Review Article

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A comprehensive review on green synthesis of titanium dioxide nanoparticles and their diverse biomedical applications

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Abstract: Metal oxide nanoparticles (NPs) have found a variety of applications in numerous industrial, medical, and environmental fields s, attributable to recent advances in the nanotechnology field. Titanium dioxide nanoparticles (TiO2-NPs) have gained importance as metal oxide NPs due to their potential in various fields, particularly nanomedicine and other biomedicine fields. Several studies have confirmed that NPs produced via the biosynthesis route using natural resources have significant advantages such as fewer toxic contaminants, less subsequent complex chemical synthesis, environmental friendliness, cost-effectiveness, and stability when compared to NPs produced by conventional methods, and its production with controlled shapes and sizes. Therefore, considerable effort is being expended to implement biological synthesis methods with these proven advantages. TiO2-NPs can be

made using a variety of biological, chemical, and physical methods. Physicochemical methods are costly, emit high levels of toxic chemicals into the atmosphere, and consume a lot of energy. On the other hand, the biological approach is an environmentally safe, cost-effective, dependable, convenient, and easy way to synthesize TiO₂-NPs. In this review, the bio-mediated synthesis, as well as various biomedical applications of TiO₂-NPs, were discussed.

Keywords: bio-mediated synthesis, green fabrication, TiO₂ nanoparticles

1 Introduction

The emerging field of nanotechnology mainly focuses on materials that have a particle size in the range of 1-100 nm, and these particles are known as nanoparticles (NPs). These NPs have remarkable physical and chemical properties, different from their bulkier counterparts [1–3], owing to the increase in the surface-to-volume ratio. The unique properties of NPs have been summarized in terms of optical, electrical, thermal, photochemical, energy, biomedical science, and catalytic properties [4–6]; these can be well channelized in "nano industries" for better and sustainable industrial applications to protect the biological life [7]. In this regard, transition metals have gained a lot of attention due to (i) the incomplete d-orbitals in their atomic electronic configuration and (ii) and their tendency to undergo variable oxidation states. Thus, the physical and chemical properties of these metals can be tailored for a vast range of applications in the areas of physics, chemistry, and materials science [8–11]. These metal elements can also form diversified oxide compounds, which serve as a promising candidate to broaden the horizon of research in the exploding fields of environment, agriculture, medicine, cosmetics, energy storage, fuel cells, semiconducting devices, sensors, and catalysts [12–17].

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For any material, particle size plays a very crucial role in determining its basic properties:

- (a) Structural properties: bulk oxides are robust and have low phase stability, whereas NP oxides can well undergo structural transformations and have low surface free energy because of their reduced particle size [18,19].
- (b) Electronic properties: bulk oxide surfaces are the long-range effects of the Madelung field, which are limited in a nanostructured oxide [20,21]
- (c) Physical and chemical properties: bulk oxides have a wide band gap and low reactivity, whereas the NP oxides have a low band gap and thus show good conductivity and chemical reactivity [17,22].

Thus, oxide NPs being limited in size and having a high density of corner surface sites can exhibit unique physical and chemical properties [17].

Titanium oxide (TiO₂) NPs are among the most versatile and prominent oxides with an annual production of more than 10,000 tons in 2011 [23] due to their low cost, good chemical stability, high refractive index, strong oxidation properties, and oxygen vacancies in their lattice [2]. The wide band gap of titanium dioxide nanoparticles (TiO₂-NPs) is one of the critical properties to be used as semiconductors in optical industrial applications [24,25]. Owing to the unique electrical or ionic properties of TiO₂-NPs, they can be further tailored to find their application in the field of sensors and electronic devices [17]. They are white in color, water-insoluble powder with a very high refractive index, n = 2.4, and can be used as a pigment in paint industries [26]. TiO₂ naturally exists in three polymorphic forms, namely rutile, anatase, and brookite having crystalline structures and are extensively used in gemstone industries [17]. TiO₂-NPs also have enormous and successful applications in various fields of sensors [27], as photocatalysts for decomposing the wastewater pollutants [28,29], as anti-microbial and antibacterial agents [30,31], as food additives [32], and in cosmetics [14,33].

Thus, a facile mediated synthesis is a crucial step to control the morphology and structure of NPs compared to bulk powders. So, in this review, we discuss an environmentally safe, non-toxic green chemistry approach for the synthesis of TiO₂-NP_S, which has an advantage over the conventional industrial approach in terms of reagents handling and safety process [2,34]. To the best of our knowledge, we have also tried to summarize the different green synthesis research approaches for TiO₂-NP_S. Simultaneously, their various applications in biomedical (i.e. antibacterial, anticancer, antifungal, and antiviral) and

environment have been discussed, which may clear our thoughts in this field and lead us to intrigue toward more sophisticated nanostructures in the coming years.

2 Synthesis of TiO₂-NPs

2.1 Background

The conventional methods for the synthesis of metal oxides can be broadly classified in two different approaches, i.e. top-down and bottom-up (Figure 1). In the top-down approach, the bulk macroscopic particles are broken down into nanoscopic particles through various physical methods such as milling, etching, sputtering, pulse laser ablation, evaporation—condensation methods, etc. [34,35]. However, in a bottom-up approach, the atomic nuclei are joined together by a self-assembly process and nanosized particles are formed using several techniques and processes like chemical vapor deposition, sol–gel process, hydrothermal, sonochemical, flame spraying, spinning, green synthesis, etc. [35–37].

The bottom-up approach has gained interest due to its advantage of size and structural control in the synthesis of NPs. However, the chemical methods are cost-effective, mass production is limited, requires high energy, high temperature and pressure, uses toxic and volatile reagents that cause a hazard to the environment and human life. So, the scientific community has explored a new method of synthesis of NPs that is a biological method, which is environmentally benign, non-toxic, uses less expensive chemicals, and requires low energy for cost-effective production [38,39].

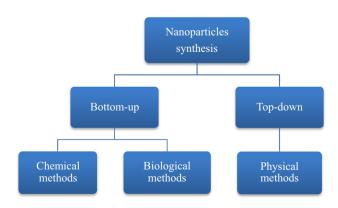


Figure 1: Nanoparticle synthesis methods (bottom-up and top-down approaches).

46 — Suresh Sagadevan et al. DE GRUYTER

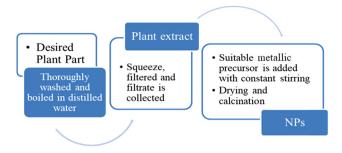


Figure 2: Flow chart representation of plant-mediated NP synthesis.

2.2 Biological methods for TiO₂-NP synthesis

In a broader perspective, the biological methods incorporate the "green synthesis" [40] of metal oxides that can be further divided into (a) photosynthesis (where the synthesis can be carried out using plant and its extracts) and (b) biosynthesis (synthesis from bacteria, algae, fungi, and actinomycetes extracts). Green synthesis is the most competent, naturally versatile, ecologically sound, and cost-effective method for the synthesis of NPs on a large scale [26,41]. A green solvent, good reducing agent, and environmentally safe material for stabilization are the prerequisite components for the green synthesis of NPs. The following sections deal with these components in detail.

2.2.1 Plant-assisted synthesis

Plant-mediated synthesis of NPs is found to be more stable than microbe-mediated synthesis [42]. Phytochemical synthesis of NPs was found to be simple, easy, costeffective, and give high yield while maintaining sustainable developments [43]. Plant extracts can be generally obtained from any part of the plants, namely flowers, roots, seeds, and leaves. The desired part of the plant from where the extract has to be obtained is thoroughly washed and then boiled in solvent (ethanol or distilled water) for a few minutes followed by filtration. The resultant filtrate is the plant extract to be used as a reducing agent to which a suitable metallic precursor (titanium tetra isopropoxide, titanium tetra chloride, and titanyl hydroxide are generally used [2]) is added with constant stirring to obtain NPs [6,7,26,43-45]. The flow chart representation of the synthesis of plant-mediated NPs is shown in Figure 2.

Leaves are more widely utilized for extracts as they contain a rich source of metabolites. They are more feasible to derive extract without producing any toxic agents. Most of the above-listed extractions (Table 1) are simple, low cost, non-toxic, facile, and have shown their compatibility in various industrial and environmental applications without damaging the ecosystem.

Table 1: Different plant extracts obtained from various plant parts for the synthesis of TiO2-NPs

| S.No. | Plant name | Precursor | Size (nm) | Morphology | References |
|--------------|---|-------------------------|-----------|--------------------------|------------|
| (A) | Stabilizing agent – leaves | | | | |
| 1. | Psidium guajava (Guava) | $TiO(OH)_2$ | 32.58 | Spherical | [46] |
| 2. | Annona squamosa (sugar apple) | $TiO(OH)_2$ | 23 | Rutile, spherical | [47,48] |
| 3. | Nyctanthes arbor-tristis L. (night flowering jasmine) | TTIP | 100-150 | Spherical | [49] |
| 4. | Catharanthus roseus (Rosey periwinkle) | TiO ₂ powder | 25 | Clustered | [50] |
| 5. | Ledebouria revolute (African hyacinth) | TiO ₂ powder | 47 | Tetragonal | [51] |
| 6. | Azadirachta indica A. (neem) | TTIP | 124 | Spherical | [52] |
| 7. | Solanum trilobatu (purple fruited pea eggplant) | TiO ₂ | 70 | Oval | [53] |
| 8. | Syzygium cumini (jamun) | TiO ₂ | 11 | Spherical | [54] |
| 9. | Moring olifera (drumstick) | TiO ₂ | 100 | Spherical | [55] |
| 10. | Eclipta prostrate (false daisy) | $TiO(OH)_2$ | 36-68 | Spherical, polydispersed | [56] |
| 11. | Murraya koenigii (curry tree) | TTIP | 2-15 | Spherical | [57] |
| 12. | Cinnamomum tamala (bay leaf) | TiO ₂ | 8-20 | | [58] |
| 13. | Jatropha curcas (Jamal ghota) | TiCl ₄ | 13 | Spherical | [59] |
| 14. | Piper betle (betel) | TNB | 7 | Spherical | [60] |
| (B) | Stabilizing agent – flowers | | | | |
| 15. | Calotropis gigantea (Crown flower) | $TiO(OH)_2$ | 160-220 | Spherical, oval | [61] |
| 16. | Hibiscus rosa-sinensis | Titanium oxysulphate | 7 | Spherical | [44] |
| (C) | Stabilizing agent – root | , , | | • | |
| 17. | Acanthophyllum laxiusculum | TTIP | 20-25 | Spherical | [62] |
| 18. | Euphorbia heteradena Jaub | $TiO(OH)_2$ | 20 | Spherical, rutile | [63] |
| (D) | Stabilizing agent – seeds | · · · - | | • | |
| 19. | Cucurbita pepo | TiCl₃ | _ | _ | [64] |
| 20. | Cicer arietinum L. | TiCl ₄ | 14 | Spherical | [65] |

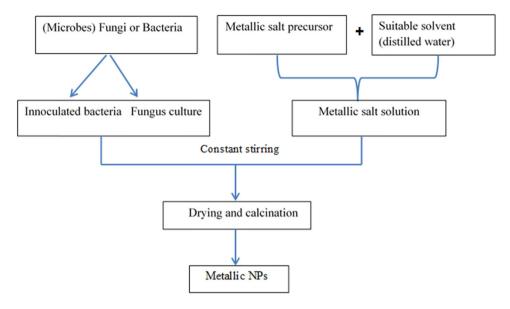


Figure 3: Pictorial representation of microbe-mediated NP synthesis.

2.2.2 Microbe-assisted synthesis (fungi and bacteria)

Fungal extract for the synthesis of NPs has a major advantage over bacterial extracts as they are economically viable, large-scale production, easy extraction, ecofriendly, and have a large surface area [66]. Fungi have been reported as a good source of metabolites and enzymes that can reduce bulk salts into elemental ions that are necessary for the synthesis of NPs. One of the studies done on Aspergillus flavus fungus explored that it was most useful for the synthesis of TiO2-NPs because of its biodegradable nature [67]. The synthesis of NPs from Saccharomyces cerevisiae fungi is yet another approach toward eco-friendly products along with the benefits of downstream processing [68]. Various shapes and sizes of TiO₂-NP_S can be obtained through fungal-mediated synthesis. Green synthesis of NPs through microbe-mediated approach is illustrated in Figure 3.

Bacterial-assisted synthesis of NPs can be done through two approaches: intercellular and extracellular approaches. The intercellular approach is time-consuming, so the extracellular approach is widely used because it takes less time as it does not need any downstream process for the collection of NPs from the organisms [42]. Thus, in recent years, TiO₂-NP_S of different morphologies have been obtained through microbes as listed in Table 2.

3 Biological applications

With the recent advancements in nanotechnology, vast research and growth have been observed in the biomedical application of NPs, such as pharmaceuticals, diagnostics, cosmetics, electronics, etc. Nanomaterials possess unique physiochemical characteristics, which make them

Table 2: Various microbial species with different morphologies for the synthesis of TiO₂-NPs

| S.No. | Microbial species | Shape | Size (nm) | References |
|-------|--|-----------------|-----------|------------|
| 1. | Bacillus mycoides | Polydispersed | 40-60 | [69] |
| 2. | Bacillus subtilis | Spherical | 10-30 | [70] |
| 3. | Bacillus subtilis | Spherical | 66-77 | [71] |
| 4. | Lactobacillus | Spherical | 40-60 | [72] |
| 5. | Planomicrobium sp. | Spherical | 100 | [73] |
| 6. | Aspergillus niger | Spherical | 73.58 | [74] |
| 7. | Aspergillus flavus | Spherical | 62-74 | [67] |
| 8. | Fusarium oxysporum | Quasi-spherical | 9.8 | [75] |
| 9. | Aspergillus niger, Rhizoctonia bataticola, Aspergillus fumigatus, and Aspergillus oryzae | _ | _ | [76] |

interesting and useful in different fields of research. Their small size (1–100 nm), reactivity, and high surface area ease the entry inside the cells and help them to interact with biomolecular and cellular pathways that render them useful in drug therapeutics [77]. The mechanical and photochemical properties of TiO_2 , make it more desirable for its use in cosmetics (sunscreens) [78], electronic devices (solar cells) [79], and medicine (dental and bone implants, vascular stents) [80–82]. Therefore, in the following subsections, we discuss in detail the biomedical applications of TiO_2 -NPs as shown in Figure 4.

3.1 Antibacterial applications of TiO₂-NPs

Various metallic NPs have been studied toward different strains of bacteria. Titanium NPs displayed an eco-friendly biocidal property, which was ascribed to their powerful oxidizing potential. Titanium NPs are broadly utilized toward an extensive range of infectious microbes comprising several bacterial strains, endospores, fungi, algae, protozoa, viruses, microbial toxins, and prions [83]. A biological approach has also been used for the synthesis of TiO₂-NPs for their antibacterial applications [84]. Titanium NPs activate the creation of reactive oxygen species (ROS) during the attack of microbial cells [85]. Furthermore, the ROS terminates the microbes by disturbing the cell wall's integrity, predominantly by phospholipids oxidation, consequently by lowering adhesion and change in ionic balance. Once it goes into the cytosol, it tends to prevent the respiratory cytosolic enzymes and alters macromolecules structures, constructing a significant result on cellular

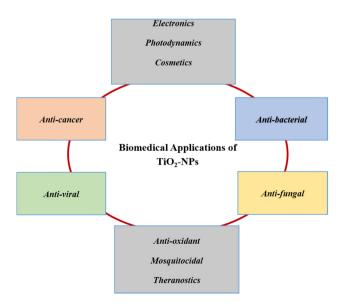


Figure 4: Biomedical and other applications of TiO₂-NPs.

integrity and gene expression. Furthermore, it reduces phosphate uptake and communication between cells [86]. A schematic representation of the ${\rm TiO_2}$ -NP effect on bacterial cells is shown in Figure 5.

Titanium NPs destroy the microbes in an identical method. But, the biologically procured titanium NPs showed better antibacterial activity as compared with the green and chemically synthesized NPs. The significant factors that affect the antibacterial activity are morphology, size, and shape of the NPs, membrane composition, and type of bacteria. Green synthesized titanium NPs effectively impede both Gram-positive and Gram-negative bacteria; they are more effective toward Gram-positive bacteria owing to the structural complexity of Gram-negative bacterial cell walls [87]. The antimicrobial property of bio-interfered titanium NPs could be more efficient when exposed to UV fluorescence light irradiation [88]. TiO₂ nanocomposites showed magnified antileishmanial activity, and at the same time green synthesized TiO2-NPs were exposed to Leishmanial cultures; it showed the reduction in cell viability and smallsized growth, and DNA fragmentation was noticed [89]. Green synthesis of TiO₂-NPs using the leaf extract of Euphorbia prostrata worked as an antileishmanial agent to induce cell death [90]. Titanium NPs also displayed an enhanced antimicrobial activity in contrast to the standard antibiotic disks [91]. Hence, the improved antibacterial activity of titanium NPs significantly decreases the event for the development of antibiotic combat of pathogenic stains.

3.2 Toxicity of TiO₂-NPs

An *in vitro* cytotoxicity study has been completed using the (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium

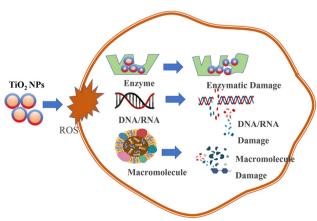


Figure 5: Schematic sketch of the TiO_2 -NP effect on the bacterial cells.

bromide) (MTT) assay (3-[4,5-dimethylthiazol 2-yl]-2,5diphenyl tetrazolium bromide) as a basic method. This method changes the color of the stain in the cells by the MTT dye. The mitochondrial activity method has distinctive properties such as simplicity, sensitivity, and reliability, which is also able to measure toxic effects of different cell lines and hence determinable for in vivo animal studies [92]. Vijava Lakshmi et al. estimated the viability assay using osteoblast-like MG63 cell lines treated with TiO₂-NPs at different concentrations for 24 and 48 h. The significant increase in the cell viability levels and the proliferation rate of MG63 cell lines determines the toxicity level and morphological parameters of both treated and untreated cells. The synthesized nano TiO₂ particles do not show any toxicity and do not restrict the proliferation, and thus, provide evidence of biocompatibility in MG63 cell lines. This is because of the transformation of anatase to rutile without disturbing the other phases in the course of sintering at 900°C for 2 h. TiO₂-NPs are more inert as compared to the highly active, high refractive index anatase form. Titanium NPs appear as agglomerated platelet-like particles and not fiber-like. The fiber-shaped particles are more toxic, namely carbon nanotubes and fullerenes [93]. Researchers have also studied the cytotoxicity assay of A549 cell lines using green synthesized titanium NPs, which showed higher efficiency for anticancer activity. This is due to the production of superoxide radicals in cancer cells. The other group also studied MTS activity using KB oral cancer cells for the evaluation of the anticancer activity of the plain and bio-modified NPs. It is noted that Withania somnifera – Eclipta prostrata-modified titanium NPs showed superior anticancer activities in contrast to bio-modified and pure samples. Hence, these results demonstrated that bio-modified samples have greater activities compared with pure titanium NPs [94].

3.3 Antiviral properties of TiO₂-NPs

The antiviral properties established in many of the NPs such as Ag, TiO₂, and carbon nanotubes are used to illustrate the antiviral mechanisms such as cell binding inhibition and capsid degradation. Antiviral properties of the nanoparticle unorders to bring a variety of factors including air and water *in vitro*. TiO₂-NPs exhibited superior antiviral activities at 6.25–100 µg·mL⁻¹ doses as compared to the Newcastle disease virus (NDV). Titanium NPs could destroy the lipids through the viral envelope via the G-sol because the glycoprotein spikes are harmful and are restricted by the adjunct, which would not allow infections. Hence, titanium

NPs would be a potential platform for the treatment of New castle disease virus infections and also an ideal candidate for the evolution of new antiviral drugs in the near future [95]. Titanium oxide nanostructures were used to act against the broad bean stain virus (BBSV) in faba bean plants. The faba bean treated with titanium oxide nanostructures exhibited a superior reduction in the disease in the following two weeks of infection with the broad bean stain virus in contrast to untreated plants [96].

The virus is composed of genetic material (DNA or RNA) and a protein coat named capsid. Viruses are a major threat to mankind among infectious diseases, such as influenza viruses, hepatitis virus B and C, HIV, herpes, and the current chaotic coronavirus. Advancements in nanotechnology have offered us effective combating therapeutic strategies against various diseases, including antiviral infections. Nanoconjugates such as silver, TiO2, and carbon have been shown to target viruses by direct contact via different methods. Nanomaterials destroy the viral protein coat by physical destruction or photocatalytic oxidation, which is one of the important methods of targeting viruses. TiO2-NPs interact with the viral envelope via an unknown mechanism and disintegrate the virus. In another study, it was revealed that TiO₂ interacts with the capsid proteins, followed by their degradation and inactivation by photocatalytic oxidation. Examples of this type of destruction are reported in influenza and MS2 bacteriophage viruses [97–99].

In another study, TiO_2 nanoconjugates exhibited antiviral effects against the influenza virus (H3N2) via a direct interaction mechanism [100]. TiO_2 NPs have also demonstrated antiviral activity against the avian influenza virus (H9N2). Besides influenza virus, replication of H5N1 and H1N1 viruses was inhibited by the use of DNA-tagged TiNPs [101]. During the current hard times of pandemic, a disinfecting solution composed of TiO_2 and silver ions was used in the streets of Milan, Italy. Nanocolloids of TiO_2 have also antiviral activity against NDV at a minimum concentration of $6.25\,\mu g \cdot mL^{-1}$, which could be due to the lipid disruption of the viral coat [102].

A study was carried out to determine the antiviral activity of ${\rm TiO_2}$ nanostructures on BBSV, which affects the faba bean plant [103]. The study showed that after the application of ${\rm TiO_2}$ nanostructures, the PR1 gene (pathogenesis-related gene 1), i.e. the defensive regulatory gene in the salicylic acid signaling pathway was highly expressed, decreasing the disease intensity. This was most likely achieved by the interaction of ${\rm TiO_2}$ -NPs with viral particles due to their nanosize and zeta potential. A different study reported that the application of nanostructures of ${\rm TiO_2}$ led to improved germination and growth in plants [104]. The suggested mechanism

includes the increased stimulation of the production of carbohydrates and elevated photosynthesis, as it has light-absorbing properties [105]. Enzymes of nitrogen metabolism (such as glutamate dehydrogenase, nitrate reductase, glutamine synthase, and glutamic–pyruvic transaminase) can also be regulated by ${\rm TiO_2}$ by increasing the absorption of nitrates. The function of these enzymes is to convert inorganic nitrogen to chlorophyll and proteins [106–108]. Different modes of the action of ${\rm TiO_2}$ -NPs are shown in Figure 6.

3.4 Anticancer activity of TiO₂-NPs

TiO₂, an inorganic compound, can produce ROS after it is being illuminated by UV light in aqueous media. Production of ROS leading to cell death makes TiO₂ the successful candidate in the use of photodynamic therapy (PDT) for the treatment of various diseases. TiO₂-NPs, their nanocomposites, and hybrid biomolecules have been studied as photosensitizing agents for the treatment of cancers and resistant bacterial infections. TiO₂-NPs can be used as drug carriers for targeted delivery such as those reported for doxorubicin, cisplatin, and temozolomide [78]. A study was carried out

by Chen et al. [109] to enhance the therapeutic potential and to reduce the adverse effects of doxorubicin. TiO₂-NPs were synthesized, and doxorubicin was loaded onto them, followed by the evaluation of their anticancer potential. The cytotoxic activity of DOX-TiO₂ NPs, evaluated by MTT assay, was increased against the SMMC-7721 hepatocarcinoma cell line. Western blot analysis revealed that the Bax/Bcl-2 protein ratio was increased significantly after the treatment with DOX-TiO₂-NPs, suggesting the enhanced accumulation of DOX in cancer cells via endocytosis [110], leading to the induction of apoptosis by caspase-dependent pathway. It is to be noted that TiO₂-NPs alone (10 ug·mL⁻¹) had a cell viability of 95% making it non-toxic [109]. A similar study by Ren et al. [111] showed that resistant breast cancer cells had more drug accumulation and internalization when delivered via nanocomposites, evading the P-glycoproteinmediated pumping system for doxorubicin. Liu et al. [112] modified TiO2-NPs with hyaluronic acid (HA), loaded cisplatin onto it as a chemotherapeutic agent for ovarian cancer, making it a pH-responsive drug release system. The accumulation of cisplatin was found to be increased in A2780 cells via endocytosis, exhibiting significant anticancer activity.

Murugan et al. in 2016 [113] evaluated the possible mechanism of action of synthesized TiO_2 -NPs as an

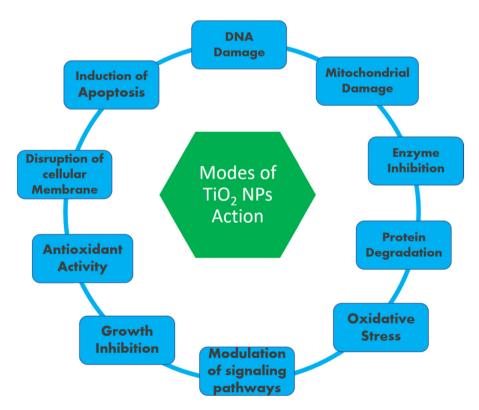


Figure 6: Different modes of action of TiO2-NPs.

anticancer agent against MCF-7 breast cancer cells. MTT assay results demonstrated dose-dependent cytotoxic effects against MCF-7 cells with the IC_{50} of $60 \,\mu\text{g}\cdot\text{mL}^{-1}$, supported by the data of the previous studies [114,115]. Furthermore, AO/EtBr staining through fluorescence microscopy was done for the determination of apoptosis. Morphological data by 4′,6-diamidino-2-phenylindole (DAPI) staining showed nuclear fragmentation, which is a marker of apoptosis. Western blot analysis of TiO_2 -NP-treated cells showed that expression of cytochrome c was activated, suggesting the trigger of apoptosis via mitochondria-mediated pathway [116,113].

It is reported that the surface modification of nanocarriers through targeting moieties enhances the specificity of drug delivery [117,118]. Venkatasubbu et al. [119] modified TiO₂-NPs by polyethylene glycol (PEG) followed by folic acid (FA) and then attached Paclitaxel (PAC) (standard anticancer drug) to it. The anticancer effects of all nanocomposites were evaluated in DEN-induced hepatocellular cancer animal models. The results demonstrated that surface-modified PAC attached to TiO2-NPs showed higher anticancer activity as compared to PAC alone. The surface modification of TiO2 with FA (TiO2-PEG-FA-PAC) helps in the targeting of overexpressed FA receptors in liver cancer cells, resulting in the increased targeted accumulation of PAC-NPs to the site of cancer cells, reducing the toxicity of the drug. TiO2-PEG-FA-PAC also showed a concentration-dependent decrease in cell viability of HepG2 cells after treatment. The higher anticancer activity of TiO₂-PEG-FA-PAC was also demonstrated by biochemical (such as serum levels of alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase, total bilirubin, direct bilirubin, total protein, albumin, gamma-glutamyl

transferase, α feto protein) and hematological (such as red blood corpuscles, white blood corpuscles, hemoglobin, platelets, packed cell volume, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, mean platelet volume, platelet distribution width) parameters.

Another study reports the anticancer effect of FA-modified TiO₂-NPs against MG63 osteosarcoma cells. A 2-fold reduction in IC₅₀ values against cancer cells was observed after treatment with conjugated FA-TiO₂-NPs. Apoptotic markers were also exhibited by the FA-TiO₂-NPs treated cells, for instance, chromatin condensation, membrane blebbing, cytoplasmic cell shrinkage. Annexin V/PI apoptotic assay exhibited 38% of FA-TiO₂-NP- treated cells in early and late apoptotic phases as compared to 16% of cells treated with only TiO2-NPs. Moreover, cell cycle analysis showed that FA-TiO₂-NP-treated cells had a great sub-G1 cell population, which is indicative of an amplified generation of ROS inducing higher apoptosis. TiO2-NPs have been reported to produce ROS, which acts as downstream signaling molecules of the p53-dependent apoptotic pathway. Increased expression of Cyt c, cleaved caspase-3, and PARP on the western blot also indicated the induction of caspasedependent cellular death mechanism, showing the anticancer therapeutic potential of surface-modified TiO₂-NPs. The ROS generation damages the mitochondrial membrane and its potential, which in turn initiates the release of cytochrome c into the cytoplasm, triggering the intrinsic apoptotic cascade [120]. Other scientific studies have also shown promising anticancer effects by TiO₂-NPs against prostate cancer cells [121], liver cancer cells (HepG2) [122], and colon cancer cells [99,123]. Figure 7 illustrates the mechanism of action of TiO2-NPs

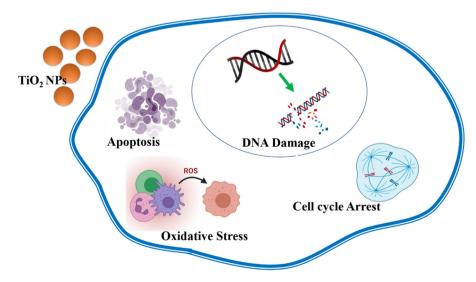


Figure 7: Illustration of anticancer mechanistic events of TiO₂-NPs against cancer cells.

against cancer cells, whereas Table 3 provides the summary of the studies showing anticancer activity by TiO₂-NPs discussed above.

3.5 Antifungal activity of TiO₂-NPs

TiO₂-NPs have also shown antifungal activity against different species of fungus [125]. In a study by Irshad et al. [108], TiO₂-NPs were synthesized via sol-gel and green synthesis method, and their antifungal activity was evaluated against pathogenic plant fungus of wheat rust. Ustilago tritici. This fungus, which is one of the major causes of serious loss in wheat crops, was inhibited at different concentrations by TiO2-NPs. The use of fungicides and pesticides is hazardous to health, therefore, the use of NPs is a safer option due to their less adverse effects and safe therapeutic index [126]. Antifungal activity has also been reported by TiO₂-NPs in Fusarium oxysporum [127], Fusarium graminearum [128], Candida albicans [129], Macrophomina phaseolina [130], Coniophora puteana, and Poria placenta [131]. The application of TiO₂-NPs has also been proposed as a protective material on buildings having cultural heritage value to prevent the biodeterioration of mortars [132]. The data from both, laboratories and on the heritage, building exhibited that the use of TiO2 has shown to be an effective biocidal (lichens and phototropic microbes) and preventive material against building deterioration [131]. The antifungal activity exhibited by TiO₂-NPs is much weaker due to the difference in the structure of the cellular envelope when compared to its antibacterial action [133]. Chen et al. [134] evaluated the effects of TiO₂-NPs against the fungal mold A. niger on the surface of Paulownia wood and the fungal growth was suppressed by the treatment. In another study, De Filpo et al. [125] evaluated the antifungal effects of TiO2-NPs against the wooddecaying species of fungus: brown (Mucor circinelloides)

and white rot (*Hypocrea lixii*) fungi, and it was found that photocatalytic activity of coated TiO₂ protects the wood from fast decay as compared to the uncoated wood samples. The synthesized nanocomposites of polyvinyl alcohol (PVA) and TiO₂ were tested against two fungal strains [*Candida albicans* (ATCC 14053) and *Penicillium chrysogenum* (MTCC 5108)], as shown in Figure 8. The PVA-TiO₂-NP biofilms exhibited significantly more effective antifungal activity, as compared to PVA alone [135].

3.6 Antioxidant activity of TiO₂-NPs

In contrast to having the potential of inducing oxidative stress as a killing mechanism, TiO2-NPs have also been studied for their effective antioxidant activity. Nanomaterials synthesized via plant-mediated synthesis methods have shown greater biocompatibility, stability, and controlled release of antioxidant functional groups. 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and 2,2-Diphenyl-1-(2,4,6-trinitrophenyl)hydrazin-1-yl(DPPH) free radicals were scavenged by TiO₂-NPs in a reduced time. TiO₂-NPs are also reported to have protective effects against ROS. Plant-mediated synthesized TiO2-NPs have functional groups like phenols and tannins, which help in the stabilization of TiO₂-NPs and their increased antioxidant potential [121]. In a study, green synthesis of TiO₂-NPs via *Psidium* guajava, displayed more antioxidant activity in comparison to ascorbic acid due to the phenolic content present in the leaf aqueous extract (85.4 mg·g⁻¹) and TiO₂-NPs (18.3 mg·g⁻¹) [136]. Similarly, the Artemisia haussknechtii leaf aqueous extract mediated green synthesis of TiO2-NPs showed antioxidant effects via different assays. The experimental assays included DPPH scavenging assay, reducing power assay, metal ion chelating activity, total phenolic, and flavonoid content. The results demonstrated that TiO₂-NPs showed higher DPPH scavenging activity (68.43%

Table 3: Studies showing anticancer activity of TiO₂-NPs alone, modified TiO₂ NPs, and drug-loaded TiO₂-NPs against different cancer types

| Modification of TiO_2 | Anticancer drugs loaded | Cell line used/in vivo | Cancer type | References [109] |
|-------------------------|-------------------------|------------------------|--------------------------|---------------------|
| N/A | Doxorubicin | SMMC-7721 | Hepatocellular carcinoma | |
| HA | Cisplatin | A2780 | Ovarian cancer | [112] |
| N/A | Doxorubicin | MCF-7 | Breast cancer | [111] |
| | | ADM | | |
| N/A | N/A | MCF7 | Breast cancer | [114,115] |
| PEG, FA | Paclitaxel | Hep G2 <i>in vivo</i> | Hepatocellular carcinoma | [119] |
| FA | N/A | MG63 | Osteosarcoma | [120] |
| N/A | N/A | D145 | Prostate cancer | [122] |
| N/A | N/A | HepG2 | Liver cancer | [124] |
| N/A | N/A | HCT116 | Colon cancer | [123] |

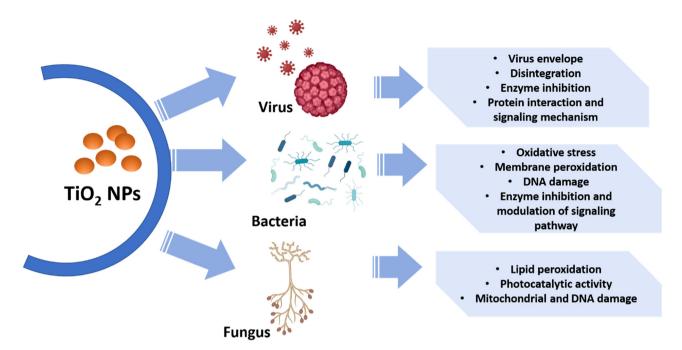


Figure 8: Approaches through which TiO2-NPs induce antiviral, antibacterial, and antifungal activities.

at $500 \, \mu g \cdot mL^{-1}$ concentration). The property of an antioxidant to donate an electron was determined by reducing power assay, and the reducing power of TiO_2 -NPs was found to be greater than ascorbic acid (control). Ajmal et al. [137] also reported the antioxidant potential of TiO_2 -NPs, synthesized by using fruit peel agrowaste. The scavenging assays used were DPPH free radical, hydrogen peroxide free radical, and nitric oxide along with the reducing power assay. Dose-dependent antioxidant effects were observed by TiO_2 -NPs as compared to the ascorbic acid used as a control.

3.6.1 Theranostics

The combination of diagnosis and therapeutics has given rise to a new branch of medicine known as theranostics. The use of theranostics help scientists and medical practitioners to specifically target the signaling pathways at a molecular level. This is a part of anticancer PDT. Nanocomposites of zinc(II) phthalocyanine (MCZnPc) and MCZnPc anchored onto TiO₂-NPs labeled with I were synthesized to evaluate their anticancer potential. MCZnPc and MCZnPc-TiO₂-NPs were against HeLa cells (human cervical cancer) and EMT6 cells (mouse mammary cancer). The cells were irradiated with light (684 nm) after 3 h incubation (in dark) and demonstrated higher cellular uptake of labeled nanocomposites. Hence, this study showed the theranostic potential of TiO₂-NPs against cancer [138].

In a recent study carried by Nakayama et al. [139], it was demonstrated that doping of samarium with TiO₂-NPs increased radiosensitivity and cytotoxic effects in cancer cells. The X-ray absorbance was increased leading to the generation of more ROS upon irradiation when compared to TiO₂-NPs alone. TiO₂ platforms have also been used to detect small biomolecules, cancer cells, and pathogens in blood via label-free microfluidic immunosensors, photoelectrochemical biosensors, field-effect transistors, and amperometry [140–144]. Nanoconjugates of TiO₂, polyethyleneimine (PEI), and FA have been reported to build a controlled (NIR laser-controlled) drug delivery system [145]. The triggered and sustained release of TiO₂-NPs by X-ray illumination can create electron–hole pairs structurally by degradation of organic linkers [146,147].

3.6.2 Toxicological evidence

Although TiO₂-NPs have low toxicity and are generally considered nonhazardous to humans, the studies have shown its toxicological data, arising concerns toward its safe applications. TiO₂-NPs have been declared as group 2B carcinogen, as they can be possibly carcinogenic to humans subjected to their administered dosage [148]. Considering the progressive applications of nanobiotechnology in the energy sector, agriculture, biomedicine, and pharmaceuticals, nanotoxicity is one of the major concerns. In different studies, a high dosage of TiO₂-NPs

has been reported to induce toxic effects in microorganisms, fungi, plants, and vertebrates including mice and humans. TiO2-NPs are reported as a potential cause of induction of DNA damage in mice and humans (epidermal cells, bone marrow cells). Both biocompatibility and toxicity of nanomaterials depend upon their different attributes including shape, size, dosage, route of administration, cell type, in vivo model, and biochemical properties. However, the current methods of green synthesis of TiO2-NPs and other nanomaterials have provided an advantage of slow ion release into the colloidal mixture, in comparison to the chemical and physical synthesis methods. A study was conducted to check the lethal effects of TiO2-NPs in zebrafish and it was observed that a concentration higher than 2.5 mg·L⁻¹ induced various physical malformations (curved tail, egg coagulation, spinal curvature, delay in hatching of the embryos). Other elicited toxic effects were behavioral alterations, organ toxicity, and even mortality [149]. In 2009, Trouiller et al. [150] reported that TiO₂-NPs induced inflammation, oxidative DNA damage, and genotoxicity in mice. In a comprehensive approach, the toxic effects by administration of TiO₂-NPs via drinking water were observed by conducting comet assay, micronuclei assay, measurement of inflammatory markers, and in vivo DNA deletion assay. It was found that TiO₂-NPs induced both single- and doublestrand breaks, chromosomal damage along with the formation of micronuclei, and initiated proinflammatory response (TNF α, INF y, and IL-8). Yamashita et al. [151] showed that TiO2-NPs were able to reach the placenta, fetal organs (brain and liver), and caused pregnancy complications in mice. TiO₂-NPs (35 nm in diameter) were administered through the intravenous route and instigated detrimental effects to both mother mouse and fetus. In addition, the higher dosage of TiO₂-NPs (100 µg·mL⁻¹) has also shown cell accumulation, nuclear condensation, and cytoplasmic shrinkage in vitro in healthy cell lines [152-154]. However, due to the unique physicochemical properties of TiO₂-NPs

and recent studies on its use in the field of biomedical research, TiO_2 NPs hold great therapeutic potential against various diseases. Modification of TiO_2 -NPs via different materials, drug loading, targeted delivery, high absorption, and different methods of synthesis impart diversity toward its use and aptitude [121].

3.7 Drug delivery systems using TiO₂-NPs

The foremost goal of the drug delivery systems is to maximize the therapeutic activity, reducing the adverse events. an appropriate encapsulation of drug. The drug release profile has been constructed into different shapes of drug delivery system, like spherical, capsule, and porous structures. Hence, the drug can be located on the surface of TiO₂-NPs, which could result in a controlled and sustained release pattern. TiO₂-NPs are being modified with any specific molecules that have control toward the targeted cells and get localized in the tissue-specific cells to enhance the efficiency [155]. Titanium NPs have been used as the nanocarrier for loading different types of drugs, namely sodium phenytoin, valproic acid, temozolomide, and daunorubicin. At first, it showed a burst release rate, and controlled release was observed for hours. Therefore, titanium NPs could deliver a drug with enhanced efficacy, dose optimization, controlled and sustained drug release pattern, and also a decrease in toxicity levels [156]. A schematic representation of the drug delivery system using TiO₂-NPs is shown in Figure 9.

3.7.1 Stimuli-responsive release systems

A stimuli-responsive system releases a drug in response to the signal. There are two types of stimuli such as internal and external stimuli. The advantages of these stimuli-responsive systems are to minimize the adverse

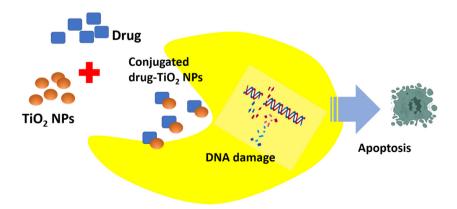


Figure 9: Schematic sketch of the drug delivery system, using TiO₂-NPs. NPs are conjugated with the desired drug, and they are taken by the cell, cause DNA damage, and induce an apoptotic pathway.

effects and improve biocompatibility for cancer therapy applications with terms of controlled and tissue-specific release of the drug [157].

Researchers developed a multifunctional porous structure, titanium oxide nanoparticle, surface-functionalized with poly ethyl imine to promote the photocatalytic activity of titanium oxide nanoparticles, for ultraviolet triggered drug delivery systems. It was further encapsulated with an anticancer agent and tightly packed by PEI tagging of titanium oxide nanoparticles to prevent the drug leakage or release into the nonspecific tissues. FA was covalently tagged on the surface of titanium NPs, which over express the folate receptor, to target the cancer cells [158]. A schematic sketch of stimuli drug loading and release are shown in Figure 10.

3.7.2 PDT of TiO₂-NPs

PDT for cancer involves using a photosensitizing agent upon the exposure of laser light of a specific wavelength to destroy the cancer cells. Apart from the other treatments like surgical, radiological, and chemotherapeutic treatments, PDT is being used and named as a secondary and very encouraging noninvasive treatment used for cancer therapy [159]. When TiO₂-NPs were exposed to UV light with a wavelength below 385 nm, photo-influenced electrons and holes might be created. Further, these photoinfluenced electrons and holes would react

with hydroxyl ions or water to form oxidative radicals, which can destroy the microorganisms and tumor cells. On account of the increasing prevalence of cancer and also by considering the advantages of PDT, researchers focussed on titanium oxide, which can be used as a photosensitizer for the treatment of cancer because of its increased photocatalytic capability, low toxicity, and photostability [160].

3.7.3 Radiotherapy

Radiotherapy is most commonly used for the treatment of cancer as compared to other conventional treatments. In radiotherapy, ionizing radiation is used to kill cancer cells. The development of new techniques and methods is to circumvent destroying neighbor healthy tissues surrounding the tumors. The effectiveness caused by the radiation to the tumor cells is a vital factor for determining appropriate and required dosage to target cells and not to injure the normal cells. Radio sensitizing agents such as gemcitabine and fluorouracil are used to kill the cancer cells [161].

Disadvantages of radiotherapy:

- A dosage formulated and injected into the tumor tissues could also harm the normal cells
- In contrast-enhanced radiotherapy, the contrast agents that have high atomic numbers are capable to deliver to the target tumor cells

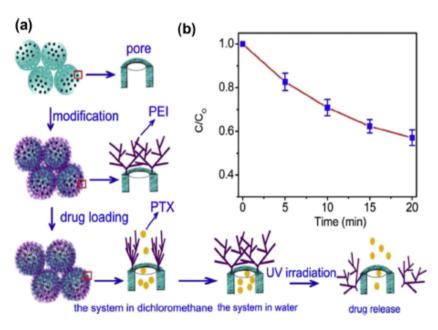


Figure 10: (a) Schematic sketch of stimuli drug loading and release. (b) The photocatalytic degradation of the FA-PEI on the surface of modified porous TiO₂ nanoparticles (MTNP). Reproduced from ref. [145] with permission of Elsevier.

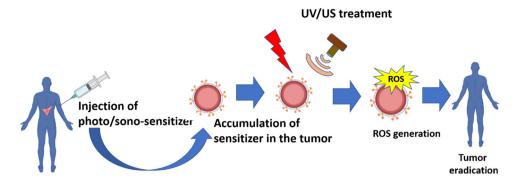


Figure 11: The schematic view of PDT and radio therapy (SDT).

 An increased atomic number of contrast agents has divergent absorbance properties; therefore, they will not harm the normal healthy cells.

In general, the gold nanoparticle is used as a contrast agent in contrast-enhanced radiotherapy due to its biocompatibility, high Z atomic number, and it could pass the cell membrane (smaller size of around 100 nm particle) and get localized with the cells. A research group of Youkhana [162] worked with TiO2-NPs as radiosensitizers to treat the two different cultured mammalian cell lines. human keratinocyte (HaCaT) and prostate cancer (DU145) cells. An accurate radiation dosage of anatase TiO2 was formulated. The cytotoxicity results indicated that cells were nontoxic till 4 mM and further at increased concentrations the cells remained constant without any changes. In summary, TiO₂-NPs could be used for for imaging applications. Hence, TiO₂ would be a better platform for theragnostic applications [162]. The schematic view of PDT and radio therapy (Sonodynamic therapy [SDT]) is shown in Figure 11.

3.8 Biosensor applications of TiO₂ applications

At present, nanotechnology has paid very good attention in the research area of biosensors because of its potential advantages like the small size and higher surface-area-to-volume ratio. Nanoparticle-dependent biosensors come up with sensitive and rapid biological detection. As various types of nanomaterials have been utilized in nanotechnology biosensors, this article is completely on nano biosensors with TiO₂-NPs [163]. A schematic sketch of TiO₂-based photoelectrochemical cell (PEC) biosensor is shown in Figure 12.

At present, researchers are more concerned with the novel hybrid systems based on biomolecules and TiO₂ nanostructures, which resulted in great attention in the construction of bio-nanohybrid devices, namely biomolecule-sensitized solar cells and PECs. Further interfacing of biomolecules and TiO_2 nanostructured thin film has also gained attention including biosensors [164]. Moreover, TiO₂ NPs have been used to fabricate different detecting devices, such as humidity, oxygen, and hydrogen sensors. These nanosized semiconductors have shown to be a better electrode material in the area of biosensors because of their specific features, porous structure, high specific surface area, and biocompatibility. TiO2 can also be utilized as an immobilizing matrix, which responds to the amine and carboxyl groups of enzymes and retains their biocatalytic activity. A few of the titanium-based nanocomposites are as follows: researchers have used DNA-functionalized titanium nanostructures with electron reduced graphene oxide, and also TiO₂ nanowires and chitosan to identify the specific title gene sequence from Vibrio parahaemolyticus [165]. TiO₂-based biosensor utilizes amperometric and potentiometric process or PEC techniques, determined by electrochemical method. Electrochemical biosensors are used for amperometric and potentiometric detection when the biomolecules, namely antibodies, enzymes, aptamers, or cells, which act with targeted molecules, showed effectiveness in amperometric and potentiometric detection.

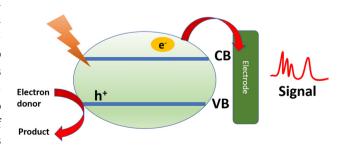


Figure 12: Schematic sketch of TiO₂-based PEC biosensors.

4 Conclusions and recommendations for future research

TiO2-NPs have gained a lot of attention because of their numerous applications. It has antibacterial, antifungal, antiviral, anticancer, antioxidant, drug delivery, and several other biomedical applications. TiO₂-NPs have been created using a variety of methods, including chemical, physical, and biological methods. Physical and chemical methods besides being costly also use a dangerous chemical that may have a harmful impact. The biological approach, on the other hand, is an environmentally sustainable, costeffective, efficient, safe, low-energy consuming, and simple method. This review summarized the synthesis of TiO₂-NPs using various biological methods, as well as their properties, mechanism of action, and various biomedical applications.

To achieve the sustainability of NP biosynthesis and improve nanoparticle stability, further research is needed to explore the potential local and common natural resources that are available even though they are still in the early stages, and significant research is needed in this direction. The use of local resources reduces development costs, making them economically competitive with conventional methods as an alternative to large-scale nanoparticle production. Understanding the biomolecule binding mechanisms involved is a prerequisite for the success of this new technology, which has significant benefits for the biomedical field. However, there is no clear description of the mechanism of biosynthesis, so there is a need to investigate the phytochemistry behind the biosynthesis. The lack of understanding of the underlying mechanisms, chemical components responsible for nanoparticle synthesis, and nanoparticle stabilization remains an open challenge in utilizing natural resources such as plants for nanoparticle synthesis.

The most difficult challenge in the biosynthesis of NPs is the separation of NPs from the biological material and contamination from biological cells, which could have an adverse effect in biomedical applications. Therefore, it is important to consider the active groups that are involved and how functional groups from natural resources are attached to the nanoparticle surface to produce NPs with greater efficacy, particularly in terms of biocompatibility and bioavailability. In conclusion, green technology through biosynthesis, as described in this article, provides outstanding findings that may encourage researchers and newcomers to continue and extend their exploration of nature's possibilities, as well as the design of innovative and safer methodologies for the synthesis of nanomaterials

with desired features and valuable properties that can be exploited in a number of fields.

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