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Green-Synthesized Titanium Dioxide Nanoparticles: Advances in Biomedical Applications, Mechanistic Insights, and Safety Considerations

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Abstract:

Metal oxide nanoparticles (NPs) have experienced flourishing development in diverse fields, such as industry, medicine and environmental science, as a result of the development of nanotechnology. In this realm, titanium dioxide nanoparticles (TiO_2 NPs) are favored due to their broad applications and potential in nanomedicine. Very recently, more attention has been given to green, or biological, synthesis of these nanoparticles, due to the significant advantages that they present, such as reduced toxicity, less dependence on toxic chemical in the synthetic process, eco-friendliness, and lower cost as well as shape and size control, when compared with traditional synthetic methods.

Traditional physical or chemical methods, however, suffer from high energy consumption and pollution of hazardous chemicals. Conversely, bio-mediated synthesis can offer a much safer and sustainable alternative for the production of TiO_2 NPs. This review details the bio-based synthesis of TiO_2 NPs and their diverse biomedical applications-raging from the antibacterial and antifungal properties to anticancer and antiviral therapies-and discusses the impact of such developments on the future of health care and environmental technologies.

Keywords: Titanium Dioxide Nanoparticles, Green Synthesis, Biomedical Applications, Photocatalysis and Drug Delivery, Antimicrobial and Anticancer Activity, Nanotoxicology

1. Introduction:

Nanotechnology is a rapidly growing area of science and engineering that is primarily centered on manipulating matter on a nanometer scale, which is typically 1 to 100 nanometers. This size regime termed as nanoparticles (NPs) is markedly different from the bulk form of the same material in physical and chemical properties. These new properties are the result of the high surface area to volume ratio which affects their reactivity and modifies their optical, electrical, thermal and catalytic properties. Thus nanoparticles have application in a wide range of areas, such as energy, medicine, environmental remediation and electronics [1–3].

Among different kinds of nanomaterials, nanoparticles based on transition metal have attracted significant attention. This multifaceted oxidation states is possible due to their specific electron configurations, in

particular, sparely filled d-orbitals. This tunability leads to adjustable characteristics that are applicable in the fields of chemistry, physics, and materials science. In addition to this, these are able to yield different metal oxides, which are versatile in the realm of research activities such as agriculture, cosmetics, fuel cells, sensors, catalysis, and energy storage devices [4–7].

Among metal oxides, titanium dioxide nanoparticles (TiO_2 NPs) have attracted the greatest attention because of their lower cost and high oxidative ability, high index of refraction, and structural stability. Indeed, already in the year 2011, an annual world-wide production of more than 10,000 t of TiO_2 NPs was achieved [8]. They have a wide gap, and in their crystal the oxygen vacancies are present, which makes them valuable in many industries: from semiconductors/ electronics to wastewater treatment / biomedical engineering [2, 9 -11].

The inherent features of TiO_2 NPs (white color, water insolubility, high refractive index (approximately 2.4) also render them appropriate for applications in the field of paint, sunscreen, and food additives. They exist in three crystalline phases: rutile, anatase, and brookite, each of which have industrial and scientific importance [12].

Owing to their widespread application scope, it is important to modulate the size, morphology, and crystalline nature of TiO 2 nanoparticles during the synthesis. Common chemical or physical methods work with high efficiency, but they usually accompanied by the use of poisonous reagents, the consumption of abundant energy and the complexity of the process, etc. On the contrary, green synthesis is considered as an eco-friendly, safe, and sustainable option. Herein, this review focuses on environmentally suitable, biologically driven strategies assuring the synthesis of NPs of TiO_2 and their diverse biomedical applications, warfare against Bacteria, Viruses, Fungi & Cancer [2, 13].

2. Preparation of TiO_2 Nanoparticles

2.1 Background

Metal oxide nanoparticles are usually engineered by two general strategies; top-down and bottom-up processes. A top-down approach is used with larger bulk materials toward into smaller nanosized particles through milling, sputtering, evaporation-condensation or pulsed laser ablation. These have proven effective, though the result is in need of advanced equipment and considerable energy [13, 14].

The alternative way is what is called the bottom-up, in which nanoparticles are built from one atom, one molecule to the next one. This include chemical vapor deposition, sol–gel process, hydrothermal and sonochemical methods, flame spray, spinning, and green synthesis. Among these, green synthesis has drawn great attention because of its eco-friendly characteristic and scalability [14–16].

Chemical means of preparation can lead to well-defined nanoparticles, but are frequently expensive in chemicals, time and temperature, and/or environmentally and toxicologically hazardous in the use of toxic solvents. Such limitations have inclined researchers towards biological synthesis, which is a more environmentally friendly, non-toxic, and economically feasible approach, consuming less energy and less severe conditions for the production of nanoparticles [17, 18].

2.2 Biological Synthesis of TiO_2 NPs

Making titanium dioxide nanoparticles (TiO_2 NPs) using bioinspired or green strategies is an environmentally friendly and sustainable strategy compared to synthetic chemical processes. The synthesis method considerably influences the properties and applications of TiO_2 NPs. Among the different methods, green synthesis also known as biological synthesis is gaining importance as it is less toxic, low energy and free from toxic chemicals. This method can be generally categorized into sense and antisense in terms of mode of action and used biological system. For example, photosynthesis-mediated pathways frequently employ plant extracts as natural reducing and stabilizing agents.

Furthermore, microorganism-mediated biosynthesis, more particularly using bacteria, fungi, actinomycetes, algae, etc., has emerged as a potential and feasible approach to large-scale nanoparticle production [19].

This biological process is not only cost effective and occurs at ambient temperatures, but also that it is operable on a large scale. Successful green synthesis normally requires the presence of the following three key elements for the reduction of a metal precursor into a nano-particle: (a) a non-toxic, environmentally-benign solvent, (b) a biological reducing agent for the reduction of the metal precursor, and (c) a capping agent to aid in the size, shape, and stability of the nanoparticles produced [9,20].

2.2.1 Synthesis via Plant

During the last few decades, in order to carry out simple, safe and eco-friendly, and cost effective synthesis of metal nanoparticles, several methods have been adopted, including plant assistance [57-68].

Plant mediated synthesis, is more noticeable of the green routes. It is less contaminant than microbiological approaches and simpler, cheaper and potentially producing higher amounts of nanoparticles. Plant organs, for example, leaves, flowers, seeds, roots can be used as the plant materials for the biofabrication of NPs since they contain phytochemicals that can act as reducing and stabilizing agents in the synthesis [21,22].

Usually the extracted plant part is first washed properly and then boiled in a solvent such as water or ethanol in order to extract the active biomolecules. Subsequently, the extract is combined (with stirring) with a titanium precursor, e.g., titanium tetrachloride ($TiCl_4$), titanyl hydroxide or titanium tetraisopropoxide (TTIP), to obtain TiO_2 nanoparticles [2,6,9,21–23].

Leaves are particularly attractive as they offer a diversity of metabolites and are convenient to process without generation of toxic intermediates. The majority of methods are simple, inexpensive and green, which are feasible for industrial application with environmental concerns. Several works have reported successful synthesis of TiO_2 -NPs using different plants. These plants also include Psidium guajava, Azadirachta indica, Catharanthus roseus, Syzygium cumini, Moringa oleifera, and Cinnamomum tamala, which all produce nanoparticle with different shapes, sizes, and crystal structures based on the choice of precursor and extract used [24–38].

2.2.2 Synthesis via Fungi/Bacteria

Fungi have become one of the most efficient biological agents for nanoparticle production. As compared to bacteria, fungi are a useful source for obtaining high yield, easy extractions, upscaling and eco-friendliness because of their larger surface area and the metabolites they secrete that have the capability of reducing metal salts to nanoparticles [39]. For instance, Aspergillus flavus has been utilized for the synthesis of TiO_2 NPs because of its biodegradability as well as metabolic activities, Saccharomyces cerevisiae is also an eco-friendly fungal system with simple downstream processing [40,41].

This synthesis using microorganisms occurs either intracellularly or extracellularly. However, the mere intracellular synthesises involves the rupture of the cells in order to collect the nanoparticles which indeed make the processes time-consuming. In addition, extracellular methods are desirable due to the simplicity and rapidity of the process, because the nanoparticles are generated outside the microorganism and therefore do not require highly effective purification [21].

Several researches have demonstrated the efficient biogenic synthesis of TiO_2 NPs by different strains of microorganisms. Some of them are bacterial species such as Bacillus subtilis , Lactobacillus and Planomicrobium and fungal species such as Aspergillus niger, Fusarium oxysporum and Aspergillus fumigatus. The final nanoparticles bear different shapes—from spherical to quasi-spherical—and sizes, generally 10-100 nm, which are related mostly to the bacterial strain used [42–51].

With the significant advances of nanotechnology, titanium dioxide nanoparticles (TiO_2 NPs) have gained much attention in medical science. These nanomaterials can travel through cell membranes and target biomolecules in side once inside of the cells, due to their small sizes, high specific surface areas, and their special reactivity, they are the ideal candidates in drug delivery, diagnostics of the diseases, and therapy [52]. As a consequence of their photochemical and mechanical stability, TiO_2 NPs are also commonly employed in sunscreens, solar cells, dental implants or vascular stents [53–55].

3. APPLICATIONS OF TiO_2 NPs

3.1 Antibacterial and Bacteriostatic

Other metal containing NPs such as TiO_2 NPs also showed promising antibacterial activity [33]. They show great efficacy as a result of high oxidative potential, which allows them to attack a wide variety of microbes, including bacteria, fungi, viruses, and protozoa [56].

TiO 2 -NPs produce ROS, particularly hydroxyl radicals and superoxide anions, upon contact with bacterial cells. They oxidize phospholipids of microbial membranes thereby weakening the integrity of their structure to disturb the ion balance and major enzymatic activities in the cell. Once the ROS are inside cells, they are able to damage DNA and proteins, leading to impaired gene expression and cell function [57].

Interestingly, biologically prepared TiO_2 NPs have higher antibacterial efficacy than that for chemically synthesized TiO_2 NPs. Their performance may be influenced by various parameters such as size, shape, surface charge, and the targeted bacteria. In general Gram-positive bacteria are more susceptible than Gram-negative bacteria to these nanoparticles due to the difference in cell wall structure [58]. Furthermore, UV radiation can enhance their antibacterial effects [59].

Several reports have indicated that plant-mediated TiO_2 NPs are also potent antileishmanial agents. For example, TiO_2 NPs obtained from Euphorbia prostrata leaf extract not only decreased parasite survival but also caused DNA fragmentation in Leishmania cultures [60,61]. Notably, some of these NPs have shown even better results than common antibiotics in a few antimicrobial assays [62].

3.2 Toxicity of TiO_2 NPs

For the assessment of TiO_2-NP safety, cytotoxicity tests, such as the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) test, are commonly used. This c... /c activity proportionate to the number of living cells and to mitochondrial activity. MG63 osteoblast-like cells treated with different concentrations of TiO_2 NPs for 24–48 h showed similar results—ie., no cytotoxicity or cell growth inhibition. Indeed, the cells were viable, indeed reflecting the biocompatibility of these nanoparticles [63].

The apparent safety was ascribed to the phase transition of TiO_2 from anatase to the rutile phase during sintering, a change that preserved the material's structure without creating fiber-type morphologies that are commonly more injurious (as found for example with carbon nanotubes and fullerenes) [64].

One research claimed that a green synthesized TiO_2 NP on lung cancer cells induced significant anticancer activity, probably because of superoxide radicals generation. Surface functionalization of TiO_2 NPs with Withania somnifera and Eclipta prostrata markedly potentiated this cytotoxicity, strengthening their anti-cancer activity [65].

3.3 The Antiviral Effect of TiO_2 NPs

Apart of their anti-bacterial properties, TiO_2 NPs show outstanding antiviral activities. These nanoparticles can disrupt not only viral replication rate and infectivity, but also infectivity rate and virus binding to host cells, such as by capsids degradation. For example, TiO_2 NPs can effectively neutralize Newcastle Disease Virus (NDV) and exhibit strong inactivation even at low concentrations (6.25–100 µg/mL) [66].

These particles interfere with enveloped viruses' lipid envelope and glycoprotein function to inhibit viral penetration of the host cell. More recently, TiO_2 performed suppressive effects against broad bean stain virus (BBSV) in faba bean with less disease severity and promotion of the plant's PR1 gene defense with induction to salicylic acid signaling [67].

In human viruses, TiO_2 NPs have been investigated for their antiviral activity against influenza viruses (H3N2, H5N1, H1N1) and MS2 bacteriophage. The mechanism of action usually involve the interaction with viral capsids, which leads to oxidative degradation and loss of infectivity. These results indicate that TiO_2 NPs may have a potential for the development of future-based antiviral materials [68–72].

3.4 Anticancer Properties of TiO_2 NPs

Titania nanoparticles (TiO_2 NPs) are very promising for cancer therapy, mainly because they are able to produce reactive oxygen species (ROS), by UV light irradiation. These ROS have the potential to kill cancer cells by creating oxidant stress to kill the cells, which is the main theory behind PDT (Photodynamic Therapy) [53].

In the recent studies, TiO_2 NPs particularly, when functionalized or combined with antineoplastic agents, showed better anticancer activity. For instance, DOX was delivered to hepatocellular carcinoma (SMMC-7721) cells by TiO_2 NPs. DOX-loaded TiO_2 NPs enhanced cellular uptake and cytotoxicity through MTT assays. An increase in the Bax/Bcl-2 protein ratio, markers of apoptosis, was also witnessed, which suggested that the drug-loaded nanoparticles effectively induced cancer cell death via caspase-dependent mechanism [73].

These findings have been confirmed by other studies. For example, the cellular accumulation of drug-resistant breast cancer cells suffered with nanocomposite form of doxorubicin clearly exceeded that due to normal cellular efflux mechanisms[74]. Consistently, cisplatin loaded TiO_2 NPs functionalized with hyaluronic acid (HA) effectively delivered the drug to ovarian carcinoma cells (A2780) due to the specific interaction of HA with CD44 receptors on cancer cells [75].

In one similarly important study, TiO_2 NPs were produced and screened for effects on MCF-7 breast cancer cells. The NPs exhibited dose-dependent cytotoxicity (IC50 value 60 µg/mL). Typical apoptotic signs, such nuclear fragmentation and chromatin condensation, were observed in AO/EtBr and DAPI staining. Western blotting validated the mitochondrial pathways, and a release of cytochrome c was observed, which is a characteristic of the intrinsic apoptosis [76,77].

Modification of surfaces can also make TiO_2 NPs more effective against cancer. For example, When TiO_2 NPs were loaded with paclitaxel (PAC), polyethylene glycol (PEG) and folie acid (FA) as a modification medicine were used to modify TiO_2 NPs. This surface-modified drug delivery system exhibited markedly enhanced anticancer activity compared to free PAC when tested in an hepatocellular carcinoma animal model. The folate modification enabled the nanocarriers to be selectively accumulated more in cancer cells overexpressing folate receptors, which is beneficial for drug delivery with less side effects [78].

In addition, other effects of FA-modified TiO_2 NPs on osteosarcoma (MG63) cells have been observed. These engineered NPs also decreased the IC50 value 2 times and induced early and late apoptosis in 38% of treated cells—significantly more than the 16% of unmodified TiO_2 NPs. Mechanistic studies revealed that the generation of ROS was a major factor in causing cell death, which in turn led to the activation of the p53 pathway, mitochondrial membrane destruction, and release of cytochrome c as well as activation of the caspase-3 and PARP proteins [79].

In addition to these, anticancer effects of TiO-NPs have been demonstrated in several other types of cancer such as prostate (DU145) [80], liver (HepG2) [81], and colorectal (HCT116) cancers [82,83].

3.5 Antifungal Activity of TiO_2 NPs

To assay the performance of the TiO_2 NPs on fungi, the fungal growth inhibition was tested using the agar well diffusion method.

Apart from their antibacterial and anticarcinogenic advantages, titanium dioxide nanoparticles (TiO_2 NPs) have been recognized to possess antifungal activity against different fungal pathogens. Examples of such fungi are those which affect plant's heath and structural materials. For example, Ustilago tritici, one of the most important fungi that attack wheat, was effectively controlled by the application of TiO_2 NPs through sol–gel and green synthesis routes (Raliya, et al., 2015). This is of particular importance as the chemical fungicides usually are somatic environmental and health risks, whereas nanoparticle-assisted alternatives stand out to be better alternatives [84].

Different fungal species including Fusarium oxysporum, F. graminearum, Candida albicans, Macrophomina phaseolina, and wood rot fungi Coniophora puteana and Poria placenta have also been reported to be susceptible to TiO_2 NPs [85–89]. The mechanism of action is through alteration of fungal cell wall and oxidative stress, and the antifungal effect is weaker than antibacterial effect. This discrepancy perhaps arises from differences in the composition of cell wall of fungi and bacteria [90].

Apart from the direct biocontrol, TiO_2 NPs have been explored as the novel material for biopreservation of architectural monuments of cultural values. When applied to historical buildings, TiO_2 forms a protective layer that protects limestone; this is called the biocidal effect, which protects from biodeterioration of historical buildings from lichens, mold, and other microbial sources. Both laboratory-based and in situ studies have shown the protective performance of these nanoparticle coatings [89].

In addition, the study by Chen et al. reported that the treatment of Paulownia wood with TiO_2 NPs suppressed Aspergillus niger—typically found in mold fungi. Similarly, De Filpo et al. observed that the such nanocomposites provided superior protection of the wood against decay fungi such as Mucor circinelloides (brown rot fungus) and Hypocrea lixii (white rot fungus) when embedded in the polyvinyl alcoholPVA matrix [91].

Their effectiveness of inhibition against Candida albicans and Penicillium chrysogenum was higher compared to samples treated with PVA only [92].

3.6 In Vitro Antioxidant Activity of TiO_2 NPs

The cytotoxicity of titanium dioxide nanoparticles (TiO_2 NPs) is well recognized, and they are used to induce oxidative stress for the elimination of hazardous microorganisms and cancer cells; however, they can also express beneficial antioxidant effects, particularly when synthesized via botanical green techniques. These bacterially synthesized nanoparticles usually exhibit improved biocompatibility, stability, and thus, these are suitable candidates for biomedical applications [93].

Plant-mediated synthesis imparts TiO_2 NPs with antioxidant-rich functional groups such as phenols and tannins on the surface, leading to an increase in scavenging free radical potential. For example, ABTS and DPPH assays performed on TiO_2 NPs have demonstrated that they are able to rapidly scavenge free radicals and exert a protective effect on oxidative stress [80].

In another study, TiO_2 NPs prepared by Psidium guajava (guava) leaf extract showed more antioxidant potential than ascorbic acid. This was related to the phenolic compound and 85.4 mg/g of phenolic compound in the leaf extract were detected and 18.3 mg/g in the resulted nanoparticles [94].

A comparable study with Artemisia haussknechtii leaf extract also proved the antioxidant properties of TiO_2 NPs green-synthesized. Several assays, such as DPPH scavenging, metal ion chelation, reducing power, and the determination of total phenolic and flavonoid contents were carried out to check the nanoparticles. Strong antioxidant activities, especially in the DPPH assay, were observed, where the scavenging activity of TiO_2 NPs was 68.43% at 500 µg/mL concentration [94].

Ajmal et al. also confirmed these results based on the biosynthesis method of TiO_2 NPs with fruit peel agrowaste. Both of these nanoparticles showed dose-dependent free radical scavenging activity in all of the assays employed for hydrogen peroxide as well as nitric peroxide radical. Green synthesized TiO_2 NPs revealed competitive as well as greater possession of the free radical scavenging ability, compared to the ascorbic acid as control [95].

3.6.1 Theranostics

Diagnostics and therapeutics meet each other in theranostics, a new medical modality. Through this strategy, clinicians and scientists can diagnose, monitor and treat diseases, and, in particular, cancer, while ensuring the precise targeting of molecular pathways. In this context, TiO_2 nanoparticles (TiO_2 NPs) have demonstrated great promise in PDT, which depends on specific photoactivated photosensitizers [96].

One example is the preparation of nanoconjugates between zinc(II) phthalocyanine (MCZnPc) and TiO_2 NPs. HeLa (cervical cancer) and EMT6 (mouse mammary cancer) cells were exposed to these composite platforms. Upon treatment with NIR irradiation at 684-nm after incubating for 3 h in dark, the nanoconjugates exhibited promoted cellular uptake and anticancer efficacy. This work convincingly demonstrated the applicability of TiO_2 -based theranostic platforms in the field of oncology [96].

3.6.2 Evidence of poisoning

In spite of increasing TiO_2 NPs hype, safety issues of such NPs have to be discussed. It has been reported that TiO_2 particles is biocompatible, while at high doses or certain exposure manners, TiO_2 particle may cause risk to the health of the human beings. TiO_2 is classified as a Group 2B carcinogen by the International Agency for Research on Cancer (IARC), which means that it is possibly carcinogenic to humans in specific circumstances [97].

The toxicological effects are influenced by several factors such as particle size, shape, surface charge, dose, route of administration, and the biological system used. In comparison, green synthetic approaches usually provide nanoparticles with a safer profile since exhibit slower ion release and less toxicity when compared with chemically or physically synthesized ones [80].

As for example in the zebrafish embryo study, the TiO_2 NPs had induced considerable developmental deformities on concentrations greater than 2.5 mg/L including curved tails, spinal deformations, delayed hatching and toxicities associated to behavior and organ [98]. In mice, Trouiller et al. found that oral administration of TiO_2 NPs induced inflammation, DNA damage and chromosomal aberrations in the liver, when confirmed through comet assay and micronucleus assay [99].

Furthermore, TiO_2 NPs have been reported to cross physiological barriers. A study by Yamashita et al. reveal that IV injected TiO_2 NPs in pregnant mice can be transported to placenta and fetal organs (brain and liver) and induce pregnancy complications [100]. Another in vitro trial on healthy cell lines also showed the capability of inducing nuclear condensation, cytoplasm shrinking, and cells' aggregation were high concentrations (for instance, 100 μg/mL) [101–103].

Notwithstanding, the attractive biomedical properties of TiO_2 NPs, particularly if they are biofunctionalized for specific therapy, still surpass several similar risks when adequate safety limits and green synthesis synthetic approaches are applied [80].

3.7 Drug Delivery Systems by TiO_2 NPs

Among the potential applications of titanium dioxide nanoparticles (TiO_2 NPs) in the biomedical sector is as a drug delivery system. The ultimate goal of any successful drug delivery system is to improve therapy efficiency and reduce side effects. TiO_2 NPs are good candidates for these purposes because they allow to entrap drugs such as doxorubicin [104], to protect drugs from degradation and to release them under a specific site-target mode.

Drugs can be loaded on their surface or within the structure (such as, spherical, capsule, porous) depending on the designed nanoparticles, leading to sustained and targeted drug release. Ligand- or another biomolecule-functionalized TiO_2 NPs that specifically bind to target tissues or cells can enhance the accuracy and efficiency of therapy [105].

Several drugs, including sodium phenytoin, valproic acid, temozolomide, and daunorubicin, have also been effectively loaded into TiO_2 NPs. The drug is not introduced slowly; rather it is often in an initial large part released rapidly (a burst), and continues to be gradually released. This biphasic delivery profile can be utilized to sustain therapeutic drug levels and decrease the dosing frequency and the degree of local side effects [105].

3.7.1 Intelligent Release Systems

Contemporary drug delivery systems typically are engineered to be stimuli-responsive, releasing the drug upon the receipt of particular internal (pH and enzymes) or external (light and temperature) triggers. Like in the abovementioned example, such systems are of special interest for cancer therapy, where delivery in both a precise and tissue-specific manner is required to avoid harming healthy tissue [106].

In another study, multifunctional porous TiO_2 NPs were fabricated, surface modified with polyethyleneimine (PEI) for improved photocatalytic activity. The nanoparticles were subsequently stuffed with anticancer drugs and PEI to block the early release of drugs. Folic acid (FA) was subsequently chemically conjugated onto the surface of the nanoparticles, which modify the nanoparticles to a cancer cell targeted FA receptor over expressed [107].

The previously mentioned and latest example UV light induced FA targeted Delivery vehicle (nSP) provided both safe and efficient stimuli-sensitive targeted drug release. This smart release mechanism is depicted in the original article with the help of a scheme (Fig.

3.7.2 Photodynamic Therapy (PDT) of TiO_2 NPs

Photodynamic therapy (PDT) is a novel and minimally invasive technique that employs light-activated photosensitizers, which can kill cancer cells. For PDT, TiO_2 NPs are ideally suited because they produce reactive oxygen species (ROS) when irradiated with ultraviolet (UV) light—usually < 385 nm light [53,108].

Under light irradiation, TiO_2 NPs generate electrons and holes which react with water or hydroxyl ions to generate oxidative radicals. These free radicals go on to wound or kill tumor cells and microbes. Due to their excellent photocatalytic performance, low toxicity, and good stability, TiO_2 NPs have attracted more and more attention as preferential photosensitizers for PDT and would constitute an attractive ally to the traditional therapies such as chemotherapy, radiotherapy and surgery (101].

3.7.3 Radiotherapy

Today, radiotherapy is still an important modality for cancer treatment. Yet, its collateral effects on the healthy tissue around it are one of the problems. Radiosensitizers have been developed to increase the selectivity and efficacy of radiation and might arrive to deal with this shortcoming [110].

TiO_2 NPs have been found promising as a radiosensitizer. For instance, Youkhana et al. (2011) modified human keratinocyte (HaCaT) and prostate cancer (DU145) cell lines by treating with anatase-phase TiO_2 NPs. According to the study, the nanoparticles were nontoxic (up to 4 mM). Additionally, TiO_2 NPs enhanced radiation uptake, which increased its efficacy towards cancer cells and lessens normal tissue damage [111]. Based on their properties, TiO_2 NPs may be considered as a multi-functional vehicle in theranostics, integrating diagnosis, therapy and imaging in one system.

3.8 Biosensor Applications of TiO_2 NPs

Biosensors received a broad interest, due to the possibilities nanotechnology opened, in which titanium dioxide nanoparticles (TiO 2 - NPs) have an important position. In fact, owing to the nanosize dimensions and high surface-to-volume ratio, TiO_2 NPs have been exploited as extremely versatile materials for sensitive, fast and highly selective biosensing platforms [112].

Such nanomaterials are being incorporated into hybrid architectures using biomolecules with nanostructured materials. For example, bio-nanohybrid systems such as biomolecule-sensitized solar cells and photoelectrochemical cells (PECs) are emerging as promising systems for the development of energy and sensing devices. Biomolecule-interfaced TiO2thin films have also been proven very attractive in the development of new biosensors for medical diagnoses, environmental protection and food safety [113].

Relatively speaking, TiO_2 NPs have already made their way into devices to sense gases such as oxygen, hydrogen and moisture. They are featured with a porous structure, biocompatibility and remarkable electrochemical properties, and thus represent excellent electrode materials for biosensors. In addition to the metal nanoparticles, TiO_2 works well as a support matrix as it enables the immobilization of enzymes and

does not degrade their biological activity as it interacts with functional groups (e.g., amines and carboxyls) [114].

Various creative biosensing methods based on TiO 2 have already been proposed. For example, the DNA-functionalized TiO_2 nanowires have been integrated with chitosan and reduced graphene oxide for the specific detection of genetic fragments of Vibrio parahaemolyticus, a pathogenic bacterium [115]. NP-based TiO_2 biosensors generally function on amperometric or potentiometric modes whish are either electrochemical approaches that possess high sensitivity in the immobilization of enzymes, antibodies, aptamers or even whole cells to the target analyte [116].

4. Conclusions and Suggestens for Future Reseach

Titanium dioxide nanoparticles (TiO_2 NPs) have drawn great attention owing to their diverse applications in the biomedical field. From antibacterial, antifungal, antiviral, anticancer, antioxidant, and so on, functions, to their application for advanced drug delivery and biosensing, these nanoparticles are proving themselves to have enormous potential.

Although TiO_2 NPs could be fabricated by several routes (i.e., physical, chemical and biological), biological or green synthesis approach is an emerging method. As compared to traditional methods, which typically involve toxic reagents, high energy input and environmental toxicity, green synthesis is safe, economic, and ecological decent. The present review outlined the various green synthesis approaches of TiO_2 NPs, and their efficient biocompatible bio-applications and mechanism.

However, for this green technology to fully take off, more research is needed. A significant future task would be to find potential low-cost natural resources such as ubiquitous plants for nanoparticle synthesis available locally. The use of local materials may allow achieving a cost-effective manufacturing process, this potentially being a good option for mass production, especially when resources are scarce.

The another critical area which require in depth study is the mechanistic insight into biosynthesis. Although green synthesis is proved successful, the precise functions of plant-based biomolecules during reduction and stabilization of NPs are not available. Knowledge on phytochemistry would be used to control particle size, shape, and surface properties in a more selective manner.

Besides, the purification of nanoparticles, in particular in the removal of biological contaminants, is a challenge that researchers have to face. This step is very important, particularly when TiO_2 NPs are considered for averse biomedical use. Additionally, one must consider how functional groups derived from plant or microbe sources bind to NP surfaces and affect biocompatibility and bioavailability.

To sum up, green nanotechnology presents an eco-friendly and novel route for the development of TiO_2-NP. Through further investigation especially related to the synthesizing method and biological function, TiO_2 NPs have great potential to be widely used in the field of medicine, environment and industry. This is a space ripe for innovation, and greener, safer nanomaterials are achievable.

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