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Green synthesis of titanium dioxide nanoparticles: Development and applications

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ABSTRACT

Wastewater from pharmaceutical industries contains different antibiotics and other effluents that directly affect the environment. For the degradation of antibiotics, nanotechnology is an emerging field in research that majorly focuses on molecules and atoms. Nanoparticles are fine micro-particles with more than one dimension from a size of 1–100 nm. The synthesized nanoparticles can directly be used for the process of degradation of antibiotics in wastewater. Titanium dioxide nanoparticles are majorly used among nanoparticles due to their small surface area and particle size. There are various physical, chemical and conventional (biological) methods for synthesizing titanium dioxide nanoparticles. Green synthesis is an environmentally friendly, less expensive and harmless approach, and these methods are much more efficient than any other physical-chemical means. Titanium dioxide nanoparticles are used for different purposes. In food products, these nanoparticles act as photocatalysts and are also used as a coating material in food packaging. Electrochemical biosensors are combined with titanium dioxide nanoparticles for developing nano sheet matrices. Furthermore, this review describes the usage of biological components (plants, microorganisms like fungi and bacteria) to synthesize titanium dioxide nanoparticles. The present review also focuses on applying synthesized titanium dioxide nanoparticles in various drug delivery systems and other bioactivities.

1. Introduction

Water is one of the important components of life used in the domestic, industrial, and agricultural sectors. The increase in consumption leads to an increase in the toxicity of pollutants inside water. The concentrations of emerging pollutants like pharmaceutical compounds have increased [1]. Various types of pharmaceutical compounds are observed in the aqueous environment, including antibiotics. These compounds reach the aquatic habitat through hospital effluents, the pharmaceutical industry and human livestock. The consumption of antibiotics has increased, and the concentration increases inside the aquatic environment, leading to the development of antibiotic-resistant bacteria [2,3].

To remove antibiotics from wastewater, the traditional sewage treatment method is not appropriate and is not much effective in removing the residuals of antibiotics. Nanoparticles can be used as a photocatalyst for the degradation of antibiotics and other organic pollutants [4]. Nanotechnology is defined as synthesizing and developing various nanomaterials by manipulating the matter at the nanoscale [5]. Nanomaterials are a bridge between molecular material and bulk material. They have a size range of 1–100 nm due to their different shapes, sizes, large surface area, and possess high reactivity [6]. This has become an emerging field in science in the last few years due to its wide range of applications [7]. Because of its small size, the effect can be seen in the physical, optical, chemical properties, melting point, and dielectric constant of various nanoparticles [8].

The nanoparticles are used in day-to-day lives, and they can be used in healthcare applications and various chemical applications. Broadly, nanoparticles are categorized into modules, namely, organic nanoparticles, including liposomes, chitosan, micelles and inorganic nanoparticles-metallic nanoparticles and magnetic nanoparticles [6].

Abbreviations: TiO_2NPs, Titanium dioxide nanoparticles; ZnO NPs, Zinc oxide nanoparticles; Ag NPs, Silver nanoparticles; CNT, Carbon nanotube; SEM, Scanning electron microscope; TEM, Transmission electron microscope; FSEM, Field emission scanning electron microscope; FTIR, Fourier transform infrared spectroscopy; PSA, Particle size analyzer; TGA, Thermo gravitmetric ananlysis; AFM, Atomic force microscopy.

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Titanium dioxide (TiO_2) is majorly consisting of two forms (crystalline and amorphous). In crystalline form, particles are arranged in a similar pattern having a regular arrangement. The most stable crystalline phase, which is rutile, is formed at a high temperature of 800 °C. While in the amorphous form, particles are arranged in a random manner that results in an irregular shape. Anatase is a type of amorphous form which is formed from the deposition of thin films at a high temperature of 350 °C. Titanium dioxide nanoparticles (TiO_2 NPs) are used widely because of features like cheap, high chemical stability, and strong oxidizing power. The oxygen vacancies present in the lattice of TiO_2 are due to oxygen separation and emission of electrons. The main limitations of using TiO_2 NPs are the electron-hole recombination and the small surface area [8]. TiO_2 is the most used photocatalyst to degrade antibiotics and other organic pollutants. Due to its high energy efficiency, high photocatalytic activity, low cost, non-toxic, and high stability. TiO_2 is N-type semiconductor, having an energy gap of 3.2 electron volts. Due to this reason, TiO_2 uses UV light rather than visible light [9].

Despite the drawbacks, TiO_2 NPs have a wide range of applications in cosmetics in lotions, creams, skin ointments, ultraviolet radiation, papers, food colourants, paints and inks. It has a wide range of applications in the electronic field, such as solar cells, various types of electrodes, and photovoltaic cells. TiO_2 NPs are also used in the catalysis food industry. Another application of TiO_2 NPs is biomedical, for example, in cancer therapy, drug delivery, cell imaging, and biosensors [6]. As the surface area of TiO_2 NPs is very small, the surface area must be increased for the electrical optical properties. The physical and chemical properties of TiO_2 NPs can be changed by particle size crystalline phase. In organic reactions, TiO_2 NPs are used as a catalyst that enhances reaction rate [7].

2. Nanoparticle synthesis

The synthesis of nanoparticles is done by various methods (Fig. 1). Either these nanoparticles follow “physical”, “chemical”, “biological” and “photochemical” approaches.

2.1. “Physical”, and “chemical” approach

In “Physical”, and “chemical” approach, nanoparticles are synthesized by using physical and chemical methods, and this falls under the category of the “top-down” approach. This happens by reducing the size of the desired nanoparticles. The commonly used methods are-

2.1.1. Nanolithography method

Nanolithography methods are used for making micron size products. They require costly equipment and are intensive. Nano-imprint lithography is a distinct type of lithography from traditional lithography. It’s a lot like template synthesis. A template is created first, and then a soft polymeric substance is stamped to make the pattern. Stamped material is created via the top-down process. Earlier, this method was used in the making of printed circuits and in the making of computers. But now, this technique is useful in latex spheres to create template matrices [10]. Nanolithography is used in the making of different types of circuits and matrices.

Photolithography focused ion, electron beam, nano-imprint, micro-contact printing are some of the methods that are used in printing. Nanolithographic techniques are used in the making of moulds through the process of moulding. It is basically achieved by creating a duplicate structure, shape and adding some features to the substrate of the mold. Nanolithography is also used in the deposition of thin films to increase the development of chips. These will, therefore, increase the efficiency and speed of the sensors used for the detection of gases that pollute the environment [11]. Nanolithography is used in the making of different sensors in various applied sectors, including telecommunication and electronics.

There are three ways of exposure to lithography. Contact printing is one of the methods in which the photo resisted coated wafer and photo mask are placed closely with each other. This increases the resolution patterns and can be used in detecting defective appliances. The second method is proximity printing which has 15 μm of the distance between the mask and resists coated wafer. The third method is projection printing, where the distance between the two is increased by several centimetres. Photolithography is used for making different types of films with the help of silicon material. X-ray lithography is used in the making of structures made of fabrics [12]. Lithography can be exposed using different techniques depending on the distance between the surface and the coated wafer.

The nano-UV imprint lithography technique involves the use of a substrate and a transparent mold. A UV curable monomer is attached to the substrate, and a transparent mold is placed on the monomer. The UV light rays, therefore, touch the upper surface of the mold. With this reaction, the monomer gets break into fragments. The transparent mold is detached from the structure, and the substrate containing the monomer is obtained. This process is easy for the production of nanoscale features. The feature of resolutions is extremely small, about 10 nm. This process is also cheap compared to other methods [13]. The UV lithography technique is a new method that can be used in breaking monomeric fragments.

2.1.2. Mechanical/Ball milling method for the formation of different nanoparticles

It is a low-cost approach for making nanoparticles from bulk. The simplest mechanical method is ball milling. Ball milling produces nanoparticles by attrition. Nanoparticles are formed inside a mechanical device which is known as a mill. It’s the process of transferring kinetic energy from the grinding medium to the substance being reduced. The collision process occurs when the particles are trapped between two colliding balls. A mass of powder particles covers the space. Consolidation and compaction, an industrial-scale process in which nanoparticles are “stitched back together,” are used to create material with improved characteristics [14]. Different types of nanoparticles made with the help of mechanical or ball milling methods are-

In the formation of zinc oxide nanoparticles (ZnO NPs), having 0.6–1

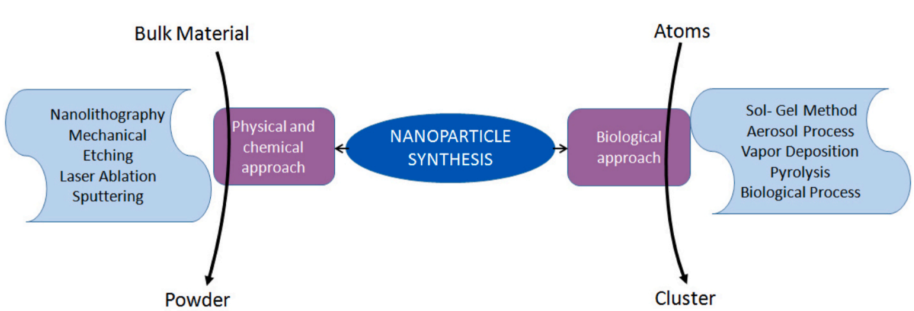

Fig. 1. An outline on methods used for synthesizing nanoparticles.

μm size of metallic powder, a ball miller of the horizontal oscillatory model is used. The time used for milling is nearly 2–50 h, depending on the size of nanoparticles [15]. In the formation of copper oxide nanoparticles, having a 60-μm size of metallic powder, a ball miller of ultrasonic wave assisted ball model is used. The time used for milling is nearly 256 rad/s, depending on the size of the nanoparticles [16]. A ball miller of the horizontal oscillatory model is used to form ZnO NPs, having a 500 nm size of metallic powder. The time used for milling is nearly 1 h, depending on the size of the nanoparticles [17].

Silver nanoparticles (Ag NPs) have 5–40 μm of metallic powder size and require 22 h of milling time to form 28 nm size NPs [18]. Titanium dioxide nanoparticles with 0.5-μm metallic powder require the Szegvan attritor ball miller method. The time used for milling is 10 h to produce 10–20 nm size of NPs [19].

2.1.3. Laser ablation by irradiation of metal to form different nanoparticles

Simple strategies for synthesizing nanoparticles from various solvents include laser ablation synthesis in solution. Irradiation of various metals submerged in solution with a laser beam condenses plasma, resulting in nanoparticles. The stable nanoparticle synthesized using the laser ablation method does not require any type of chemical or stabilizing agent [20]. Different types of nanoparticles are made with the help of Neodymium-doped Yttrium Aluminium Garnet (Nd-YAG) laser sources. Zinc oxide nanoparticles required an ablation duration of 40 min with a metallic zinc foil target material. 5–19 nm sizes of NPs are usually synthesized [20]. Copper oxide nanoparticles having a size of 8–10 nm requires 10 min of ablation time and have a target material of copper [21]. Copper oxide nanoparticles having a size of 9–26 nm require 10 min of ablation time and copper metal as a target material [22]. Gold nanoparticles required an ablation duration of 4 min with the target material of a pure gold plate. 9.5–15.12 nm sizes of nanoparticles are synthesized [23]. Using pure gold metal as a target material, nanoparticles of 23.5 nm can be made with an ablation duration of 10 min [24]. Using silver foil as target material, nanoparticles of 10 nm can be made using Nd-YAG laser source [25].

2.1.4. Sputtering by ejecting particles to form different nanoparticles

Sputtering is a phenomenon in which nanoparticles are deposited by ejecting particles from it. For the deposition of thin layered nanoparticles, annealing is the process that is done. The shape and size of nanoparticles depend on factors like the thickness of the layer, temperature, and the duration of the annealing process [26]. Different types of nanoparticles are synthesized using the process of sputtering. Zinc oxide and copper oxide nanoparticles use argon as the sputtering gas source for a time of 5 min, using copper as the target material. The size of nanoparticles synthesized is 16–20 nm [27,28]. Titanium dioxide nanoparticles are prepared using argon dioxide as the sputtering gas to synthesize 28–35 nm of nanoparticles [29]. Iron nanoparticles are formed using argon and helium as the sputtering gas. The target material is iron, and 10–20 nm of nanoparticles are synthesized using this process [30]. Gold nanoparticles use nitrogen, water and ethanol as the solution medium and argon as sputtering gas to target gold wire and synthesize 3.5 nm of gold nanoparticles [31]. Silver nanoparticles use metallic silver as the target material and argon gas as sputtering gas [32].

2.2. "Biological" approach

Nanoparticles are synthesized using biological methods, which fall under the "Bottom Up" approach. This happens through the oxidation and reduction process of atoms or molecules, which are considered small entities. Various types of plants extract to microorganisms synthesize nanoparticles using biological methods [33]. Biological synthesis is considered as an eco-friendly, cost-effective way of synthesizing nanoparticles. Plant parts such as the root, fruit, stem, seed, and leaf are used to make nanoparticles. The actual mechanism of plant-based nanoparticle creation is still unknown. Organic acids, proteins, vitamins, and secondary metabolites such as alkaloids, flavonoids, terpenoids, and polysaccharides have been shown to be responsible for the formation of diverse types of nanoparticles [6,34].

Green synthesis of nanoparticles using different biological metabolites can help overcome chemical and physical methods because there is little use of chemicals and other agents during biological synthesis. Green synthesis is the most skilful, normally flexible, biologically sound and practical technique for the synthesis of nanoparticles. The regular concentrates from various plants are being utilized as the reducing and capping agent in green science. These extracts favour the promising properties of the nanoparticles, like decreased secondary effects and high effectiveness. With the revolution in green innovation, different nanoparticles can be combined like Ag, Au, Cu, Zn, Pt, Pb and so forth. The biomass filtrate of algae, bacteria, yeast, fungi and plant extract is used in the synthesis of nanoparticles (Table 1). Different metallic nanoparticles like gold, silver, titanium, platinum, copper, magnetite, zirconium, silica and quantum dots can be synthesized using microorganisms like fungi, bacteria, actinomycetes, and viruses [43]. The nanoparticles formed using biosynthesis require different oxidation and reduction processes by proteins, sugars, and enzymes. Each microorganism combines different metallic ions with microbial synthesis nanoparticles [44].

The challenges that can make green synthesis difficult include scaling up nanoparticles produced from biological synthesis require more commercial studies. The method of fabricating nanoparticles requires more procedure and explanation. Optimization processes that need a green synthesis of nanoparticles require specific shapes and sizes so that they can support biological activities. In the green synthesis of nanoparticles, the correlation between chemical science, biological science and industrial engineering is used to produce nanoparticles that can be used for commercial activities [45]. The other ways for synthesizing nanoparticles under "Bottom-up" category are-

2.2.1. Sol-gel method of forming TiO_2 nanoparticles

There are many methods of synthesizing TiO_2 NPs like batch and semi-batch two-stage mix method or micro emulsion method. But the sol-gel method is the most simple and effective "bottom-up" approach. The word sol-gel is made of two words, sol and gel. The word sol means the colloidal solution formed in a continuous liquid, whereas the word gel means a solid molecule dispersed in a liquid. The chemical solution is treated as a catalyst. There are many precursors of titanium, including $TiCl_3$, $Ti(OCH(CH_3)_2)_4$ (TTIP), $TiCl_4$, and Ti(OBu) (Ramesh, 2013).

The advantages of using the sol-gel method are a high degree of purity of nanoparticles obtained, a versatile and easy method, and help in obtaining fine microstructure of nanoparticle by modulation of product. Using the process of condensation and hydrolysis of precursor material, TiO_2 NPs were obtained. In the solution of ethanol (EtOH) and distilled water (H_2O), titanium butoxide (TBT) precursor is added. The ratio used is TBT: H_2O: EtOH = 1:1.5:20.2. To dissolve the precursor, ethanol is added. Water is used for the hydrolysis process. Titanium butoxide and ethanol mixture are stirred using a magnetic stirrer for at least 15 min. Distilled water was added dropwise to the above solution, and the precipitate of nanoparticles was observed. The sol obtained is treated with different temperatures of heat at different time intervals. With each treatment, the temperature is increased. Using Fourier transform infrared spectroscopy, the chemical structure of TiO_2 NPs was observed [46,47].

2.2.2. Pyrolysis and flame spray pyrolysis in a high-pressure furnace

In the simple pyrolysis method, a precursor, which can be liquid or vapour, is burned with a flame. The precursor used in this process is placed in a high-pressure furnace so as to retrieve the nanoparticles. Flame spray pyrolysis is a type of commercial method used in the production of nanoparticles. It is a cost-effective method that is used to produce nanoparticles at a large scale. Using flame spray technique of pyrolysis, nanoparticles are produced at a rate of a few kilograms per

Table 1
Synthesis and characterization of nanoparticles obtained from different microbes.

Microbe	Characterization	Size (nm)	Shape	Type	References
Bacteria					
Bacillus subtilis	UV–vis spectrophotometer, SEM, X-ray diffraction (XRD), Atom force microscopy (AFM), FTIR	66–77	Spherical, oval	Gram +	[35]
Bacillus mycoides	UV–vis spectrophotometer, TEM, FTIR	40–60	Spherical	Gram +	[36]
Aeromonas hydrophilli	FTIR, XRD, AFM	28–54	Spherical	Gram -	[37]
Staphylococcus aureus	UV–vis spectrophotometer, SEM, XRD, Raman spectroscopy	20	Spherical	Gram +	[38]
Lactobacillus sp.	XRD, TEM	8–35	Spherical	Gram +	[39]
Lactobacillus johnsonii	UV–vis spectrophotometer, FTIR, TEM	4–9	Irregular	Gram +	[40]
Halomonas elongata	UV–vis spectrophotometer, XRD, FTIR, SEM, Dynamic light scattering (DLS)	20–25	Spherical	Gram -	[41]
Fungi					
Aspergillus flavus	UV–vis spectrophotometer, SEM, XRD	62–74	Spherical	–	[39]
Aspergillus niger	UV–vis spectrophotometer, SEM, XRD	200–800	Spherical	–	[42]
Saccharomyces cerevisiae	XRD, TEM	8–35	Spherical	–	[39]

hour. TiO_2 NPs are used in water treatment plants and photovoltaic cells, so they are mostly produced through flamed spray pyrolysis. In catalysis, photocatalytic conversion takes place by doping the iron or cobalt transition metals. This doping results in the reduction of bandgap and reduces the recombination rate of electron-hole pairs.

This method is used to produce crystallized nanoparticles. Annealing is done, and after annealing, the resulting nanoparticles are made in phase segregation at an iron content of about 3%. In another example, iron-doped titanium nanoparticles are formed using radiofrequency plasma with about 15–20% iron content. By flame spray pyrolysis, iron-doped titanium nanoparticles are produced using titanium precursor of tetra isopropoxide and iron precursor of iron naphthenate. Using this method, iron-doped titanium nanoparticles show an increase in production up to five times rather than using annealing methods. Due to its stability and solubility, ferrocene is a source used in the iron doping of titanium nanoparticles. In synthesizing carbon nanotubes, thin films, and metal oxides such as Fe_2O_3, ferrocene is used as a catalyst in the flame spray pyrolysis method [48]. This method is used to produce TiO_2 NPs to obtain spherical shape, crystalline, catalytic, and low dimensionality nanoparticles. This technique uses a resonant process between the absorption band of the precursor that is gaseous in form and the laser frequency emission. This combination leads to pyrolytic flame in the form of a chemical reaction. The CO_2 laser is used as radiation inside a chamber reaction at a wavelength of 10.6 μm.

The sample of titania used in laser pyrolysis consists of different morphological and varied dimensions samples. $TiCl_4$ is a titanium precursor to convert liquid $TiCl_4$ into vapours inside a bubbler using the carrier as synthetic air. This air and $TiCl_4$ mixture are put inside a mixer chamber containing C_2H_4 that absorbs laser radiation and increases energy transfer. These mixed gases are passed through the inner nozzle. In the pyrolytic flame, the nanoparticles are cooled rapidly to obtain the proper dimension. The resulting nanoparticles can be characterized by X-ray diffraction, microscope and spectroscopy [49].

2.2.3. Spinning process used to form nanofibres

Spinning is used to make nanoparticles through an instrument called a spinning disc reactor consisting of a rotating disc with a controllable temperature regulator. The reactor is filled with inert gases and nitrogen to prevent chemical reactions, and oxygen is continuously removed from the reactor. Inside the reactor or the chamber, precursors and liquids such as water are pumped [49]. Nanofibers are made using compressed air by solution blow spinning technique, and they can be easily scaled up and used to produce both composites and nanofibers. Titanium isopropoxide solution is used as a precursor. The primary source of TiO_2 nanofibers comes from this precursor solution and is prepared using 7% polyvinyl pyrrolidone mixed with ethanol and acetic acid solvent at a ratio of 3:1. The 10% mixture was heated at 60 °C, followed by vigorous mixing and is cooled down. The precursor made is fed using a nozzle into a feed tube of solution blow spinning apparatus at fixed air pressure and feed rate. The nanofiber collector is made of ethylene terephthalate for the membrane sample. This collector is used for accumulating composite nanofibers. These composite nanofibers are then fed for the step of calcination to produce TiO_2 nanofibers. Scanning electron microscope and X-ray diffraction techniques are used for the characterization of nanofibers [50]; Mehmet et al., 2020).

2.3. "Phytochemical" approach

The method of photoreduction is used in this approach. The inhibition of aggregation of particles takes place by the photoreduction of inert layers of titanium and silver nitrate. This approach uses highly advanced instruments and requires expensive equipment for experiments [51].

Different plant extracts contain phytochemicals such as amino acids, carbohydrates, phenolic acids and proteins. These extracts, therefore, exhibit different functions that are used in the fabrication of nanoparticles which are toxic-free and expensive chemicals. Phytochemical mediated synthesis involves the selection of solvent media used for extraction of phytochemicals, followed by the usage of plant extracts and the study of how many nanoparticles are grown and nucleated [52]. Flavonoids, terpenoids, carbohydrates and phenolic acids are effective biomolecules.

3. Different types of nanoparticles

Various types of nanoparticles have been synthesized for many applications. The broader classification of nanoparticles is given (Fig. 2). Different types of nanoparticles known so far are:

3.1. Natural nanoparticles

Are created in nature with the help of biological species or human activity. Natural resources can be used to create artificial surfaces with unique micro and nanoscale templates and features for technological applications. The nanomaterials obtained naturally are present throughout the atmosphere in the form of troposphere, in the lithosphere in the form of rocks, soil, and lava, in the hydrosphere inside oceans, lakes or rivers and in the biosphere in the form of microbes and humans.

3.2. Synthetic nanoparticles

Synthetic nanoparticles are created with the help of mechanical grinding, engine exhaust, and smoke, as well as physical, chemical, biological, and hybrid processes. These nanomaterials are also known as engineered nanoparticles. The manufacturing of engineered nanoparticles has increased, and the consumers' usage of these manufactured products has increased. The challenges behind these particles made are they don't rely upon the existing knowledge of the manufacturer rather. Many environmental behaviours are studied before manufacturing in bulk. Many varied sources are used to produce synthetic or engineered nanoparticles [53].

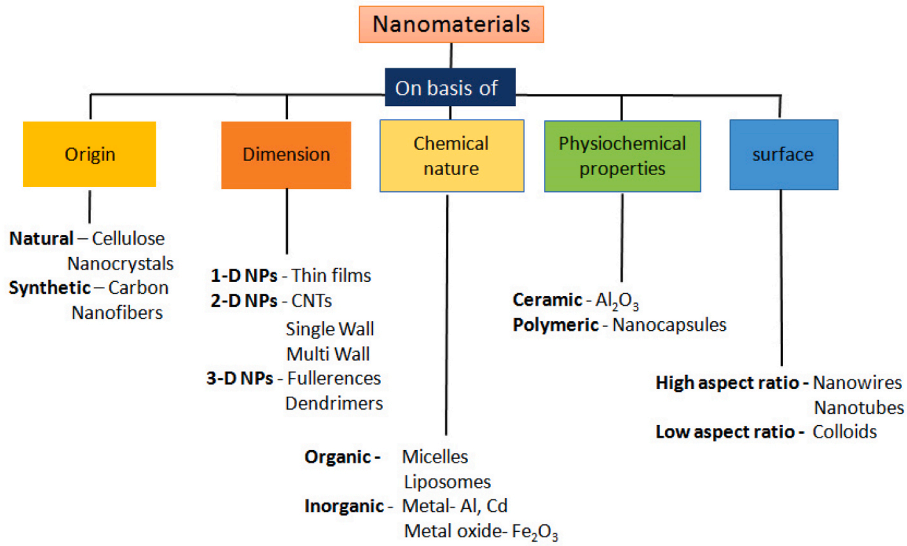

Fig. 2. Broader classification of nanoparticles on the basis of origin, dimension, chemical nature, physiochemical properties and surface with examples.

3.2.1. *Zero dimensional nanoparticles*

Are crystalline structures made up of hundreds to thousands of atoms that range in size from 2 to 100 nm. Nanoparticles have been used in manufacturing different products. With respect to that, there are two types of nanoparticles:

3.2.2. *Engineered nanoparticles*

Are materials manufactured for industrial purposes and constitute different organic and inorganic elements. These manufactured nanoparticles are used widely in biomedical devices, electronic devices, and the food processing industries. The nanoparticles used in pharmaceuticals and drug industries have increased by over 17% each year.

3.2.3. *Incidental air-bone nanoparticles*

These have a diameter of fewer than 100 nm. The incidental nanoparticles are ultrafine and present mostly in indoor air.

3.2.4. *One-dimensional nanoparticles*

For many years, one-dimensional systems like thin films and fabricated surfaces have been used in electronics, electrical, chemistry, and engineering. Nowadays, widely used solar cells, catalysis, thin films (sizes 1–100 nm), and monolayers. Information storage systems, fibre-optic systems, chemical and biological sensors, magneto-optic and optical devices are all examples of applications for thin films [54]. One dimensional nanoparticle has a nanoscale dimension for one direction but is equivalent for all directions. In manufacturing sensors, one-dimensional nanoparticles like nanofilms and nanowires are used. Nanofibers are larger in diameter but are not visible to naked eyes. The size ranges from 50 to 300 nm. Nanofibers are biochemically and electrostatically aligned in nature. On the other hand, nanowires are mostly used in the making of lasers, solar cells, high sensitivity sensors and nanophotonics.

3.2.5. *Two-dimensional nanoparticles*

Are a group of nanoparticles where two dimensions in the order of magnitude are greater than the nanometer range of the third dimension. These are plate-like in shape, and manufacturing is not much advance. Examples include surface coating, thin films, and surface coating. The structural bulk materials are improved and are kept unchanged to improve the properties like wear resistance, corrosion resistance, and friction. Carbon nanotubes (CNTs) are elongated tubular structures with 1–2 nm diameter. A CNT can be classified as semiconducting or metallic based on diameter. CNT has a structure that looks like a graphite sheet rolling on itself. CNTs are further classified as single-walled (SWCNTs) and multi-walled (MWCNTs). SWCNTs are made up of a single rolled sheet. The smallest diameter of single-walled nanotubes is 0.7 nm. Multiple rolled sheets make up MWCNTs. They have a minimum diameter of 100 nm. A graphene nano foil with a honeycomb carbon lattice is coiled into a hollow cylinder to make nanotubes. Carbon tubes range in length from a few micrometres to many millimetres [14].

3.2.6. *Three-dimensional nanoparticles*

3-dimensional nanoparticles have three dimensions on the nanoscale and possess a nanocrystalline structure. These are composed of nanosize crystals made of different orientations. They are further classified as-

3.2.7. *Fullerenes*

C_{60} is found in fullerenes, spherical cages containing 28 to more than 100 carbon atoms. This hollow ball looks similar to a soccer ball and is made up of interconnecting carbon pentagons and hexagons. Fullerenes are a type of substance with unusual physical characteristics. Due to the presence of lubricants, these molecules do not react with one another.

3.2.8. *Dendrimers*

Dendrimers are a new type of polymer with a controlled structure and have dimensions of nanometers. Dendrimers used in drug delivery and imaging consist of a diameter ranging from 10 to 100 nm and contain many functional groups on their surface, making them suitable for drug delivery. They are considered the building blocks for the large-scale synthesis of organic and inorganic nanostructures with dimensions ranging from 1 to 100 nm [55].

3.3. *Organic nanoparticles*

Organic nanoparticles are solid particles usually made of polymeric and lipids compounds. The size varies from 10 nm to 1 μm. The nanoparticles obtained from organic sources are usually water-soluble. Some nanoparticles, like micelles and liposomes, have a hollow core. They are known as nano-capsules and are sensitive to thermal and electromagnetic radiation such as heat and light [56], because of their distinct properties, they are considered an alternative for drug delivery.

There are some methods for preparing organic nanoparticles. They are-

a) Nano- precipitation- organic compounds are directly precipitated without the process of emulsification. The solvent displacement mechanism is, therefore, used in the preparation of precipitates of nanoparticles. The end result leads to the formation of emulsified micelle polymers confined in nature.

b) Through emulsification-this process initiates with the formation of nano-droplets of a particular size and shape. These nano droplets are further solubilized. The formed nanoparticles are further formed through polymerization and gelation techniques [57]. The result leads to the formation of surfactants.

The organic nanoparticles exclude any carbon or inorganic-based compounds. They have a special formation of non-covalent interactions that are weak in nature. These interactions lead to forming a particular design of molecules that are therefore used in transforming organic nanoparticles into specific shapes and structures [58]. These could be either liposomes, micelles or dendrimers.

3.4. Inorganic nanoparticles

Metal-based nanoparticles are synthesized from metals with a size range of some nanometers. They use destructive or constructive processes. Almost all metals can be used to synthesize nanoparticles. Some of them are-aluminium (Al), cadmium (Cd), cobalt (Co), copper (Cu), gold (Au), iron (Fe), lead (Pb), silver (Ag), and zinc (Zn), are the most widely employed metals for nanoparticle synthesis [34]. The size of metallic nanoparticles depends on the reduction of particle size in nanometer. Also, the bandgap of the structures of electronic products is changed to the electronic level by the appearance of the atoms on the surface. When the nanometer size is decreased, the atoms present on the surface will become more active. This is due to the distance between unsaturated sites and atomic coordinates. This active surface area has a wide range of applications in the adsorption and catalysis processes [59].

Metal oxide-based nanoparticles are synthesized to change the characteristic properties of metal-based nanoparticles. Aluminium oxide (Al_2O_3), cerium oxide (CeO_2), iron oxide (Fe_2O_3), magnetite (Fe_3O_4), silicon dioxide (SiO_2), titanium oxide (TiO_2), and zinc oxide (ZnO) are the most typically metal oxides produced [34]. In several applications like catalysis, semiconductors and sensors, metal oxide nanoparticles are used due to changes in the surface properties directly related to the bandgap energy of metal oxide nanoparticles. They are biocompatible and can be modified by doping metal ions and fatty acids. For example-when the modification of Al_2O_3 is done with a fatty acid, the nanoparticle gets precipitated in water solution due to the hydrophobic interaction of fatty acid with the surface of Al_2O_3 [59].

3.5. Green approach (conventional or biological methods)

The synthesis of TiO_2 NPs using a biological process is through various types of microorganisms, including bacteria, actinomycetes, yeast, fungi and algae. Apart from microbes, various types of plant extracts are also used. The cell-free extract or the tissue of the whole organism can be used for TiO_2 NPs synthesis. Synthetic techniques for the combination of TiO_2 NPs have been distinguished as harmful to the climate. The blend includes high temperature and tension, which prompts impediments in the large-scale manufacturing of TiO_2. It uses reducing agents that are derived from natural sources, and this can also be used for the amalgamation of numerous metallic mixtures. Additionally, the utilization of plants, their waste materials, natural product concentrate and microorganisms used in the blend chops down the use of harmful and costly synthetic substances.

Additionally, it tends to be used for the practical mass-scale creation of TiO_2 NPs. Thusly, green techniques for synthesis are imperative to deliver stable, proper estimated and dispersible nanoparticles with low energy utilization. Green synthesis is considered an eco-friendly approach for the synthesis of TiO_2 NPs. In green synthesis, cellular extracts of algae, fungi, bacteria and plants are used. Due to non-volatility and non-toxicity, the aqueous biological extract is used as the media to synthesize nanoparticles. The extract consists of a mixture of carbohydrates, polymers, vitamins and other surfactants. This mixture enhances the dispersity of the nanoparticles dispersed in it [60].

3.5.1. Green synthesis using plant extracts

Green synthesis is considered to be an eco-friendly and sustainable approach. Various plant parts and their extracts are used. The green synthesis procedure is an easy process to produce nanoparticles. Using green synthesis, large-scale production of nanoparticles is possible with overall low costs and energy requirements. Highly toxic chemicals are used in various physical and chemical syntheses, so the green synthesis of nanoparticles is a good approach (Jagpreet et al., 2018).

The plant contains different carbohydrates, enzymes, proteins, and alkaloids involved in synthesizing nanoparticles. Green synthesis mostly uses extracts from leaves due to its high metabolites [61]. The nanoparticles prepared from biological sources show good results in antimicrobial humidity sensors compared to those synthesized using chemical or physical methods. TiO_2 NPs obtained from biological sources are more used in large-scale industries. TiO_2 NPs were synthesized using pomegranate peel to disinfect the water sources without causing environmental or water pollution. Plant synthesis of nanoparticles is much more efficient and obtains a higher yield than microbial synthesis. Plants have special compounds known as metabolites and biochemicals that are used as stabilizing and reducing agents in the synthesis of nanoparticles.

3.5.2. Intracellular synthesis

Intracellular synthesis is a type of synthesis that involves the use of cellular enzymes and takes place inside plant tissue cells. The nanoparticles can be recovered by destroying the cell wall of the plant cell. Extracellular synthesis is a type of synthesis that involves the use of plant extract as a raw material. Phytochemical synthesis is a type of synthesis that involves the usage of phytochemicals for the synthesis of nanoparticles. The flavonoids and phytochemicals stabilize and reduce agents [62,63].

Specific plant parts are used in the synthesis of TiO_2 NPs. These plants consist of different phytoconstituents like terpenoids, flavones, phenolic compounds, alkaloids, steroids and tannins. Different sizes and shapes of TiO_2 NPs were synthesized using different plant extracts. Some of them are cubic in shape. Others are spherical and oval in shape.

4. Nanoparticle characterization techniques

Several techniques have been used to characterize the synthesized nanoparticles. In several cases, size, crystal structure, elemental composition and varieties can be evaluated by more than one technique. Details about various methods of characterization of different plant-derived TiO_2 NPs are presented in Table 2.

4.1. Fourier transform spectroscopy

It is a spectroscopy technique that involves molecules for the analyses of functional groups of chemicals with a region between 400 and 4000 per centimeter. Special FTIR tools find different biomolecules for capping and stabilizing the synthesized nanoparticles. The working principle of Fourier transform spectroscopy works by examining electromagnetic radiation and is sent to an interferometer. One then, at that point, gauges the optical power at the result of the interferometer as a component of the arm length difference, using a photodetector. The arm length difference is typically controlled by precisely moving a mirror over some distance. If the optical input to the interferometer were monochromatic, a sinusoidal oscillation of the detected power and the time of that oscillation would be the optical frequency. If the light obtained is polychromatic, the recorded interferogram will be a superposition of different frequency parts.

Table 2
Details about various methods of characterization of different plant derived Titanium dioxide nanoparticles.

Plant names (family)	Part of plant used	Characterization	Phyto-constituents	Size of Titanium oxide (nm)	Shape of Titanium oxide nano- particles	References
Nyctanthes arbor-tristis (Oelaceae)	Leaves	Scanning electron microscope (SEM), X-ray diffraction (XRD), particle size analyzer (PSA)	Terpenoids, flavones, ketones, aldehyde amides	100–150	Cubic	[64]
Psidium guajava (Myrtaceae)	Leaves	FTIR, XRD, FESEM	Guavanoic acid	32.58	Spherical	[65]
Azadirachta indica (Meliaceae)	Leaves	SEM, TEM, FTIR	Terpenoids, flavonoids	TEM –15-50; SEM- 25–87	Spherical	[66]
Trigonellafoenum –graceum (Fabaceae)	Leaves	FTIR, XRD, UV-vis, HR- TEM, HR- SEM	Volatile oils, phenolic compounds, alkaloids	25	Spherical shaped polydisperse nanoparticles	[67]
Mentha arvensis (Lamiaceae)	Leaves	FTIR UV–visible absorbance spectroscopy, SEM, XRD	Saponins, Aalkaloids, flavonoids, phenol,terpenoids, steroids, carbohydrate, proteins	20–70	Spherical	[68]
Allium eriophyllum (Alliaceae)	Leaves	XRD, UV–visible absorbance spectroscopy, SEM, TEM	Neophytadiene, 3 beta- stigmast-5-en-3-ol	22.8	Spherical	[69]
Eclipta prostrata (Asteraceae)	Leaves	XRD, FTIR	Flavonoids,triterpenoids,beta-amyrin, stigmasterol	36–68 average size-49.5	Micro-spheres	[102]
Sesbania grandiflora (Fabaceae)	Leaves	Scanning electron microscope with energy persive X- ray spectroscopy (SEM- EDX), FTIR, UV-vis spectroscopy	Alkynes, alkanes,secondary alcohols, flavonoids	160–220	Spherical, diamond shapes	[70]
Aloe barbadensis (Asphodelaceae)	Leaves	UV–vis spectroscopy, FTIR	Terpenoids, flavonoids, proteins	20–50	Spherical	[71]
Kniphofia foliosa (*Asphodelaceae*)	Roots	Thermo gravitmetric analysis (TGA/ DTA), FTIR, TEM, XRD, UV–vis spectroscopy, FTIR	Anthraquinones, phenylanthraquinones	8–10	Spherical	[72]
Strychnos spinosa (Loganiaceae)	Leaves	UV–vis spectroscopy, FTIR, XRD, SEM	Flavonoids, tannins, steroids, alkaloids, saponins, glycosides	40	Spherical	[73]
Blighia sapida (Sapindaceae)	Leaves	UV–vis spectroscopy, SEM, XRD, FTIR	Flavonoids, tannins, steroids, alkaloids, saponins, glycosides	50	Spherical	[73]
Artemisia haussknechtii (Compositae)	Leaves	Energy dispersive X ray spectroscopy (EDX), FESEM, AFM	Flavonoids, phenols	5–10	Spherical	[74]
Curcuma longa (Zingiberaceae)	Rhizome	X-ray diffraction, SEM, UV-visible spectroscopy	Volatile oils, curcuminioids, demethoxycurcumin	80–110	Spherical	[75]
Jatropha curcas (Euphorbiaceae)	Leaves	Field emission scanning electron microscopy (FESEM), FTIR. X- ray energy dispersive spectroscopy (EDS)	Polyphenols, alkaloids, antioxidants, terpenoids, steroids, tannins, flavonoids	10–20	Spherical	[76]
Echinacea purpurea (Asteraceae)	Leaves	UV–vis spectroscopy, total reflection X-Ray fluorescence analysis (TXRF),SEM	Alkamides, polysacchrides, cichroic acid	120	Spherical	[77]
Ageratina altissima (Asteraceae)	Leaves	XRD, FTIR, FESEM, UV-vis spectroscopy	Alkaloids, tremetone	60–100	Spherical	[78]
Vigna unguiculata (Fabaceae)	Seeds	FTIR, SEM	Flavonoids, glycosides, alkaloids	12–15	Oval shape	[79]
Moringa oleifera (Moringaceae)	Leaves	XRD, UV–vis spectroscopy	Terpenoids, flavones, ketones, aldehyde amides	12.22	Spherical	[80]
Cassia fistula (Fabaceae)	Leaves	UV–vis spectroscopy, XRD, AFM, SEM, TGA	Bioflavonoids,triflavonoids, sennoside A,chrysophanol	-	Spherical	[7]

4.2. UV–vis spectroscopy

UV-vis spectroscopy is based on the adsorption mechanism of spectroscopy. The Principle of UV–visible spectroscopy depends on the retention of ultraviolet light or visible light by chemical compounds, which creates distinct spectra. At the point when matter absorbs ultraviolet radiation, the electrons present in it go through excitation. This makes them bounce from a ground state to an energized state. It is essential to note that the distinction in the energies of the ground state and the energized state of the electron is dependably equivalent to how much ultraviolet or visible radiation is consumed by it. This mechanism works under UV–visible spectrum at 200–800 nm wavelength. Different metallic nanoparticles work on different wavelengths, ranging from 2 to 100 nm. For the characterization of nanoparticles, 250–400 nm of wavelength are commonly used. A graph between absorbance and wavelength is generated to see the UV–vis spectrum of the synthesized nanoparticles.

4.3. Scanning electron microscope

This technique uses electrons to form a micro-image, and as a result, that image can be seen through a microscope. The electron source and lens are placed at the top of the microscopic column. These electrons will thus emit a beam that activates the emission of primary and secondary electrons. The electronic beam interacts with the specimen to produce signals, which will give the specimen topographic information. With this technique, the morphology of synthesized nanoparticles can be observed, including shape, size and distribution. The purity of synthesized nanoparticles can also be observed in the microscope.

4.4. X-ray diffraction

The crystal and atomic structure of nanoparticles are observed through this technique. X-rays are created in a cathode ray tube by warming the filament to deliver electrons, speeding up the electrons towards an objective by applying a voltage. At the point when electrons have adequate energy to dislodge internal shell electrons of the objective material, X-ray spectra are delivered. These spectra comprise a few parts. These X-rays are collimated and coordinated onto the sample. As the sample and detector rotate, the force of the reflected X-rays is recorded. X-ray diffraction is most commonly used to form synthesized nanoparticles and analyze the crystal structure. The size of obtained crystalline nanoparticles can also be calculated using this characterization method.

4.5. Atomic force microscopy (AFM)

The surface area and topography of nanoparticles synthesized can be observed using atomic force microscopy. Atomic force microscopy works on the standard of surface detecting using a very sharp tip on a probe made of silicon. The mechanism is that this nanoscale tip is connected to a little cantilever which frames a spring. As the tip contacts the surface, the cantilever twists, and the bending is identified utilizing a laser diode and a split photodetector. This bending is characteristic of the tip-sample interaction force. A scanning electron microscope can also be used for this purpose. Still, in atomic force microscopy, 3-D images of the nanoparticles can be seen where the volume and height of nanoparticles can be observed.

4.6. Dynamic light scattering (DLS)

Dynamic light scattering (DLS) is a tool used for the particle size distribution of nanoparticles in many industries and laboratories. To find the average diameter of nanoparticles, dispersion light intensity fluctuates. Due to its speed and accuracy, nanoparticles are detected using this technique. Many cancer biomarkers and metallic particles are detected using this method [81].

The TiO_2 NPs synthesized from the root extract of the *Kniphofia foliosa* plant are considered to show antibacterial activity as this extract gives excess electrons to TiO_2. As a result, superoxide radicals are formed, producing reactive oxygen species (ROS) in the bacterial cell. This ROS breaks the cell membrane of Gram-positive and Gram-negative bacteria strains. TiO_2 NPs obtained from *Curcuma longa* extract are used in reducing the fungal growth and pathogen attack of *Fusarium graminearum*. The nanoparticles show agglomeration, which benefits the reduction of fungal species. TiO_2 NPs synthesized from the leaves of *Jatropha curcas* are used in the treatment of tannery wastewater that contains different inorganic and organic pollutants and is toxic to living forms. In a bioreactor, the tannery wastewater sample and TiO_2 NPs are agitated for the process of photocatalytic degradation.

5. Biosynthesis by microorganisms

Various microorganisms such as bacteria, fungi, algae, and yeasts make gold, silver, iron, lead and titanium nanoparticles. Making titanium nanoparticles through the use of microbes is an effective, environment-friendly, and cheap way of producing nanoparticles [82]. This process of synthesizing nanoparticles using microorganisms is also advantageous due to certain properties of selective adsorption of metallic ions, ionic strength, temperature and pH. The availability of biosorption ability is also an advantage of this process. Many large quantities of nanoparticles can be synthesized using this technique (Fig. 3). Aqueous forms of microorganisms with metal cations can be converted to metallic forms of nanoparticles. Different varieties of nanoparticles of varying shapes and sizes can be obtained [83].

5.1. Biosynthesis by bacteria

Bacteria are the most proficient in synthesis as they help in the reduction of metallic ions to metallic nanoparticles. As in the case of plants discussed above, bacteria have two types of synthesis intracellular and extracellular. The bacterial system uses the extracellular mode of synthesizing metallic nanoparticles due to easy genetic transfer and economical use. The most cost-effective, easy and reproducible bacteria are *Aeromonas hydrophila*, *Lactobacillus* sp., and *Bacillus subtilis*. For example, from *Halomonoas elongate*, TiO_2 nanoparticles are synthesized. From this, antibacterial activity is checked in Petri plates. This ROS formation occurs when the bacterium's cell wall is damaged and TiO_2 nanoparticles are synthesized.

TiO_2 is a cost-effective biosynthetic approach that uses *Acinetobacter baumannii* bacteria for improving photocatalytic dye treatment with 78 per cent efficacy in a short period. Bacteria such as *A. hydrophila*, *Lactobacillus* sp., and *B. subtilis* were found to produce TiO_2 in a simple, easy, repeatable, and cost-effective manner. The use makes TiO_2 NPs of expensive chemicals, high pressure or temperature. *Planomicrobium* sp. may be used to make TiO_2 NPs that are environmentally friendly and less expensive [84]. In biomedical research and electrical sensors, magnetotactic bacteria containing magnetosomes that are a part of intracellular organelles containing greigite and magnetite crystals covered with the lipid bilayer are used in the fabrication of magnetic nanoparticles. These nanoparticles produced are of uniform size and crystalline structure. The disadvantage of using magnetotactic bacteria is the difficulty of culturing them at a large scale for the production of nanoparticles. In recent research, the genes responsible for the formation of magnetosomes were transferred from magnetotactic bacteria to non-magnetotactic bacteria for the synthesis of nanomagnets using

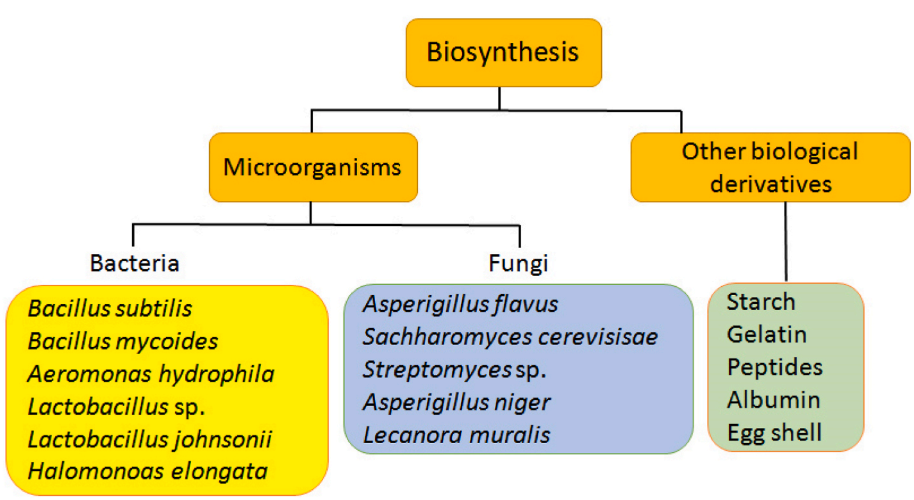

Fig. 3. Biosynthesis of nanoparticles by different types of microorganisms (bacteria and fungi) and using biological derivatives.

magnetosomes. For example–to a simple bacterium named *Rhodospirillium rubrum,* the genes of a magnetotactic bacteria named *Magnetospirillium gryphiswaldense* were transferred successfully (Hind et al., 2018).

5.2. Biosynthesis by fungi

Fungi are considered an ideal microbe for synthesizing nanoparticles. Some unique features include easy handling, large surface area and simple downstream processing. The nanoparticles synthesized by fungi reduce NADH in the body of a fungus that acts as a reducing agent and mediates fungal proteins that stabilize the synthesized nanoparticles. By reducing enzymes intracellularly or extracellularly, fungi produce various metallic nanoparticles. The reproduction rate of fungi is faster [85,86].

Furthermore, compared to bacterial extract, the fungal extract has received a lot of attention due to its benefits of easy extraction, large-scale manufacturing, ecological feasibility, and enhanced surface area of synthesized TiO_2. *Aspergillus flavus* is used and considered a biodegradable green synthesis method of TiO_2 NPs. The fungus used in downstream processing *Saccharomyces cerevisiae* is an environmentally friendly, more reproducible form of fungus most prominently used to synthesize TiO_2 NPs [84].

5.3. Biosynthesis by other biological derivatives

With the use of microorganisms, plant extracts titanium nanoparticles are synthesized. But different biological derivatives can also be used to synthesize the nanoparticles. It mainly includes:

5.3.1. Cellulose fibers

Cellulose and its components are widely used to make lubricants, thickeners, and composites. Without the change in morphology, TiO_2 NPs can be synthesized from cellulose. Nano-dimensional cellulose is used to produce different metallic electrical wires. The nanocomposites obtained from cellulose are also used in making biosensors. Cellulose nanocrystals are less expensive than other nanoparticles and are considered stiff and strong than other metals.

5.3.2. Starch

Green synthesizes of TiO_2 NPs can be done in an eco-friendly manner using starch as a biological source. Starch is considered to have good catalytic properties. Potato starch is easily available and cheap; it is readily used in the synthesis of TiO_2 NPs through the sol-gel procedure. The precursor of titanium is hydrolyzed for the formation of the nanoparticles.

5.3.3. Eggshells

The eggshells contain calcium carbonate. The process of grinding and calcination is used. The so-formed eggshell powder is used to produce efficient nanoparticles. This biological source is used for nanoparticles that require high porosity and surface area. The amount of eggshell helps the overall nanoparticle formation process and is thus considered a convenient approach.

5.3.4. Egg albumen

Out of the total weight of the egg, 60% weight is egg albumen, and it contains different types of proteins. Ovalbumin, lysozyme, ovo-transferrin, ovo-mucoid and ovo-mucin are the proteins present in egg albumen. The denaturation of these globular proteins results in the formation of a matrix for TiO_2 so that the nanoparticles formed can be absorbed easily. The matrix is slowly decomposed, and the resulting small TiO_2 NPs are obtained with high crystallinity. It is considered a gelling agent which is used to synthesize nanoparticles more effectively.

5.3.5. Rice straw

Rice cultivation results in the formation of residues, mainly straw and husk. The stalk of the rice plant left is known as rice straw. The precursor of TiO_2 is used with different concentrations of rice straw powder. The obtained solution is heated to form a gel. Further, the gel is dried, and the nanoparticles are formed. It is a green method by which TiO_2 NPs can be synthesized.

5.3.6. Gelatin

Gelatin provides high surface density and is mostly obtained from collagen. The titanium precursor and gelatin are mixed to form a solution, and the solution is dried and calcinated to form crystals. The pyrolysis process obtained TiO_2 microspheres with improved hydrogen capacity [84,87].

6. Applications of TiO_2 nanoparticles

Titanium dioxide nanoparticles have diverse utilities and applications (Fig. 4). These nanoparticles play a vital role in food packaging and preparation of other food products, cosmetic industry and personal care products, and photovoltaic cells for converting solar energy into electrical energy.

6.1. Photovoltaic cells

The present green energy available today is solar power, as the sun is a sustainable form of energy. Among all the available sources of solar cells, dye-sensitized solar cells are mostly used. In these types of cells, TiO_2 NPs are used for the conversion of solar energy into electrical energy because of the semiconductor behaviour. TiO_2 nanofilms are attached to the conductive glass plate of solar cells with different dyes.

ZnO and TiO_2 are known to show good photocatalytic activity under UV light. Among other metal oxides, TiO_2 is used due to the large bandgap of semiconductors and the high efficiency of photo-conversion. This makes TiO_2 a material used in photovoltaics photocatalysts. The samples of TiO_2 NPs were analyzed under UV-A radiation with a wavelength of 365 nm. The dyes used in the process are methylene orange and methylene blue, and the suspension formed is magnetically stirred over 150 min to the photocatalytic effect. Also, different types of photoanodes are prepared using dye-sensitized solar cells. The photodegradation efficiency of TiO_2 NPs was observed under UV light for both the dyes methylene blue and methylene orange [88].

6.2. Food products

TiO_2 is used for the whiteness of sauces, cheese and creams, and they are also widely used in chewing gum and other beverages. The size of food-grade TiO_2 has been decreased, and the ratio of nanoparticles is increased. These nanoparticles act as photocatalysts in food packaging and can be used with good antibacterial activity [89,90]. TiO_2 nanoparticles are used as a coating material in food packaging film. The *E. coli* present on the surface were inactivated, and UV, fluorescent light and the antimicrobial effect were seen. The film coated with nanoparticles had less growth of *E. coli,* proving that this film can be used as an antibacterial for packaging food material.

6.3. In cosmetics

TiO_2 is a white pigment used in many consumer care products like toothpaste, creams, and ointments. Due to their slippery taste, they are used in various cosmetics. TiO_2 is used as an inorganic UV absorber in sunscreen products applied on the skin that prevents irritation of the skin. The products contain different sizes, shapes and crystals of TiO_2 NPs. Specifically, spherical-shaped nanoparticles are used in sunscreen products. In some cases, silica-coated TiO_2 NPs are used in sunscreen products to increase efficacy (Ozioma et al., 2020).

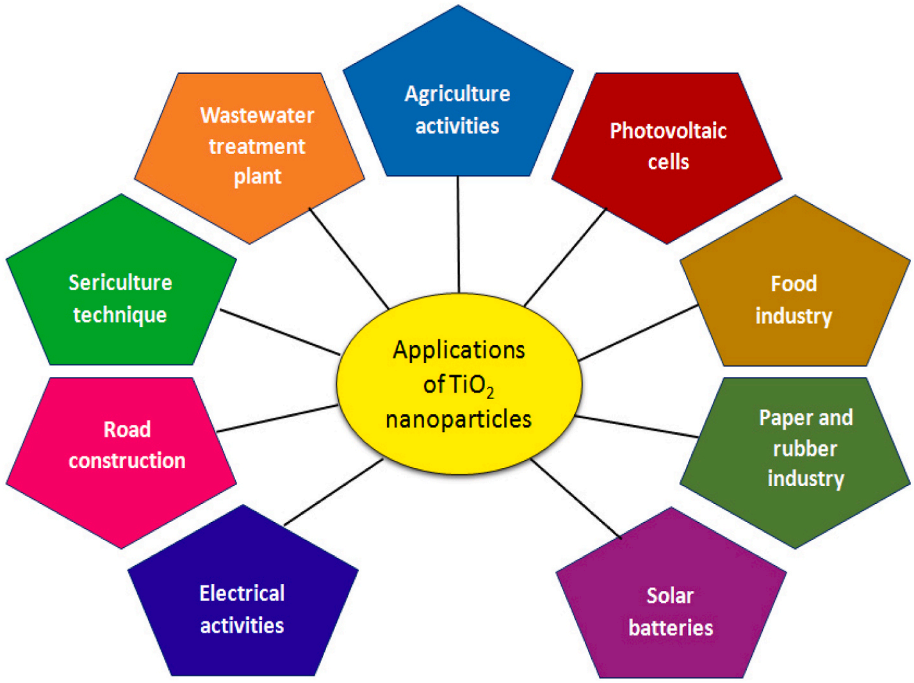

Fig. 4. Applications of Titanium oxide nanoparticles.

6.4. Environmental air purification

Air pollutants like nitrates and other compounds threaten the health of humans and animals. TiO_2 NPs are used for improving the purification of air. Titanium mesh filters are used to remove the smoke generated by cigarette smoking. TiO_2, when triggered by the rays of the sun, helps in the conversion of air pollutants to the least toxic carbon dioxide.

6.5. In sericulture

TiO_2 NPs, when fed to *Bombyx mori,* result in the development of reproductive organs and genes. The efficiency of silkworms can be increased, and thus reproduction could be done subtly [91].

6.6. Wastewater treatment plants

TiO_2 NPs extract heavy metals in the water through a solid phase extraction mechanism. There are various dyes like Rhodamine R present in the surface or groundwater. These dyes are degraded using a mixture of ultraviolet radiation with TiO_2 NPs. These particles also help remove wastewater pesticides and other toxic compounds [92].

6.7. In cancer treatment

TiO_2 NPs help induce cytotoxicity to the tumour cells, which will help minimize the cancerous activities among all patients of all age groups [93].

6.8. Efficient drug delivery system

TiO_2 NPs are used widely in drug delivery systems**.** The particles take the shape of various capsules, tablets and other shapes. The nanoparticles and the drug combined perform the drug's controlled release activity. Valproic acid and daunorubicin are drugs that use TiO_2 NPs as carriers. The advantage of using these combined drugs is that they show prolonged drug exposure, increase therapeutic efficiency, and help reduce toxicity.

6.9. Cell observation and imaging

Cell imaging methods help in the early diagnosis of the disease with the help of molecular biomarkers. Cell imaging is also used to know the treatment efficiency of the disease. TiO_2 NPs are used in combination with fluorescent dyes and labelled markers under the process of fluorescent analysis.

6.10. Electrochemical biosensors

TiO_2 NPs have high conductivity and more stability. The sensors using these nanoparticles are developed with the help of nano-sheets sol-gel matrices. These matrices help in assembling various antibodies and proteins. These biosensors help in analyzing biological molecules such as tumours. The size and shape of these nanoparticles help in determining efficacy in biosensors. Electrochemical methods generally do TiO_2-based biosensing of target analytes. Electrochemical biosensors are typically based on amperometric and potentiometric recognition. When the biological components like antibodies, catalysts, aptamers or cells tie to or respond with target particles, the conductive properties of a medium between terminals change, bringing about a discernible current sign, a perceivable potential or charge gathering.

6.11. In genetic engineering applications

There are some traditional methods of diagnosing the mutated DNA and other genes, but they are not as effective. Genetic engineering uses recombination of DNA where insertion, deletion, and other gene alterations occur. TiO_2–DNA nano-composites help in the photocatalytic capacity of TiO_2. The linkage of molecular markers with TiO_2 is through dopamine [94].

6.12. Antibacterial application in orthopedic implants

Osteomyelitis is a type of bone infection caused by bacteria and fungus. TiO_2 NPs doped with Ag help in providing antibacterial properties. In orthopedic fractures, metal pins are attached, and these metal pins are susceptible to various types of bacteria. So, TiO_2 NPs coating is done so that these bacteria do not grow. Like other organ substitutions, the drawn-out progress of dental embeds, to a great extent, relies upon quick recuperating with joining into the jaw bone and surface. Among a couple of characteristics that define a dental embed framework, the surface treatment, topography, and main embed are the principal boundaries for both short-and long-haul durability of dental implants. TiO_2 NPs coatings on embedded surfaces not only deliver drugs to the target but also diminish organ poisonousness. TiO_2 have a high capacity to be applied to the Ti inserts since they increase biocompatibility and the surface region of the implant [95].

6.13. Bioactivities: TiO_2 nanoparticles

6.13.1. Antibacterial activity

In various sectors like pharmaceuticals, food and food packaging, and water disinfection, the attack of various microorganisms leads to the manufacturing of antimicrobial substances. Because of the vast antibacterial activities of many metals and metallic oxide compounds, antibacterial substances take place. The most common type used is TiO_2 NPs because of their semiconducting material, large surface area, low cost, non-toxic nature and easy control. The antimicrobial property of TiO_2 NPs is used due to their excellent photocatalytic activity and more chemical stability (Pina et al., 2016).

The removal of various microorganisms from water surfaces could be done effectively with the help of Ag/TiO_2 nanoparticles. The two strains of microorganisms used are- *Escherichia coli* C600 (Gram-negative bacterium), and *Saccharomyces cerevisiae* W303a (fungus unicellular yeast). Both the strains were cultured in potato dextrose and Luria- Bertani agar media (Pina et al., 2016).

TiO_2 NPs, when exposed to ultraviolet radiation, become activated against pathogenic bacteria. There are significant antimicrobial activities when the metal oxide nanoparticles attach to the microbial DNA and proteins. The photocatalytic effect of antibacterial TiO_2 NPs is that photons with energy equal to the band gap excite the electrons when exposed to light. These excited electrons react with the oxygen, and the oxygen breaks the cell wall of microorganisms (Naggar et al., 2016).

6.13.2. Anticancer activity

An anticancer drug named doxorubicin is effective in treating various types of cancers. In the TiO_2 nanoparticles, doxorubicin was loaded inside, forming a nanocomposite of doxorubicin-loaded titanium dioxide (DOX- TiO_2) NPs. This nanocomposite is used as a drug delivery system (Fig. 5). TiO_2 NPs act as a drug carrier for loading an anticancer drug named doxorubicin. A color change from red to pink during the loading process is observed, and this color change is due to the binding of doxorubicin and TiO_2 NPs to form a complex of DOX- TiO_2. Besides color change, the zeta potential is also used to find the binding of doxorubicin and TiO_2 NPs. The zeta potential value decreased when loading the drug inside TiO_2 NPs, which gives a signal of effective binding [96].

6.13.3. Anti-diabetic activity

Diabetes is a disorder where blood glucose level increases. Various medicinal plants are used due to their phytochemicals that have anti-diabetic properties. These phytochemicals have various functionalities, which lead to plant-based anti-diabetic medicines. Nanoparticles are used due to their fast release to target drugs and nano-sized particles [97].

6.13.4. Antimicrobial wound dressing

The nanoparticles have multiple uses in therapeutics. The bactericidal effect of nanoparticles can be seen with the release of reactive oxygen species (ROS) due to the direct contact of nanoparticles with the bacterial cell wall. On the bacterial surface, lipopolysaccharides are present in the Gram-negative bacterial cell wall and peptidoglycan on the Gram-positive cell wall. Due to the hydrophobic interactions, positively charged nanoparticles bonded to the cell surface lead to the formation of pores. The nanoparticles bind inside the bacterial cell, affect the metabolic pathways, and induce ROS formation. The nanoparticles majorly used are Ag, TiO_2, and ZnO. The nanoparticles inhibit the growth of bacteria and are used in wound dressings [98].

Chitosan material is used with TiO_2 nanoparticles for effective wound dressing. While the addition of chitosan, TiO_2 NPs decrease the size of the scaffold produced. Another advantage is that the addition of these nanoparticles leads to a decrease in swelling. The use of a chitosan-pectin mixture with TiO_2 NPs led to the increased tensile strength of the dressing material used for the wound (Table 3). The wound's healing is faster than other dressing materials used. In antimicrobial testing, there was also a decrease in the bacterial count [100].

7. Conclusion

The interest in green synthesis is due to its advantages of being innocuous to the environment. Different parts of plants are used for synthesis purposes, and their characterization using various techniques helps form TiO_2 NPs of varied shapes and sizes. The green synthesis of TiO_2 NPs can be used in biomedical, and the delivery of drugs and antibiotics in wastewater of pharmaceutical industries can be degraded using nanoparticles. Because of the less use of precursors, TiO_2 is widely used to remove microbes from water surfaces. The nanoparticles inhibit

Table 3
Effect of various substances used with titanium dioxide for antimicrobial wound dressing.

Substance used with TiO_2	Formed product	Results	References
Chitosan + TiO_2 NPs	Composite	Wound healing is fast, more antimicrobial activity	[99]
Chitosan + pectin + TiO_2 NPs	Film layer	Fast healing, more antimicrobial activity, tensile strength increased	[101]
Chitosan + TiO_2 NPs	Scaffold	Decrease swelling, decrease of pore size	[100]

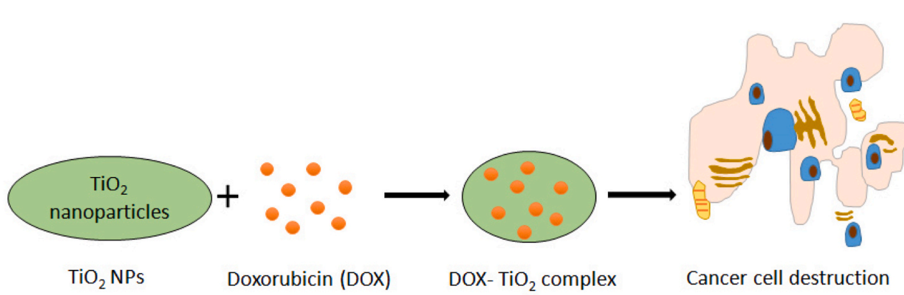

Fig. 5. Combination of TiO_2 nanoparticles with doxorubicin drug in the treatment of cancer.

the growth of microbes and are used in wound dressing. Moreover, nanoparticles synthesized using the green routes are more effective than chemical or physical means.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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