Chapter

Nano Titania Applications in Cancer Theranostics

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Abstract

Titanium is one of the most abundantly utilized nanomaterials for human consumption. Biomedical applications of nano titania include sunscreens, drug delivery, prosthetic implants, bioimaging probes, and antimicrobial and antirheumatic agents for various treatment of diseases, including autoimmune disease, neurogenerative diseases, cardiovascular, musculoskeletal, and cancer. Its applications as a drug delivery vehicle and photosensitizer in cancer therapy and diagnosis are highly appreciated, especially for skin and natural cavities applications. The reactive oxygen species (i.e., H_2O_2, $OH^{\cdot}$, OH_2, $^1O_2$, etc.) generation properties of nano titania after activation with light or ultrasound make it ideal for apoptosis induction in neoplastic cells. In addition, the singlet oxygen ($^1O_2$) generating properties make it suitable for bioimaging deep-seated and superficial tumors after activation. Nano titania is highly biocompatible with negligible adverse effects. In this chapter, we will focus on the anticancer effects of nano titania on various types of cancers by employing it as a drug delivery vehicle and sensitizer for external source-activated modalities viz. photodynamic and sonodynamic therapy.

Keywords: nano titania, anticancer effects, theranostics, photodynamic therapy, sonodynamic therapy

1. Introduction

Nanotechnology has opened a new avenue to investigate and explore the potentials of materials at the nanoscale with known functionality at the macroscale. The biomedical applications of nanoscale materials are supported by the evidence that most of the cellular organelles, cell membranes, protein ligands, and DNA sizes are ranged from 2 to 20 nm [1]. The interaction of materials with cellular organelles at the nanoscale can significantly enhance their desired biomedical application with enormous traceability. Nanotechnology is applicable in various areas of the healthcare system due to the distinguished biological and physicochemical properties of nanomaterials. Various nanostructures with distinct characteristics have been utilized in drug delivery, diagnostic probes, prosthetic implants, and biotechnological applications. Out of many, titanium dioxide (TiO_2) has been extensively utilized [2].

TiO_2 are metallic oxide nanoparticles, widely used, and are of great interest in modern therapeutics. They are semiconductive, highly stable, and possess

anticorrosive and antibacterial characteristics. Titanium is the second most abundantly consumed metal, with daily 1–2 mg/kg consumption for children and 0.2–0.7 mg/kg for adults in the USA [3]. It is well distributed on the earth's crust and abundantly found in T, $TiCl_4$, and TiO_2. The anatase is the most reactive crystalline form of TiO_2 compared to brookite, rutile, and TiO_2-B1 as various polymorphs [4]. Titanium is well recognized for its exceptional characteristics, such as low weight, good mechanical strength, high wear resistance, and biocompatibility [5, 6]. They are less toxic than other nanomaterials and relatively economical to fabricate [7, 8]. Anatase and rutile exist in a tetragonal structure, whereas brookite is rhombohedral [9]. Moreover, an amorphous form of TiO_2 can also be found [10].

Their white appearance is attributed to their high refractive index and is used in skin care products as a white pigment. They possess catalytic activity upon exposure to UV light and can be utilized for water treatment to remove the chemicals from them [8]. In addition, TiO_2 has also been used as an additive in food products [11–14]. TiO_2 is one of the most produced nanoparticles due to its wide range of applications [15]. TiO_2 has been employed in biomedical applications such as molecular imaging, drug delivery system, and therapeutic approaches alongside conventional therapies or substitutes [16, 17]. Akira Fujishima was the first to discover its anticancer effect against human cervical cancer cells (HeLa). Photoactivation with UV light could generate hydroxyl ($OH^{\cdot}$), per hydroxyl ($H_2O^{\cdot}$), and singlet oxygen ($^1O_2$) as Reactive Oxygen Species (ROS) [18]. These ROS then interfere with cellular signal pathways and induce apoptosis by damaging the mitochondria. Different biomedical applications of nano titania are shown in **Figure 1**. This chapter focuses on combining various applications of titanium NPs in biomedicine, especially in various cancer

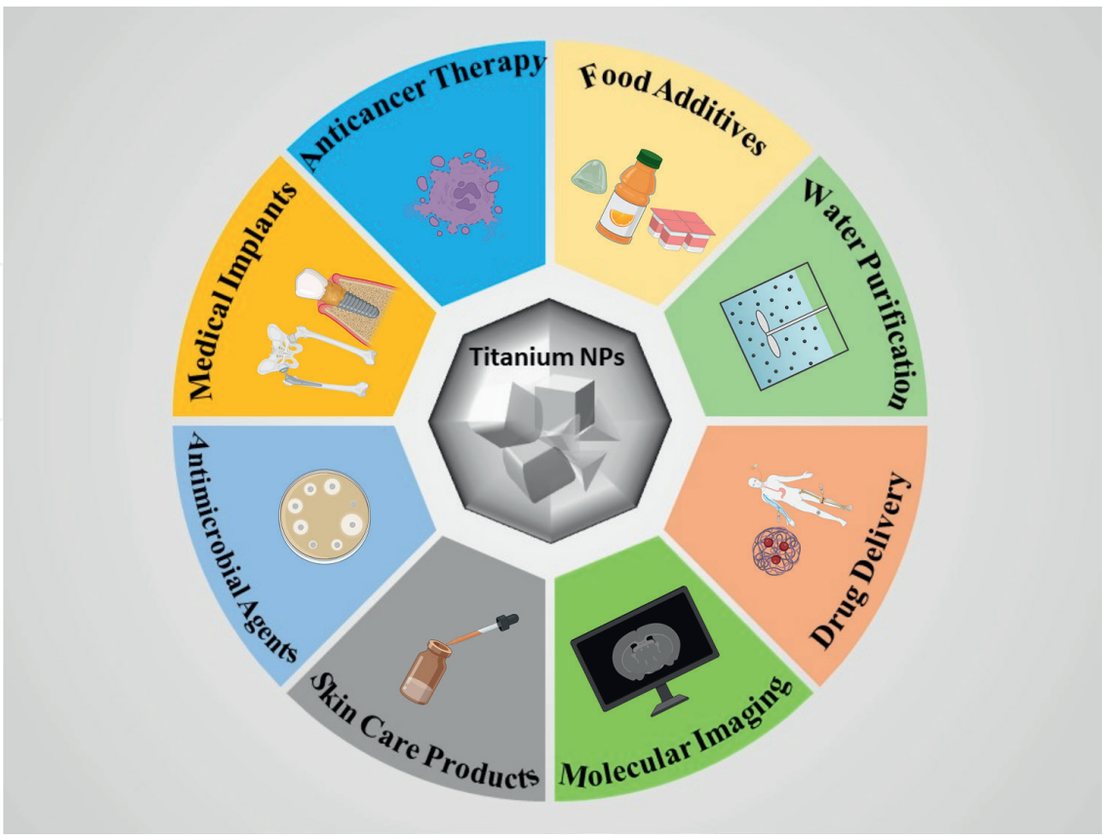

Figure 1.
Various biomedical applications of titanium-based nanoparticles (developed by using BioRender).

therapeutics and diagnostic purposes. We will also spotlight its applications in the specialized modalities viz. photodynamic and sonodynamic therapy as photosensitizers. In targeted cancer therapies, the use of nano titania as a delivery vehicle is highly favorable and this will be the main focus of this chapter.

2. Antimicrobial activity of Titania nanoparticles

Antimicrobial activity is one of the major applications of biomedical science. Pathogenic microbial species such as *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Proteus vulgaris* are known to affect humans by causing various infections. Prescribed antibiotics occasionally cannot kill or cause growth inhibition of these pathogenic bacteria, and they often develop multidrug resistance. Therefore, there is an urgent need to develop novel and nano-based therapy to eradicate bacterial infections. Mahendran et al. synthesized biomolecule-coated TiO_2 nanocatalysts by using rhizome extracts. They observed that nano titania catalysts showed robust antimicrobial activity. This potential antimicrobial activity was produced against *P. aeruginosa* and *S. epidermidis*. They further observed the resistance against nano titania catalysts in gram-positive than gram-negative bacteria [19].

Fungal diseases cause deterioration in mangoes post-harvesting, affecting their quality and shelf-life. In the last few years, edible coatings have been investigated to preserve fruits and vegetables. Nano titanium dioxide is an immensely active nanomaterial with antibacterial, anti-ultraviolet, super lipophilic, and non-toxic characteristics. Chitosan is a good food preservative, antioxidant, and antibacterial agent for coating fruits and vegetables. Xing et al. used Chitosan (CTS) and TiO_2 composite coating and analyzed its antifungal properties against Colletotrichum gloeosporioides (MA), Cladosporium oxysporum (ME), and Penicillium steckii (MF). They found that CTS/TiO_2 composite exhibited a better antifungal effect than chitosan coating alone. CTS/TiO_2 coating killed the molds, induced leakage of intracellular proteins and nucleic acid, disrupted the cell membrane integrity, retard the mycelial growth, and increased the conductivity value of fungal suspensions [20]. Maneerat and Hayata used TiO_2 coating films and examined the antifungal effect. They showed a significant reduction in the penicillium rot development in apples and lemons [21].

3. Sonodynamic therapy

Sonodynamic Therapy (SDT) has recently gained much attention as a new anticancer treatment strategy that is relatively cheap, minimally invasive, and possesses deep penetration power. In this therapy, ultrasound waves activate the sonosensitizers (sound-sensitive agents), killing tumor cells by producing ROS [22]. The use of ultrasound offers some advantages in comparison to the use of light in cancer treatment which includes sonoporation (cell permeabilization mediated by ultrasound waves) and deeper penetration (depending on the frequency of ultrasound) which could be up to 15 cm in soft tissues [23–25]. Sonosensitizers refer to the use of chemical compounds that could increase the cytotoxicity of ultrasound. Nano-sonosensitizers are considered potent sonosensitizers, as compared to conventional organic sonosensitizing agents, owing to their high bioavailability achieved by improved pharmacokinetics, pharmacodynamics, and

biodistribution properties. Generally, nano-sonosensitizers can be categorized into two main types: (1) nanoparticles which include TiO_2, and (2) nanoparticles assisted sonosensitizers, consisting of nanoparticles loaded with organic molecules with controlled release at the target site [26]. Among many nanoparticles, the use of TiO_2 NPs is preferred because of their inert behavior in the biological system, easy fabrication, and cost-effectiveness. TiO_2 is a semiconductor with a large energy band gap, allowing for electron transitions from the valence to the conduction band when exposed to UV light. This facilitates the generation of free radicals, including the enormously reactive singlet oxygen. However, UV radiations are not clinically ideal due to low penetration power. Using ultrasound can overcome this due to its greater in vivo penetration ability with low frequency [27]. Various studies have reported the use of TiO_2 NPs as anticancer agents in vitro and in vivo systems, especially when combined with ultrasound irradiation.

TiO_2 NPs, in association with high-intensity ultrasound waves, were used for sonodynamic therapy of squamous cell carcinoma cells (HSC-2). The authors reported that the toxicity of TiO_2 with ultrasound was much higher than that of TiO_2 or ultrasound alone, which increased with the increase in intensity and exposure time [28]. SDT with TiO_2 NPs was evaluated for the treatment of melanoma. C32 (melanoma cell line) was treated with ultrasound waves of 1 MHz frequency. The apoptotic effect was more significantly observed in the TiO_2-based SDT than in either treatment alone. In addition, the apoptotic percentage of cells was increased by 2.73 times than untreated cells [29]. Aksel et al. reported that TiO_2 NPs mediated sonodynamic, photodynamic, and Sono-Photodynamic (SPDT) Therapy for prostate cancer. SDPT combines sonodynamic therapy and photodynamic therapy along with TiO_2 NPs as sensitizers. The results showed a reduction in cancer cell viability after TiO_2-mediated sono-photodynamic therapy. The production of singlet oxygen affects the intrinsic pathway, which might be responsible for producing antiapoptotic effects [30].

4. Photodynamic therapy

Photodynamic Therapy (PDT) is an emerging non-invasive therapy that received clinical approval. This therapy is preferred over conventional anticancer treatments due to its high efficacy, specificity, and subtle side effects [1, 31]. This therapeutic strategy utilizes photosensitizers (chemicals, drugs) with light in the presence of molecular oxygen to stimulate the generation of ROS, thereby inducing tumor cell death. However, the combination of PDT and drug is expected to produce a more significant effect as an anticancer treatment since PDT alone is relatively inefficient in eradicating cancer [32–35]. The photosensitizer should ideally enter the target cells/tissues without affecting the neighboring healthy tissues (**Figure 2**).

Moreover, the treatment can be confined to an elevated concentration of photosensitizers. This promising strategy can be applied to inhibit microbial growth and treat cancer and infectious diseases [35]. The effectiveness of PDT relies on the type of photosensitizers used. Several materials, including inorganic [33], organic, and porphyrin-based materials [34], have been used as photosensitizers in PDT. However, several drawbacks have been associated with these materials, such as inadequate dispersion in water and photostability. In addition, these materials cannot absorb light of longer wavelength, i.e., greater than 700 nm, which results in improper light penetration and subsequent reduction in cell killing effect. This causes unwanted toxicity and damage to cancer and normal cells or tissues.

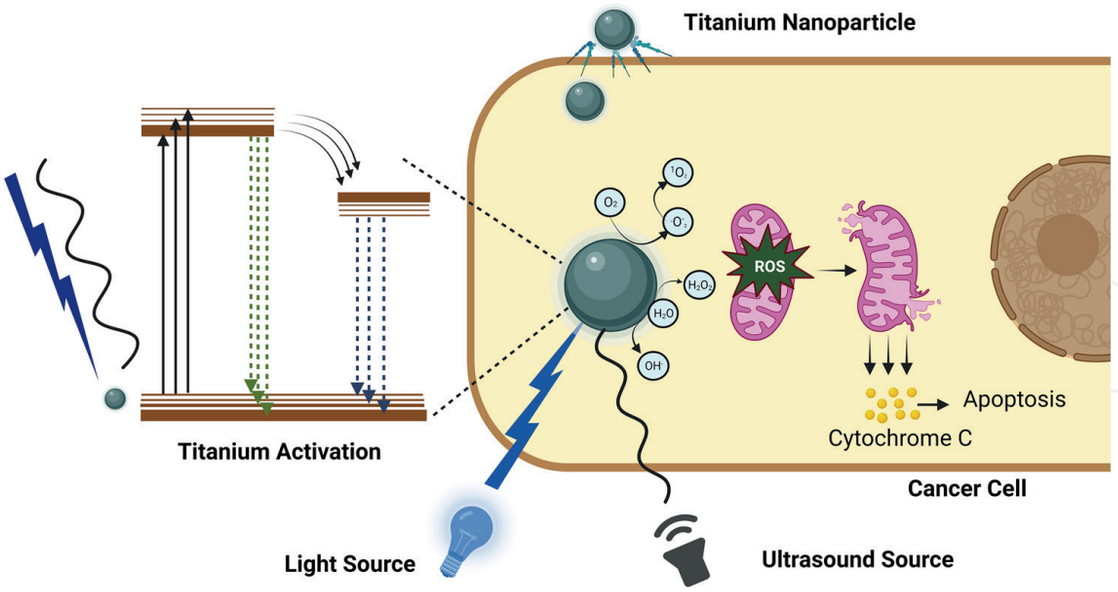

Figure 2.
TiO_2 NPs-based photodynamic or sonodynamic therapy of cancer cells. The ROS generated after photo-sonoactivation results in mitochondria damage leading to cytochrome c release to induce apoptosis in cancer cells (developed by using BioRender).

Metal oxide nanoparticles have been widely studied as photosensitizing agents in PDT due to the drawbacks associated with porphyrin-based photosensitizing agents. TiO_2 NPs gained immense interest due to their distinct characteristics, enabling them to effectively kill tumor cells upon optical irradiation. Irradiation of TiO_2 NPs, with an energy greater than or equal to the bandgap, causes the redox reaction on the surface of these NPs, which leads to the generation of reactive oxygen species, including superoxide anions, hydrogen peroxide, and hydroxyl radicals [36, 37]. TiO_2 is more stable than other conventional photosensitizers because they are nanosized particle with anti-photodegradable stability. TiO_2 NPs have been used as photosensitizers in several types of tumor cell lines, which include HepG2 (hepatocellular carcinoma cells) [38], HeLa (cervical cancer cells) [39], MDA-MB-468 and MCF7 (breast cancer cells) [40], leukemia cells (K592) [41], and lung cancer cells (NSCLC) [42].

TiO_2 NPs are considered marvelous photosensitizers; however, their possible toxicity impedes their applicability in PDT [8, 43]. TiO_2 can be excited in its pristine form by short-wavelength ultraviolet irradiation. Lagopati et al. conducted a study in which they used TiO_2 as photosensitizers against breast cancer cells (MCF7 and MDA-MB-468). TiO_2 nanostructures were prepared by using the sol-gel technique. The results showed significant effects of the applied modification against MDA-MB-468 cells [44]. Modifying TiO_2 NPs with Quantum Dots (QDs) have received significant attention since they allow TiO_2 to absorb light of much longer wavelengths and, thereby, deeper tissue penetration. In PDT, QDs usually possess dual-function properties and act as energy transducers and carriers for photosensitizers. Ramachandran et al. synthesized TiO_2 NPs by microwave-assisted synthesis and TiO_2 conjugated with N-doped graphene QDs (N-GQDs/TiO_2) by two-pot hydrothermal method. N-GQDs/TiO_2 nanocomposites generated ROS, particularly singlet oxygen, upon activation with the light of the near-infrared region. This induced cell death in MDA-MB-231 cells more significantly than in the HS27 cell line (human foreskin fibroblasts) [45].

5. Drug delivery vehicle

Nano titania holds a higher reputation among various nanodrug delivery materials due to its amenability to a vast array of surface functionalization for targeting tissues, easy forming composites with other metals, porous texture, and highly biocompatible nature [46]. Its excretion also occurs via a standard excretory route, i.e., the hepato-urinary system. Nano titania has been reported to carry not only anticancer drugs but also other types of drugs, such as dexamethasone [47], DNA fragments [48], norfloxacin [49], ciprofloxacin [50], and aspirin [51], etc.

TiO_2 nanowhiskers were employed in cancer therapeutics to deliver Temozolomide (TMZ) to Glioblastoma Multiforme (GBM) orthoptic models. These TiO_2 nanowhiskers traversing the Blood-Brain Barrier (BBB) were accelerated by ultrasonication. Additionally, the ultrasound could also assist in releasing TMZ from TiO_2 and generate ROS to induce apoptosis [52]. Likewise, Kim et al. have also reported ultrasound-driven doxorubicin delivery to cancer cells by TiO2 nanoparticles [53]. Among other anticancer drugs, 5 fluorouracil drug delivery to cancer cells by ZnO-doped TiO_2 was performed by Faria et al. The ZnO doping could shift their absorption from UV (TiO_2 only) to red (TiO_2-ZnO), making it a perfect candidate for photodynamic therapy [54]. Liposome-covered TiO_2 nanotubes have also delivered the 5 fluorouracil to HeLa cells [55]. Doxorubicin's successful loading on TiO_2 nanotubes and efficient delivery to cancer cells is another example of TiO_2 employment as a drug delivery vehicle. The drug release was lower pH dependent [56]. Similarly, paclitaxel delivery via Polyethylene Glycol (PEG) and folic acid surface decorated TiO_2 nanoparticles was reported by Venkatasubbu et al. [57].

Not only in cancer theranostics but TiO_2's role as a vehicle in other diseases, including rheumatoid arthritis, has also been explored. The porphyrin derivative, i.e., Tetra Sulphonatophenyl Porphyrin (TSPP), was loaded on TiO_2 nanowhiskers by an adsorption process assisted by its porous nature [58–60]. The TiO_2 could deliver the TSPP to inflamed tissue and release it upon photoactivation with 532 nm light.

6. Anticancer effects

Cancer remains a critical global threat due to severe complications such as unbearable physical pain, severe cytotoxicity, side effects, and compromised therapeutic efficacy of conventional therapeutic strategies, including surgical interventions, chemo- and radiotherapy [61–73]. Various studies are aimed at investigating the new therapeutic approaches, including Photodynamic Therapy (PTD), Chemodynamic Therapy (CDT), Sonodynamic Therapy (SDT), Photothermal Therapy (PTT), Starvation Therapy (ST), and Immunotherapy (IMT) having lower side effects and high-level efficiency [26, 74–79]. New therapeutic approaches have been effectively applied as a substitute to conventional therapies and merged with imaging techniques for diagnosis, which is quite optimistic for the diagnosis and treatment of cancer [80, 81]. Cancer theranostics, a combination of diagnostics and treatment, has recently gained much interest [82]. Several therapeutic strategies can be integrated with various imaging techniques to synthesize multifunctional tumor-targeted nanoprobes, having a significant therapeutic effect and improving tumor identification [83].

In recent years, a newly established field of nanomedicine has been instigated to offer various solutions. Nanomedicine is the implementation of nanomaterials, possessing particle sizes ranging from 1 to 100 nm, to diagnose, observe, prevent,

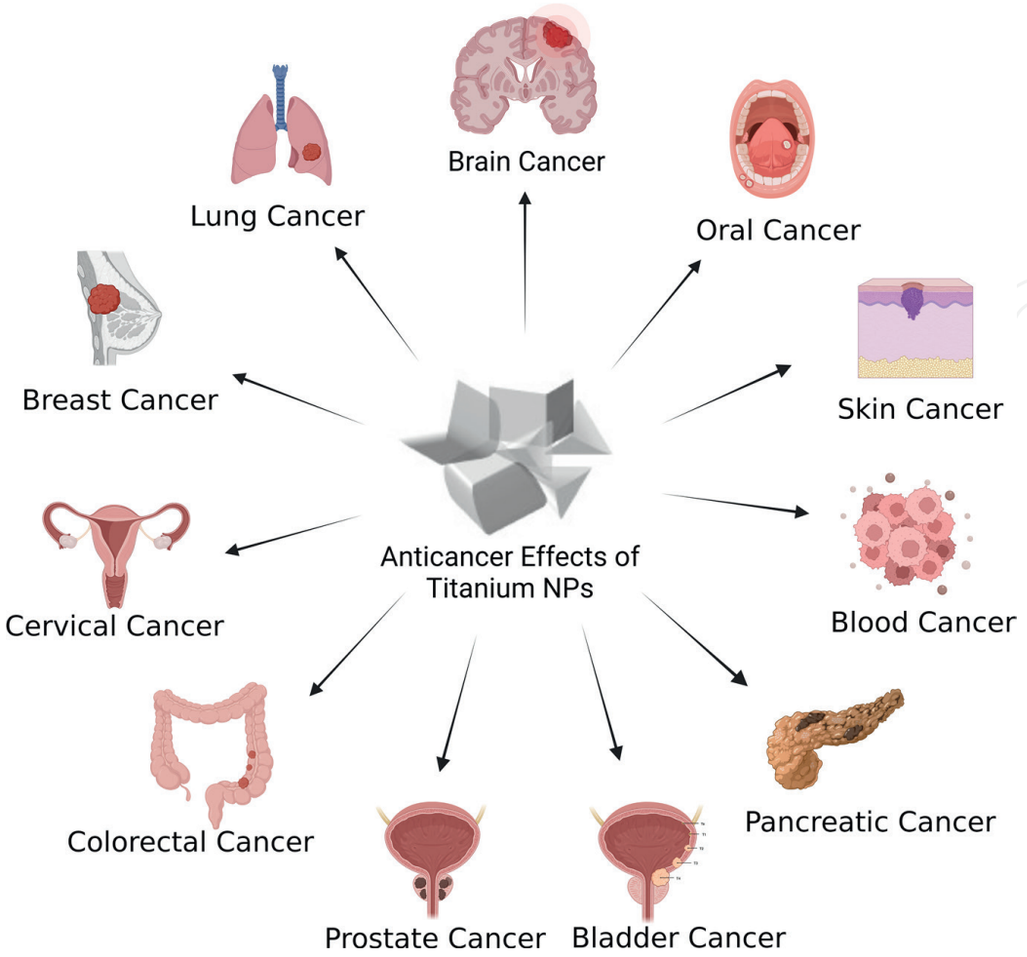

Figure 3.
Different types of cancer that can be treated with nano titania (developed by using BioRender).

and treat disease [84]. Nanoparticles (NPs) have been extensively used as anticancer therapeutic agents, particularly in cargo delivery, i.e., genes, chemotherapeutic drugs, or contrast agents [70, 85–87], or alone, using their inherent toxicity, e.g., associated with the release of reactive oxygen/nitrogen species [88, 89]. Additionally, nanoparticles can be coated with a chemical or biological material to facilitate their stealth characteristics and minimize their tendency to aggregate in biological fluids. Moreover, they can be coupled with selected ligands to enhance their targeted cell delivery [90]. NPs can impulsively accumulate in the tumors because of the Enhanced Permeability and Retention (EPR) effect. They can easily pass through the tumor vasculature due to large pores, and inadequate lymphatic drainage allows their retention, expediting their therapeutic efficacy without being associated with the targeted ligands [91]. Nano titania-based anticancer therapy is well-known (**Figure 3**). Below are various types of cancers treated with nano titania.

6.1 Breast cancer

Breast cancer is the primary cause of mortality in women ranging from 35 to 55 years of age in industrialized countries. The prevalence of breast cancer is relatively high because the breast is among the most vulnerable organ to malignancy (after the liver, lungs, and stomach) [92, 93]. Conventional treatment modalities

include surgery, chemo-, radio- and hormonal therapy, or a combination of these therapeutic options [94–96]. The complete removal of the tumor is challenging due to limited access to the region for surgery, side effects associated with conventional therapy, and the development of drug resistance. Hence, the five-year survival rate is limited to 20% [97]. Recently, pembrolizumab and atezolizumab, immunotherapeutic drugs, have received FDA approval. However, only triple-negative breast cancer patients can use these therapeutic drugs [98]. Therefore, designing a targeted drug delivery technique for anticancer therapy with minimal cytotoxicity in normal tissues is persistently required [99]. In this context, nanoparticles seemed to be a promising approach possessing low cytotoxicity, target specificity, mature drug distribution in the tumor, and fast elimination of the drug from the body [99–102].

TiO_2 nanoparticles are among the prominent nanoparticles with both in vitro and in vivo applications. TiO_2 nanoparticles exhibit distinct morphology and surface chemistry, adequate biocompatibility, employ intrinsic biological activity, reduced side effects, and insignificant eco-toxicity [103]. Previously, it was reported that TiO_2 induces ROS generation by interfering with the EGFR signaling cascade, leading to apoptosis induction in tumor cells compared to nearby physiological cells [104]. However, there is little information about the therapeutic role of TiO_2 in breast cancer compared to conventional therapeutic drugs, i.e., doxorubicin is lacking. Doxorubicin is among the most effective therapeutic drugs in ovarian and breast cancer [105]. However, its clinical application is restricted due to adverse effects, of which cardiotoxicity is the most significant [106]. Iqbal et al. synthesized TiO_2 NPs from leaf extract of Zanthoxylum armatum and evaluated their safety and anticancer activity. They demonstrated that TiO_2 NPs and doxorubicin were equally effective against breast cancer in vivo and ex vivo. TiO_2 NPs exhibited anticancer activity by inducing ROS-dependent cell death in 4 T1 breast cancer cells. In vivo analysis in 4 T1 breast cancer cells containing BALB/c mice revealed that TiO_2 NPs exerted doxorubicin comparable to anticancer activity and without any cardiotoxicity and body weight alteration as compared to doxorubicin [107].

Kim et al. analyzed the possible cytotoxicity in breast cancer cells. They used two cell lines, Hs578T and MDA-MB-231, which overexpress Epidermal Growth Factor Receptor (EGFR). EGFR is a transmembrane protein activated by binding growth factors and transmitting cellular signals inducing cell survival and propagation. They tried to elucidate the effect of alterations in extracellular signaling receptors mediated by TiO_2 nanoparticles rather than focusing on the toxicity induced by TiO_2-mediated ROS generation. They showed that the cytotoxicity caused by TiO_2 nanoparticles in breast tumor cells is due to the interference in the EGFR-regulated signaling pathway, which reduced cell adhesion, survival, and propagation, thus inducing apoptosis [104]. Mahendran et al. used *Gloriosa superba* rhizome extract to synthesize crystalline TiO_2 nanocatalysts. These TiO_2 nanocatalysts caused exorbitant mitochondrial depolarization and DNA damage when treated with MCF-7 cells, primarily due to the persistent release of TiO_2 nanoparticles and the generation of free radicals [19].

6.2 Pancreatic cancer

Pancreatic cancer is the third major contributor of deaths caused by cancers in the United States [108], with a five-year survival rate of about 10% only [109, 110]. Only about 15–20% of cancer patients can avail the surgical treatment due to delayed diagnosis [111], and even after tumor resection, the five-year survival rate remains about 20% only [112–114]. Immune Checkpoint Blockade (ICB) therapeutic approaches have been developed which are based on the applicability of monoclonal

antibodies against PD-L1 (programmed cell death ligand 1) and CTLA-4 (cytotoxic T-lymphocyte antigen 4), able to support tumor eradication and protection from recurrence and metastasis [115–118]. However, these approaches failed to exhibit significant results in patients diagnosed with pancreatic cancer [119–121]. Hence, the combination of ICB and therapeutic approaches, able to enhance T-cell infiltration and activation in the tumor, can be promising for treating and preventing tumor relapse and metastasis [122–124].

Ultrasound exposure represents a non-invasive, inexpensive, and well-portable therapeutic tool [125–127] and is well-studied in the perspective of cancer treatment, in addition to its general utilization in imaging systems [126, 128–130]. Ultrasound-activated sonodynamic therapy (SDT) can cause tumor cell death by inducing high levels of ROS generation, causing apoptotic or necrotic immunogenic cell death [131, 132]. Titanium diselenide ($TiSe_2$) is a 2D transition metal dichalcogenide extensively used in photodynamic therapy due to its good photoresponsivity [133]. Chen et al. synthesized TiSe2 nanosheets and evaluated the combination of $TiSe_2$-mediated sonodynamic therapy with PD-1 blockage for pancreatic cancer treatment in vitro using Pac02 cells and in vivo model of pancreatic cancer. They reported the generation of ROS by $TiSe_2$ nanosheets upon exposure to non-invasive US irradiation and induction of immunogenic death of malignant cells, thereby promoting the maturation of dendritic cells and infiltration of activated T cells within the tumor. Besides inhibiting primary pancreatic tumor growth, this combinatorial therapeutic approach also inhibited the growth of distant tumors and lung metastasis [134].

6.3 Lung cancer

The limited therapeutic efficiency of Non-Small Cell Lung Carcinoma (NSCLC) is due to the resistance to chemotherapeutic drugs. The median survival rate is about 6 months only. Nanoparticles are progressively emerging as a new tool against drug resistance because of their limited toxicity and ability to act on numerous targets in cancer cells due to their distinct physicochemical features [135]. Two-dimensional (2D) titanium carbide (Ti_2C) possesses ultra-high surface area and enhanced cell membrane penetration ability as compared to other conventional nanoparticles [136]. It also contains many reactive groups that can be utilized as potent protein interaction sites affecting their structure and function. The chemo drug resistance reversal ability of Ti_2C was evaluated by Zhu et al. by using the characteristics of 2D Ti_2C on the NSCLC cell line. The cells were treated with cisplatin, the standard drug for treating end-stage NSCLC, with and without Ti_2C. They found that Ti_2C reversed the resistance of NSCLC to cisplatin by reducing the antioxidant reserves in the cells and decreasing the expression of primary drug resistance genes. They also reported drug resistance reversal in the NSCLC model in vivo [135]. Balachandran et al. synthesized TiO_2 nanoparticles using a novel wet chemical technique using titanium tetra isopropoxide precursor, characterized by SEM, TEM, XRD, and UV–visible spectroscopic analysis. The synthesized nanoparticles exhibited good photocatalytic activity and were evaluated for anticancer effect in A549 (lung cancer) cells. The cells were treated with TiO_2 and exposed to UV light. After 4 hours, TiO_2 caused approximately 85% of cell decomposition [137].

6.4 Colorectal cancer

Colorectal Cancer (CRC) is among the most common malignancy in humans. Its prevalence is increasing despite several advances in therapeutic and diagnostic

interventions. CRC is caused due to gradual transformation of epithelial cells found in the intestinal lumen to tumor cells. Cancer treatment aims to utilize an anticancer agent that can induce apoptosis. These days, nanoparticles (NPs) are considered novel anticancer agents. Nanosized titanium dioxide nanoparticles (TiO_2 NPs) with about <100 nm diameter possessing whiteness and opacity are publicly accepted. The biological properties of TiO_2 NPs depend on their size, physicochemical properties, and surface area since particles with a large surface area are more chemically reactive [138]. Wei et al. reported the green synthesis of TiO_2 from the extract of *Calendula officinalis* and evaluated its effects on colorectal carcinoma cell lines WiDr, LS123, DLD-1, and SW1417 [SW-1417]. TiO_2 reduced the viability of all colorectal carcinoma cells in a dose-dependent manner [139]. Vigneshwaran et al. synthesized TiO_2 nanoparticles from Lactobacillus and evaluated its cytotoxic effects on the HT-29 cell line. They reported ROS generation in HT-29 cells by the treatment with TiO_2 NPs and the induction of apoptosis by intrinsic pathway [140].

6.5 Cervical cancer

Cervical cancer is the malignancy of the uterine cervix. It is ranked fourth in commonly occurring cancer in women globally and second in the low and medium Human Development Index (HDI) [141]. The key risk factors include late menopause, increasing age, obesity, elevated estrogen levels, breast cancer, no childbirth, diabetes mellitus, and tamoxifen use. Some gene mutations can also cause cervical cancer [142]. The treatment strategies for cervical cancer include radiotherapy, immunotherapy, and chemotherapy [143]. Due to the severe adverse effects of chemotherapeutic drugs, research interest has been transferred to metallic nanoparticles [144–146].

Titanium nanoparticles can be used with other nanoparticles, such as zinc and silver, to evaluate their anticancer effects on cervical cancer cell lines [147]. Ag/AgBr/TiO_2 nanoparticles effectively eliminated xenograft tumors due to their photocatalytic activity [148]. Thermodynamic therapeutic potential, bioimaging, and doxorubicin delivery to cervical cancer cells by hybridized TiO_2 and zinc phthalocyanine nanoparticles were also studied [149]. Yurt et al. synthesized zinc phthalocyanine and hybridized it with TiO_2 to evaluate their photodynamic therapeutic effect and nuclear imaging potential. Intracellular localization of ZnPc and ZnPc/TiO_2 in cervical adenocarcinoma (HeLa) and breast cancer cells was observed. High uptake of ZnPc/ZnPc-TiO_2 by the cervical and breast cancer cells suggested their use as cancer theranostic agents [150]. TiO_2 has also been reported to enhance caspase-3 activity and prevent the growth of HeLa cells [151].

6.6 Brain cancer

The brain is probably the most mature organ of the human body, so its protection is a crucial issue [152]. Despite several advancements in developing therapeutic and diagnostic procedures, brain cancer is a great challenge to treat, and a successful therapeutic strategy still cannot be established. The major hurdles to establishing a successful treatment strategy for brain tumors include tumor recurrence, acquired resistance to chemotherapeutic agents, and complex central nervous system structure [153]. Glioblastoma is the most common and dangerous tumor in adults. Despite the availability of various treatments, such as chemotherapy, radiotherapy, and surgical resection, the prognosis is still inferior. Following the diagnosis, the life expectancy of glioblastoma patients is just 12–15 months, and the five-year survival rate is approximately 5% [154].

The blood-brain barrier (BBB) is a highly selective interface responsible for maintaining homeostasis, protecting from harmful agents, and providing all necessary molecules to the brain [155]. Brain disorders and tumors require the drug to cross the BBB to exert its therapeutic effect. Several lipophilic therapeutic agents can pass through the BBB, but due to its selective permeability, several other medications fail to cross it [156, 157]. Various pharmacological agents are considered potentially harmful external agents by the BBB. Thus they are removed by the efflux system, degraded by the enzymes, or hindered from crossing the BBB [158]. Only molecules smaller than 400 Daltons or less than nine hydrogen bonds are BBB permeable. Therefore, several nanomedicine-based approaches have been suggested to facilitate drug delivery across the BBB in the recent past [159, 160].

Nanoparticles have gained much interest in this regard [161–163]. It has been reported that engineered nanomaterials can cause neurotoxicity [164]. TiO_2-NPs can induce neurotoxicity due to their ability to cross BBB [165–167]. They are potential candidates for treating glioblastoma multiforme (GBM) and other tumor types. Gene and protein expression analysis revealed the reduction of antitumor drug resistance and metastasis by inhibiting angiogenesis. These characteristics would make TiO_2 promising therapeutic agents against cancer, particularly if other chemotherapeutic agents can be combined. Fuster et al. evaluated the anticancer effects of TiO_2 NPs and ZnO-NP on the T98G glioblastoma cell line and reported that TiO_2 is a more effective anticancer agent than ZnO. They demonstrated that TiO_2 exposure disrupted the BBB and induced neuroinflammation and suggested the necessity of risk assessment regarding the TiO_2 toxicity in the central nervous system [168]. Using ultrasound-sensitive piezoelectric nanoparticles, Marino et al. delivered electric stimulations to distant glioblastoma cells. Barium titanate NPs were functionalized with antibodies against transferrin receptors to target BBB and glioblastoma cells. The distant ultrasound-mediated piezo-stimulation caused a significant reduction in the proliferation of glioblastoma cells in vitro and greatly enhanced the chemotherapeutic sensitivity when combined with temozolomide [169].

6.7 Prostate cancer

Cancer is the major cause of global mortality after cardiopulmonary arrest [170]. Prostate cancer is the fifth most common cancer worldwide and ranked second in men among common cancer types [171]. The onset of cancer can be characterized by delayed progression, tumor markers, detectable preneoplastic abrasion, and high prevalence [172]. Surgery is a successful option in some cases. However, after a few years, tumor recurrence can shorten chemotherapy as a valuable therapeutic option for prostate cancer. However, associated side effects such as toxicity, fatigue, difficulty breathing, low white blood cell count, and blood clotting hamper their efficacy for tumor eradication [173]. Recently, targeted drug delivery and stimulus-responsive release have minimized toxicity and improved drug delivery and accumulation at the target site [174, 175].

Different inorganic nanoparticles such as TiO_2, graphene oxide, iron oxide, and porous silica have been used for drug delivery and anticancer therapeutic agents [173]. TiO_2 NPs are considered potent drug carriers and photosensitizers due to their low cost, toxicity, and non-photobleaching characteristics [176, 177]. ROS generation by ultrasound-activated TiO_2 NPs has been reported by various studies [29, 178, 179]. However, in comparison to light, ultrasound scattering in the tissue is weaker, making it penetrate deeply without losing energy [33]. Previous studies revealed that

combining TiO_2 with rare earth or noble metals can increase ROS quantum yield [29, 180]. Ayca et al. synthesized TiO_2 and ZnO NPs. They showed the potent inhibition of the growth of prostate cancer cells (DU-145) by TiO_2 and ZnO_2 nanocomposites [173]. Ultrasound-activated multifunctional system based on TiO_2:Gd@DOX/FA for MRI-guided therapy for prostate cancer was developed by Yuan et al. [181]. This system acts as a sonosensitizer for sonodynamic therapy and drug nanocarriers for pH-responsive drug release. Gd doping to TiO_2 improved their sonodynamic ability and their performance in MRI. In vitro and in vivo anticancer treatment proved the efficacy of TiO_2:Gd/DOX/FA in inhibiting cancer by ultrasound-responsive chemo-sonodynamic therapy without damaging other organs and as MRI agents. Aksel et al. showed the formation of apoptotic bodies in the PC3 prostate cancer cell line by TiO_2 NPs-mediated photo-sonodynamic therapy [30].

6.8 Bladder cancer

Urothelial bladder cancer is among the most widespread malignancies [182]. It is categorized into two subgroups, i.e., Muscle-Invasive Bladder Cancer (MIBC) and Non-Muscle-Invasive Bladder Cancer (NMIBC). Most bladder cancers are NMIBC at diagnosis. Frequent tumor relapse is found in about 50–70% of NMBIC [183], and 10–15% tend to progress into MIBC [3, 184]. Chemotherapy or Bacillus Calmette-Guérin (BCG) and post-transurethral resection are the therapeutic interventions used [185]. Other therapeutic options are under investigation, including photodynamic therapy, radiotherapy, immunotherapy, gene therapy, and nanodrug delivery system using nanoparticles [186]. Among many therapeutic options, a photodynamic theory is less invasive than any surgical intervention [187]. Under physiological conditions, TiO_2 NPs possess promising photodynamic characteristics and are suitable materials for cancer treatment. Studies reported the development of $Ti(OH)_4$ in which peroxide was coated on TiO_2 nanoparticles [188, 189]. $Ti(OH)_4$ could absorb visible light and showed equivalent photocatalytic activity upon exposure to UV radiations with 90% greater photocatalytic efficiency than TiO_2 NPs. Moreover, $Ti(OH)_4$ can generate hydroxyl radicals when it comes in contact with water, even after numerous photodegradation cycles [188]. In another study, a bladder cancer cell line, MB49, was treated with various concentrations of $Ti(OH)_4$, and the results demonstrated that photo exposure of $Ti(OH)_4$ stimulated ROS generation and induced dose-dependent necrosis in cancer cells [190]. Black TiO_2 NPs were used as photosensitizers triggered by near-infrared light with maximum 808 nm absorbance by T24 cells (bladder cancer cells). The cells were incubated with TiO_2 NPs and irradiated at 808 nm. The results showed concentration-dependent enhanced antitumor activity by the black TiO_2 NPs. Hence, black TiO_2 was proven a potent anticancer agent, promising photosensitizer, and maximally active at near-infrared and visible light [191].

6.9 Skin cancer

Skin cancer is the most common human malignancy due to the uncontrolled growth of tumor cells associated with the dermis and epidermis. Patients need recurrent treatment due to the aggravated and repetitive growth of tumor cells and, therefore, suffer from treatment-associated side effects and toxicity. Though the topical chemotherapeutic option is associated with less severe side effects, it is impeded due to the rapid liquifying characteristic of the polymers used in the therapy and tormenting-sized microneedles [192, 193].

Melanoma is a type of skin cancer that appears in melanocytes (skin cells) [194]. Melanocytes are the producers of melanin, which gives color to the skin [4, 195]. Ultraviolet radiations are the leading cause of melanoma, adversely affecting DNA repair, skin cell growth [196], immunosurveillance, and apoptosis. These adverse reactions allow the activation of oncogene or deactivation of tumor suppressor genes and subsequent tumor development [197]. Clinically, nanoparticles are shown to have the ability of tumor reduction and lessen the side effects [198–200]. Conventional anticancer therapies, including chemotherapy, radiotherapy, and surgery, are associated with the risk of harming adjacent healthy cells. This problem can be overcome using chemotherapeutic agents conjugated nanoparticles that can precisely target tumor cells [201, 202]. TiO_2 NPs possess unique characteristics and have been applied in various fields [203]. They also have immunomodulatory effects [204].

Titanium dioxide nanotubes (TNT) offer a larger surface for carrying molecules and have distinct physicochemical properties. They are potent anticancer agents. They have been conjugated with quercetin to evaluate their effect against melanoma. Quercetin is a flavonoid found in fruits and leafy vegetables and possesses antioxidant, antiviral, and anticancer effects. The in vitro anticancer effect of quercetin-conjugated TNT (TNT-Qu) was evaluated on melanoma cells (B16F10). The results showed inhibitory effects of TNT-Qu on the migration of B16F10 cells, enhanced DNA fragmentation, and cell cycle arrest in the cells. Moreover, TNT-Qu was more cytotoxic to the B16F10 cells than quercetin or TNT alone [205]. The anticancer effect of TNT-Qu was also evaluated on the B16F10 mouse melanoma model and two-stage chemical carcinogenesis in vivo model. The study's results demonstrated enhanced antitumor effects of TNT-Qu than either of the two alone by the topical application of TNT-Qu. TNT-Qu treatment inhibited tumor growth and increased the survival time of the two-stage chemical carcinogenesis mice models [206]. TiO_2 exhibits full-size dependent immunomodulatory effects in the nanorod form [207]. TiO_2 NPs were hydrothermally converted to nanorods that greatly enhanced the loading efficiency of resveratrol, which would be a great anticancer agent for skin cancer [208]. Polyvinyl Alcohol (PVA) is biocompatible, hydrophilic, and biodegradable [209]. PVA nanofibers are a dressing material for wound healing [210, 211]. Conjugating a polymeric form of PVA with a pharmaceutical agent improves EPR and facilitates the slow and sustained release of the incorporated drugs [212]. Ekambaram et al. reported the anticancer effect of the green synthesized TiO_2 nanorods loaded with resveratrol-incorporated nanofibers against skin cancer cells (A431). They found inhibition in cancer cell growth by activating caspase enzymes [213].

6.10 Hematological malignancies

Hematological malignancies originate from the bone marrow or blood and result from the acquisition of genetic abnormalities that lead to unrestrained proliferation, resistance to cell death, and evasion of the immune system [214]. The occurrences of hematological malignancies, including leukemia, multiple myeloma, lymphoma, myelodysplastic syndromes, and myeloproliferative neoplasm, continuously increase despite recent advances which increased the five-year rate in many types of hematological malignancies [215]. Photodynamic therapy (PDT) has advantages over conventional anticancer therapy, including no risk of drug resistance and controllable ROS generation by controlled dosimetry [216–218]. TiO_2 NPs have been used in many cancer types [40, 42, 219–221], but the biggest hurdle is the high energy band gap of TiO_2 (anatase, 3.2 EV) which needs the excitation by detrimental UV

radiations. Doping of TiO_2 with metal/non-metals resolves this issue by making TiO_2 able to activate by absorbing light of longer wavelengths [222–224]. N-TiO_2 exhibits anticancer activity and higher capability of ROS production in comparison to TiO_2 NPs [39, 225, 226]. N-TiO_2 was used as a photosensitizer in PDT for leukemia cells. Upon activation with visible light, N-TiO_2 photosensitizers induced ROS-mediated autophagy in leukemia cells (K562), which increased with the increasing doses of light and photosensitizer. In addition, low doses of PDT also showed enhanced ROS and autophagy in normal peripheral lymphocytes. However, the typical human cell model showed no cytotoxic or inhibitory effects [41].

Acute lymphoblastic leukemia occurs due to the abnormal growth of white blood cells in the bone marrow [227, 228]. It is the most common cancer in children 2–5 years of age [229]. The treatment advancements show 90% effectiveness in curing the disease, but relapse and drug resistance remain the most significant clinical challenge [230]. Recently, using nanostructured devices and nanomaterials to deliver medications against cancer is the most advanced method for treating cancer [231]. Metal nanocomposites are being investigated for theranostics, and various functional groups are being incorporated to modify metal/metal oxide nanocomposites [232]. Recently, ZnO-TiO_2-chitosan-amygdalin nanoparticles have gained much interest as potent anticancer agents. MOLT-4 (T-lymphoblast malignant cells) were treated with nanocomposite (ZnO-TiO_2-chitosan-amygdalin) to evaluate its cytotoxic effect on these cells. The results showed increased cytotoxicity, mitochondrial membrane depolarization, caspase activation, and ROS generation in leukemia cells [233].

6.11 Oral cancer

Oral Squamous Cell Carcinoma (OSCC) is characterized by local hypoxia and tumoral necrosis spreading on a large area, which is the cause of drug resistance and low chemotherapeutic response [234]. Immune suppression is also a factor that limits the therapeutic response and poor prognosis [235]. The primary therapy is surgical resection for OSCC, while radiotherapy and chemotherapy are additional treatment options [236]. However, with all the present treatment options, the five-year survival rate is still 60%, which severely damages the life quality [237]. Photodynamic theory utilizing nanoparticles as photosensitizers has gained much attention for OSCC cure and prevention [238, 239]. TiO_2 NPs have widely investigated nanoparticles as photosensitizers in photodynamic therapy since their photocatalytic activity was discovered in 1972 [240–242]. Metal polypoidal complexes have attracted scientists as photosensitizers. Ru(II) complex TLD-1433 photosensitizers have been used in clinical trials for bladder cancer (non-muscle invasive bladder cancer) in Canada [243, 244]. TLD-1433 can potentially cause DNA damage under hypoxic conditions [243, 245]. Based on this phenomenon, TiO_2@Ru@siRNA nanocomposite comprised SiRNA-loaded TiO_2 NPs modified with ruthenium-based photosensitizers. This nanocomposite shows photodynamic effects upon irradiation with visible light. It can cause lysosomal damage, HIF-1α gene silencing, production of type I and type II ROS, and eradication of OSCC cells efficiently. In addition, it also reduces the expression of immunosuppressive factors and elevates the antitumor immune response. The PDX and oral rat carcinoma model significantly improved antitumor immunity and inhibited tumor progression and growth [246]. Pure TiO_2 and TiO_2 nanoparticles modified with ginger, garlic, and turmeric were used for anticancer activity against KB oral cell line by Maheshwari et al. They found that modified TiO_2 showed better anticancer activity against oral cancer cells than pure TiO_2 [247].

7. Conclusion

In summary, the nano titania application in cancer therapy and diagnosis is highly favorable due to its biocompatible and porous nature, surface modification, and ROS generation properties. The TiO_2 surface can be coated with polymeric and metallic nanostructures to enhance drug loading ability and target desired tissue viz. tumor. Due to their inert nature, nano titania is commonly implemented as food additives and cosmetic products. However, UV light application limits its photoactivation, which is inconsistent with WHO recommended therapeutic window (600–1000 nm). Indeed, their surface coating or nanocomposite formation can shift its absorption from UV to NIR range, which holds promising effects in anticancer therapy and diagnosis via bioimaging. Their photodynamic or photothermal therapy effect suits topical and body cavity cancer resection. Employing titanium nanoparticles as drug carriers for anticancer therapy might help improve therapeutic effects and avoid undesirable side effects. Combining titanium NPs with other nanoparticles also holds great therapeutic potential in cancer. The applications of nano titania and their conjugates discussed in this chapter can be utilized to improve cancer theranostics.

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Conflict of interest

The authors declare no conflict of interest.

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