.5. The following are some important theranostic uses for titanium nanoparticles:

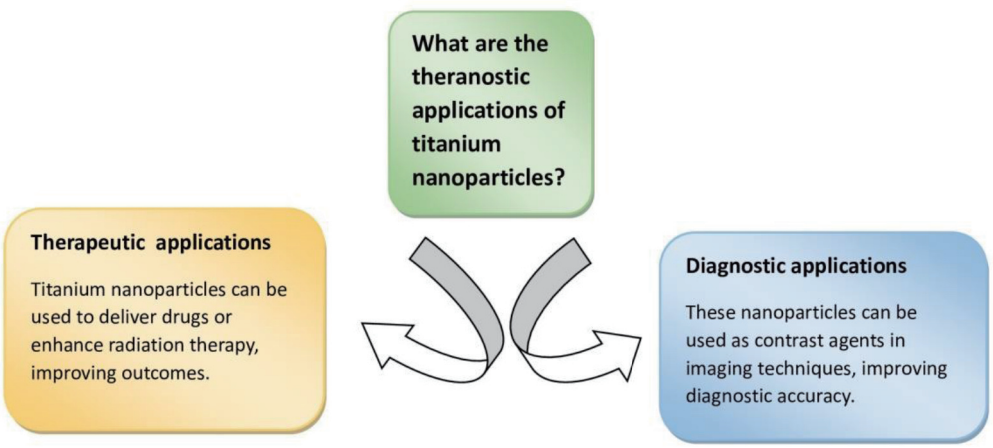


Figure 5: Theranostic applications of titanium nanoparticles.

1. Cancer therapy and diagnosis:
   • Targeted drug delivery.
   • Imaging and diagnosis.
   • Photothermal therapy.
2.Biosensing and Diagnostics:
   • Detection of biomolecules.
   • In vitro diagnostics.
3. Antimicrobial and Antiviral Applications.
4. Gene Delivery.
5. Photodynamic Therapy [PTD].
6. Immunotherapy.
7. Bioimaging for Tracking Drug Delivery

7.1. Cancer therapy

Utilizing Drug Delivery Methods to Treat Cancer with Titanium Dioxide Nanoparticles: Compared to molecular drug delivery to the tumor environment, the utilization of NPs as a nanosystem in drug delivery applications has improved cancer detection and treatment efficiency by roughly 10 to 100 times. Additionally, because the reticular-endothelial system absorbs fewer NPs, the drug's persistence in the circulatory system is increases.By attaching different ligands as well as antibodies to their surface, TiO2 NPs' great biocompatibility, non-toxicity, and exceptional affinity have led to their consideration for targeted tumor targeting. While lowering the negative side effects of the dangerous medications, precise anti-tumor drug delivery at the site of tumors can improve the effectiveness of cancer treatment. Applications of TiNP as a contrast agent in cancer imaging are given in below fig.6.

Magnetic Resonance Imaging and Computed Tomography: Using various metal-based NPs to be contrast agents prior to MRI and CT scans is one efficient method of enhancing contrast. By speeding up proton relaxation in regions of the body where the particles have higher concentrations than in other areas, contrast agents of MRI improve the contrasting effect of the tissue. Currently, efforts are being made worldwide to create novel TiO2 NPs with anti-cancer and contrast capabilities. According to Leon Smith et al., there are noticeable variations within the CT total of produced TiO2 NPs at concentrations more than 15 mg/mL. Another study used MRI and CT techniques to

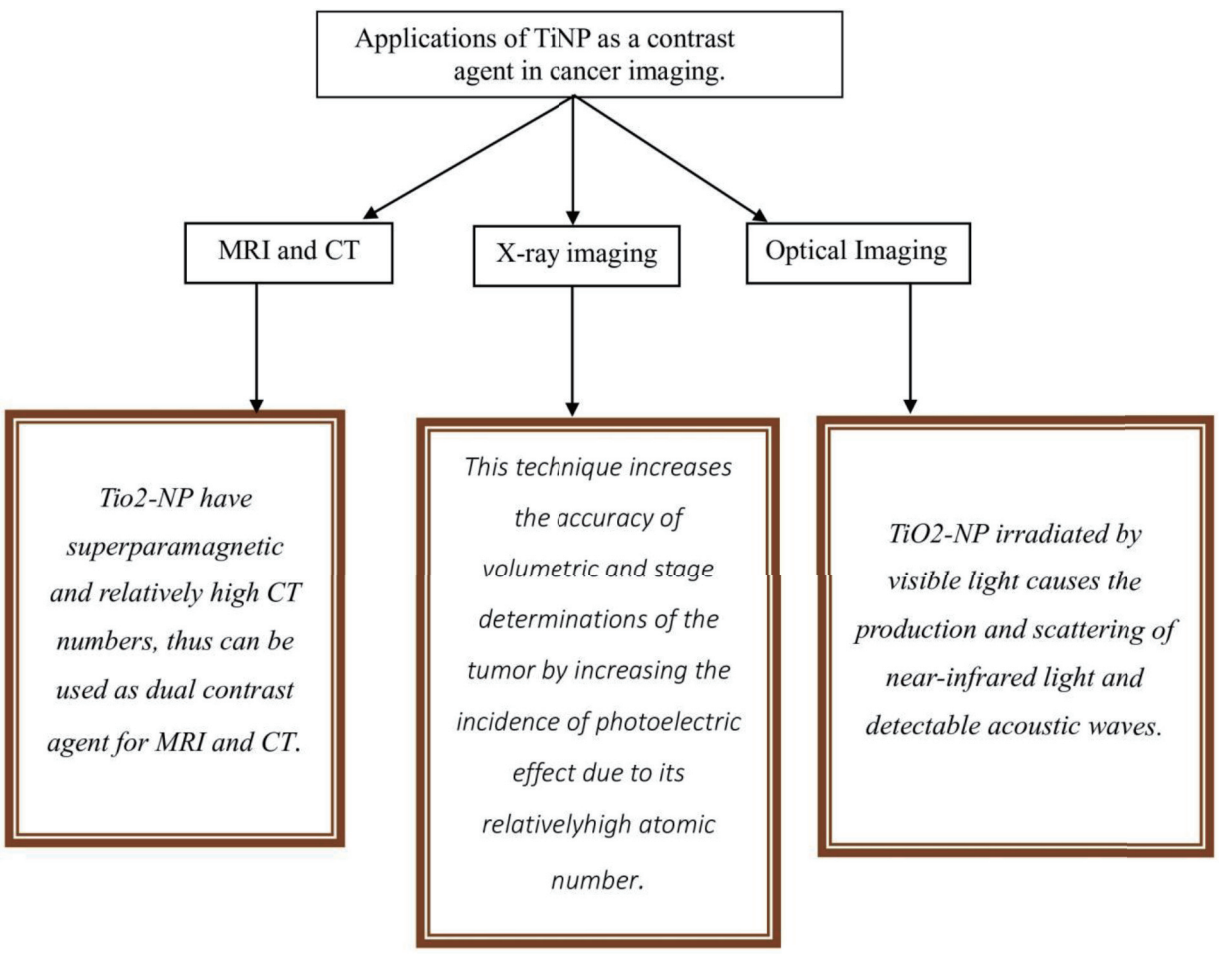


Figure 6: Different applications of TiO2 NPs in cancer.

examine the contrast-enhancing capabilities of TiO2 NPs, which had a size of roughly 50 nm. The findings showed that TiO2 NP has a great deal of promise for application in MRI T2 sequences.

7.2. Biosensing and Diagnostics

TiNPs, which combine therapeutic and diagnostic properties, have become highly promising materials in the field of theranostics. Their distinct physical, chemical, and biological characteristics make them attractive options for use in diagnostic imaging and biosensing.

TiNP enhance the sensitivity and specificity of biosensors due to their high surface area and reactive sites.

7.2.1. Role in biosensing

1. Electrochemicalbiosensors: TiNP improve electron transfer rates, enhancing the detection of biomolecules like glucose, DNA, and proteins.

2. Optical biosensors: Their strong optical properties make them suitable for surface-enhanced Raman scattering [SERS], aiding in detection of low-abundance analytes.

3. Fluorescence sensors: Functionalized TiNPs can act as fluorescent probes for detecting specific cellular markers or pathogens.

7.2.2. Diagnostic applications

1. Molecular imaging: TiNPs can be used in magnetic resonance imaging {MRI} and computed tomography [CT] due to their contrast enhancing capabilities.

2. Targeted Imaging: Surface functionalization allows TiNPs to target cancer calls, enabling early detection and monitoring of tumors.

3. In Vivo tracking: Their stability and low cytotoxicity allow for long-term tracking of cells or nanoparticles in biological systems[54].

7.3. Antimicrobial and Antiviral applications

In several biological applications, titanium nanoparticles (TiNPs) are attracting a lot of interest, especially because of their theranostic potential, which combines therapeutic and diagnostic qualities. Because of their special qualities, which include a large surface area, bioactivity, and stability, along with the capacity to alter the surface for targeted drug administration, titanium nanoparticles present an intriguing strategy for antibacterial and antiviral activities. A thorough examination of TiNPs' theranostic uses in antibacterial and antiviral activity is provided below:

7.3.1. Titanium nanoparticles' (TiNPs') antimicrobial activity

Because of their innate antibacterial qualities, titanium nanoparticles can be used to both prevent and treat bacterial infections. TiNPs combat microorganisms through the following mechanisms:

- **Production of reactive oxygen species (ROS):** When exposed to light or in aqueous settings, TiNPs can produce ROS, including superoxide ions and hydroxyl radicals. Bacterial cell death can result from ROS damage to the cell walls, membranes, as well as interior components. A common use for this process is photocatalytic antibacterial treatment.
- **Physical Destruction of Bacterial Membranes:** TiNPs' small size enables them to physically disrupt bacterial membranes. This might result in cellular contents leaking out, which would hinder the bacterial cell's ability to function and ultimately cause it to die.
- **Biofilm Inhibition:** Biofilms are infamously challenging to treat. They are collections of microorganisms that create protective coats on surfaces. TiNPs have the ability to prevent biofilms from forming and aid in their removal, which is essential in cases of persistent infections and those involving medical equipment.
- **Surface Functionalization:** To increase TiNPs' antimicrobial action, they can be customized with antimicrobial substances such peptides, antibiotics, or antimicrobial polymers. TiNPs' therapeutic index can be enhanced by surface changes that increase their selectivity for particular bacteria.

7.3.2. Titanium Nanoparticles' Antiviral Activity (TiNPs)

Through a number of methods, TiNPs also demonstrate potential in the fight against viral infections.

- **Viral Entry Inhibition:** TiNPs have the ability to engage with viral particles and stop them from entering host cells. The electrical attraction between the positively energized TiNP surfaces and the negatively energized viral membrane may facilitate this interaction. TiNPs can successfully prevent viral infection by preventing the virus from attaching to host cell receptors.
- **Photocatalytic Inactivation:** Similar to their antibacterial properties, TiNPs can harm virus particles by generating reactive oxygen species (ROS) when exposed to ultraviolet light. One method that shows promise for disabling viruses and stopping their proliferation is photocatalytic inactivation.
- **Virus-Specific Surface Modifications:** TiNPs can be customized with certain ligands or antibody to target specific viral strains. This can improve their antiviral effectiveness and selectivity by strengthening

their binding to the virus particle or infected cell.

• **Viral Particle Deactivation:** It has been investigated if TiNPs can disrupt the capsid proteins or the viral envelope, making the virus infectious. This is particularly important for viruses that are enclosed, such as corona viruses and influenza[55].

7.4. Gene delivery

In delivering genes applications, nanoparticles of titanium (TiNPs) have demonstrated great promise, especially in the area of theranostics, which combines diagnosis and treatment. They are perfect candidates for effective and focused gene delivery because of their special physicochemical characteristics, which include biocompatibility, simplicity for surface alterations, and the capacity to react with various genetic material as well as biological systems. An outline of titanium nanoparticles' (TiNPs) theranostic uses in gene transfer is provided below:

TiNPs provide a number of ways to help carry genetic material into target cells, including plasmid DNA, messenger RNA (mRNA), small interfering RNA (siRNA), and CRISPR-Cas9 systems:

• **Electrostatic Interaction:**TiNPs can bind electrostatically with negatively charged nucleic acids by being transformed with positively charged groups (such as polyethylene amine). As a result, stable complexes—also known as polyplexes or nanoparticle-DNA complexes—are created, which shield the genetic material from deterioration and promote cellular uptake.

• TiNPs are absorbed by cells by endocytosis, a process in which the cell membrane swallows the nanoparticle-genetic complex, after they have formed complexes with genetic material. This procedure enables the gene material to enter the target cell's cytoplasm or nucleus, where it can subsequently be applied therapeutically.

• **Targeting Surface Modification:** TiNPs could be functionalized using certain ligands (such aptamers, peptides, or antibodies) that can identify and attach to target cell surface receptors. TiNPs are perfect for targeted gene therapies in particular tissues or cell types because of their functionalization, which improves the accuracy of gene delivery[56].

7.5. Photodynamic therapy

TiNPs' capacity to combine therapeutic and diagnostic properties gives them theranostic potential in PDT. These features enable accurate illness area targeting and real-time therapy progress tracking.

7.5.1. Imaging and PDT Monitoring

TiNPs can track the administration and therapeutic outcomes of PDT using diagnostic imaging techniques. They can be used in a variety of imaging modalities because to their special optical characteristics:

• **Fluorescence Imaging:** fluorescent marker or quantum dots that glow when exposed to light can be used to functionalize TiNPs. This makes it possible to monitor TiNP dispersion and cellular uptake in real time during PDT. Fluorescence imaging can be used to monitor the effectiveness of treatment, determine the precise location of treatment, and evaluate the buildup of TiNPs in tumors.

• TiNPs can be paired with paramagnetic as well as super paramagnetic substances (like iron oxide) to function as MRI contrast agents in magnetic resonance imaging (MRI). This enables high-resolution imaging of infection or tumor locations during PDT. To make ensure that the light exposure is directed to the right place, MRI can be utilized to monitor the distribution of nanoparticles and validate the therapeutic zone.

• Deep tissue imaging is made possible by the combination of TiNPs and photoacoustic imaging (PAI). Ultrasound waves are produced when light is absorbed by the TiNPs and transformed into heat. This method provides both anatomical as well as functional information and can be used to monitor tumor treatment in real time during PDT.

7.5.2. Tracking and Targeting via Surface Adjustments

TiNPs can target cancer cells, cells with infections or other disease indicators by surface-modifying them with certain ligands. This targeting reduces negative effects and increases PDT's specificity. Functional groups can also be added to TiNPs so that diagnostic imaging methods can be used to monitor their distribution and behavior in vivo.

• **Targeted PDT:** By modifying TiNPs via tumor-specific antibodies as well as peptides, they can preferentially accumulate at tumor locations. This selectivity boosts the efficacy of PDT by concentrating the light-activated formation of ROS on a tumor, thereby decreasing damage to adjacent healthy tissue.

• **Biodistribution& Biocompatibility Studies:** The biodistribution of TiNPs can be investigated by imaging methods such as fluorescence, MRI, or photoacoustic imaging. This enables researchers to evaluate the nanoparticles' in vivo fate and make sure they aren't building up in non-target tissues or causing unintentional harm[50].

7.6. Immunotherapy

Due to its special qualities, including excellent

biocompatibility, simplicity of functionalization, and optical features, titanium nanoparticles have captured a lot of interest in a variety of medical sectors. In the field of theranostics, which combines therapeutic and diagnostic methods, TiNPs have demonstrated encouraging uses in immunotherapy, namely in the treatment of cancer. These nanoparticles could be designed to carry therapeutic drugs, target certain tissues, and facilitate imaging for diagnostic and treatment efficacy monitoring.

7.6.1. Important Theranostic Uses of Titanium Nanoparticles in Immunotherapy

7.6.2. Targeted Therapy and Drug Delivery

• **Functionalization:** Antibodies or ligand that attach selectively to cancerous cells or immune cells used in immunotherapy can be used to functionalize titanium nanoparticles. This improves treatment efficacy and minimizes negative effects by enabling targeted drug delivery.

• **Chemotherapy and Immunotherapy drugs:** TiNPs have the ability to encapsulate immune checkpoint inhibitors, cytokines, or chemotherapeutic drugs, which they will release in a controlled manner once they reach the target area. TiNPs, for instance, can transport immuno-modulatory medications that inhibit tumor-induced immune tolerance or stimulate T-cells.

• **Immunological Response Stimulation:** It has been demonstrated that titanium nanoparticles can trigger specific immunological pathways, which include those containing dendritic cells that can improve the immune system's ability to identify and eliminate malignancies.

7.6.3. Immuno-modulation

Immune Cell Activation: To strengthen the body's defenses against cancers, titanium nanoparticles may interact with T-cells, dendritic cells, and macrophages, among other immune system constituents. TiNPs aid in activation and recruiting of immune system cells to the tumor location by promoting immunological pathways.

• **Checkpoint Inhibition:** Immune check point inhibitors, such anti-PD-1/PD-L1 antibodies, can be delivered straight to the tumor site via TiNPs. This makes it easier for the immune system to identify and combat cancer cells.

• **Enhanced Antigen Presentation:** TiNPs may additionally be designed to show immune cells tumor antigens, which improves the immune system's ability to identify cancer cells and boosts the effectiveness of immunotherapy[57].

7.7. Bioimaging for tracking drug delivery

Because of their special qualities, including their biocompatibility, ease of modification, and potential for theranostic applications, titanium nanoparticles (TiNPs) are now attracting interest in the fields of bioimaging and drug delivery. The integrated application of therapy and diagnostics is known as "theranostics," and titanium nanoparticles have promise in both fields, especially for imaging and medication delivery.

The following describes the ways in which titanium nanoparticles are employed in theranostic applications pertaining to medication delivery tracking and bioimaging:

As the name implies, therapeutic and diagnostic capacities are combined in the field of theranostics. TiNPs' dual functionality makes them perfect for these kinds of applications:

1. Concurrent Imaging and Therapy: TiNPs can be engineered to transport medication and act as an imaging agent, providing real-time drug delivery process monitoring. For instance, TiNPs might be filled with a chemotherapy medication and used to follow its transport to the tumor site in real time by giving MRI contrast.

2. Personalized Medicine: More individualized treatment plans are made possible by the integration of imaging and medication delivery. Clinicians can maximize therapeutic outcomes by modifying dosages and treatment plans by monitoring the distribution of TiNPs within the body and the drug's release.

3. Reducing Side consequences: By guaranteeing that the medication is accurately administered to the intended site, real-time tracking of TiNPs lowers the possibility of off-target consequences. Particularly in cancer treatment, where conventional medicines frequently harm healthy tissues, this could be essential in reducing side effects.

4. Targeted Drug Delivery: By modifying the surface of TiNPs along with targeting ligands (which can be peptides, antibodies, or other biomolecules), medications can be delivered to particular cell types or regions with precision. This is particularly advantageous for cancer treatment since TiNPs can target tumor cells, lowering the systemic toxicity of conventional therapies.

5. Monitoring Drug Release: TiNPs enable real-time tracking of the release of drugs through the nanoparticles at the location of interest site using bioimaging methods like fluorescence or MRI. This guarantees that medications are efficiently supplied to the right place and permits exact control over the

treatment process.

8. Conclusion

By integrating therapeutic and diagnostic properties, titanium nanoparticles (TiNPs), in particular titanium dioxide nanoclusters, offer a potent multipurpose platform in theranostics. Applications in targeted drug administration, photodynamic and photothermal therapies, imaging (MRI, CT, fluorescence), biosensing, gene delivery, and immunotherapy are all made possible by their unique features, which include biocompatibility, high surface area, photo-reactivity, and surface modifiability.

The safety and scalability of TiNPs are further improved via environmentally friendly synthesis techniques, which include green chemistry initiatives employing plant and microbial extracts. Their antibacterial and anticancer properties are supported by their capacity to produce reactive oxygen species (ROS) once activated by light, and their application in bioimaging enables real-time monitoring of therapy outcomes.

Personalized, minimally invasive treatments with precise disease targeting and monitoring are made possible by the incorporation of TiNPs into theranostic systems. TiNPs are positioned to be critical for targeted, patient-specific treatments and next-generation diagnostics as research progresses.

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Conflict of Interest

The authors declared there is no conflict of interest.

Abbreviations

TiNP: Titanium Nanoparticles
NP: Nanoparticles
ROS: Reactive Oxygen Species
STEM: Scanning Transmission Electron Microscopy
DD: Drug Delivery
PDT: Photodynamic treatment
PS: Photo sensitizer
PTT: Photo-thermal therapy

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