DOI: 10.7860/JCDR/2024/69854.19399

Review Article

Dentistry Section

# A Comprehensive Review of Synthesis, Properties and Applications of $TiO_2$ and ZnO Nanoparticles

SUJA JOSEPH[1], DEEPAK NALLASWAMY[2], SHANMUGAM RAJESHKUMAR[3], PRADEEP DATHAN[4], LEON JOSE[5]




## ABSTRACT

Nanotechnology is an advancing field of science with the potential to improve the quality of life through its applications in the field of nanomedicine. It refers to the technology of precisely manipulating atoms and molecules and developing new materials with nanoscale dimensions. Nanoparticles (NPs) typically range in size from 1-100 nm. Nanoparticles play a major role in the prevention of infections, so they can be utilised as nanocarriers with antimicrobial therapeutic actions. This article is a literature review on different methods of synthesis, properties, and biomedical applications of Titanium Dioxide ($TiO_2$) and Zinc oxide (ZnO) nanoparticles. Since nanoparticles can be biomodified by cost-effective methods, the use and applications of NPs will increase in the future. The unique properties of nanoparticles make them useful in various fields of science such as materials, engineering, electronics, food science, and biomedicine. Due to their advantages, nanotechnology has gained the attention of researchers, especially for its promising applications in the healthcare system for better diagnosis and treatment.


**Keywords:** Bioimaging, Green synthesis, Nanobiomedicine, Nanotechnology, Titanium dioxide, Zinc oxide

## INTRODUCTION

Nanomaterials have been defined as natural, man-made, or incidental materials that comprise particles as agglomerates or masses or in an unconstrained state where 50% or a higher number of the particles display one or more outer dimensions within the range of 1-100 nm [1]. A nanoparticle is the most essential component in the manufacture of a nanostructure [2]. According to the British Standards Institution, a nanoparticle exhibits and confines its diameter and all its fields in the nanoscale [3]. The term 'nano' refers to the Greek prefix meaning very small or dwarf. Nanoscience is a conjunction of materials science, physics, and biology, which includes the synthesis of materials at atomic and molecular scales, whereas nanotechnology deals with the capacity to observe, quantify, assemble, control, and synthesise matter confined to the nanometer scale [4]. They are also denoted as "zero-dimensional" nanomaterials [5]. Nanotechnology is defined as the application of scientific knowledge to manipulate and control matter at the nanoscale [6]. The International System of Units (SI) uses the term nanoparticle to designate a reduction factor of $10^9$ times. It covers structures whose size is above molecular dimensions and below macroscopic ones (generally >1 nm and <100 nm) [7]. The American physicist Richard Feynman, considered the father of nanotechnology, introduced the concept in 1959 during an annual meeting of the American Physical Society at the California Institute of Technology in his lecture titled "There's Plenty of Room at the Bottom." He explained the method of synthesis by the manipulation of atoms, which became a roadmap for new development [4]. The term nanotechnology was first defined by Norio Taniguchi of the Tokyo Science University at the international conference on industrial production in 1974 to describe the processing of materials with nanometer accuracy and the creation of nanosized particles [4]. The present review describes the different methods of synthesis, properties, and biomedical applications of $TiO_2$ and ZnO nanoparticles.

## DISCUSSION

Nanoparticles can be classified based on the following criteria [8]:

1) **Origin:** Natural and anthropogenic.
2) **Size:** Ranging from 1-10 nm, between 10-100 nm.
3) **Chemical composition:** Organic substances, inorganic materials, and elements of the living kingdom.
4) **Dimensions of existence [7]:**
    a) One-dimensional nanoparticles: The system includes thin films ranging from 1-100 nm or monolayers, which find their application in information storage systems, the production of fiber-optic systems, chemical and biological sensors, magneto-optic and optical devices.
    b) Two-dimensional nanoparticles: Carbon Nanotubes (CNTs) are carbon atoms existing in hexagonal networks, appearing as a layer of graphite rolled up into a cylinder ranging about 1 nm in diameter and 100 nm in length. They can be single-walled or multi-walled.
    c) Three-dimensional nanoparticles:
    i) Fullerenes (Carbon 60): Spherical cage-like structures with a large number of carbon atoms, containing C60. They exist like a hollow soccer ball made up of interconnected carbon hexagons and pentagons.
    ii) Dendrimers: A novel category of controlled-structure polymers presenting dimensions ranging from 10 to 100 nm in diameter along with numerous functional groups on their surface.
    iii) Quantum Dots (QDs): These are tiny devices that contain a single droplet of free electrons made up of colloidal semiconductor nanocrystals of 2 to 10 nm in diameter. Widely used QDs include Cadmium Telluride (CdTe), Cadmium Selenide (CdSe), Indium Phosphide (InP), and Indium Arsenide (InAs).
5) **Based on carbon composition [9]:**
    a) Organic nanoparticles: Include dendrimers, micelles, liposomes, and ferritin. They are non toxic, biodegradable, and exhibit sensitivity to electromagnetic and thermal radiation.
    b) Inorganic nanoparticles: Particles that are not composed of carbon atoms constitute inorganic nanoparticles. They include metal and metal oxide-based nanoparticles.

i) Metal-based.

ii) For the synthesis of nanoparticles, commonly used metals are Cobalt (Co), Aluminium (Al), Cadmium (Cd), Zinc (Zn), etc.

iii) Metal oxides based.

Commonly synthesised metal oxides include Cerium Oxide ($CeO_2$), Aluminium Oxide ($Al_2O_3$), Iron Oxide ($Fe_2O_3$), Silicon Dioxide ($SiO_2$), Magnetite ($Fe_3O_4$), Titanium Oxide ($TiO_2$), Zinc Oxide (ZnO), etc.

c) Carbon-based: Nanoparticles made entirely of carbon atoms are referred to as carbon-based. They can be further categorised into graphene, Carbon Nanotubes (CNT), fullerenes, carbon nanofibres, carbon black, and occasionally activated carbon in nano size [9].

The major factors influencing nanoparticle synthesis include pressure, temperature, time, size and shape of the particle, pore size, and expenditure of preparation [10].

## Approaches in the Production of Nanoparticles

There are various approaches for the production of nanoparticles:

1) **Top-down approach:** This approach comprises the breaking down of bulky larger particles into particles of the nano range by the process of attrition process, milling, and electro-explosion wire techniques. Although the process is less time-consuming, it entails more energy consumption and is used in laboratory experimentation [9,10]. Methods employed in the top-down approach include physical and chemical vapour deposition, electron beam lithography, ion implantation, as well as X-ray lithography [10,11].

2) **Bottom-up approach:** This includes the diminishment of constituent materials to the very atomic level with multiple supplementary procedures leading to the growth of nanostructures. The physical forces acting on the nanostructure are utilised to pool the particles into a larger one during the assembling procedures [9]. The methodology focuses on the concept of molecular recognition or self-assembly, which refers to self-budding on more things of one's own kind from themselves. Scientists prefer the bottom-up approach because of its benefit of accurate control of particle size causing decent optical, electronic, and other related properties [11].

   Multiple methods employed in the bottom-up approach include hydrothermal synthesis, colloidal precipitation, sol-gel synthesis, organometallic, chemical route, and electrodeposition [10,11].

**Methods of synthesis of nanoparticles:**

**A. Physical methods [10]:**

1. **Mechanical method:** In the mechanical ball milling method, various forms of mills used include planetary, rod, vibratory, and tumbler. The container comprises steel or carbide hard balls. Nanocrystalline Co, Ag-F, etc., are manufactured by means of this method. The balls-to-material ratio is generally kept at 2:1. Inert gas or air is used to fill the container, and it is rotated at a very high speed around the central axis. The materials are hard-pressed between the walls of the balls and the container. In the procedure known as the melt-mixing process, molten metal streams are mixed at high velocity with turbulence to form nanoparticles.

2. **Pulse laser ablation:** Inside a vacuum chamber, the target sample is placed onto which the high-pulsed beam of laser is focused, and plasma is generated, which is formerly transmuted into a colloidal solution of nanoparticles.

3. **Pulsed wire discharge method:** The most widely used method for the synthesis of metal nanoparticles. Pulsated current is utilised to vaporise a metal wire to yield vapour, which is later cooled by the presence of ambient gas to process nanoparticles.

4. **Chemical vapour deposition:** Upon the substrate surface, a thin film of gaseous reactant is deposited at around 300-1200°C. Here a chemical reaction happens between gas and the heated substrate and combining gas, producing a thin film of the product on the substrate surface. The pressure of application ranges from 100-105 Pa.

5. **Laser pyrolysis:** Synthesis of nanoparticles using a laser beam is known as laser pyrolysis. An intense laser beam is used to disintegrate the mixture of gases.

6. **Ionised cluster beam deposition:** The arrangement comprises a source of evaporation, a beam of electrons to ionise the clusters, a nozzle providing expansion facility for the material, an arrangement to accelerate the clusters, and a substrate for nanoparticle deposition, all components stored in a suitable vacuum chamber. Through the action of an electronic beam, ionised collections are obtained.

**B) Chemical methods [10,11]:**

1. **Sol-gel Method:** This method includes various steps of condensation, hydrolysis, and thermal decomposition of metal alkoxides. The newly formed stable solution is termed as a sol. Through the process of hydrolysis or condensation, the gel is produced with remarkable viscosity.

2. **Sonochemical synthesis:** Pd-CuO nanohybrids have been effectively synthesised by sonochemical fusion with copper salt in the presence of palladium and water. The commercially used source is either palladium salts or pure metallic palladium (Pd).

3. **Co-precipitation method:** The method involves rapid diffusion of polymer-solvent into a non solvent polymer phase by mixing the polymer solution at the end. The interfacial tension at these two phases can yield nanoparticles.

4. **Inert gas condensation method:** Metals are placed inside a chamber filled with neon, argon, or helium, and the metal is vaporised. The gases start to cool in the presence of liquid nitrogen and form nanoparticles of 2-100 nm.

5. **Hydrothermal Synthesis:** One of the most commonly used methods in which a chemical reaction is initiated at temperatures ranging from room temperature to extreme levels for the synthesis of nanoparticles.

**C) Biological methods [10,11]:**

1. **Synthesis using microorganisms:** It involves either extracellular biosynthesis or intracellular biosynthesis making use of microbes capable of separating metal ions. Pseudomonas stutzeri Ag 295 is often found in silver mines, capable of collecting silver inside or outside the cell walls.

2. **Synthesis using plant extracts:** For the manufacture of gold nanoparticles, leaves of the geranium herb (Pelargonium graveolens) have been used. 1 mL 1 mmol aqueous solution of silver nitrate is combined with 5 mL of the plant extract for the same.

3. **Synthesis using algae:** Algae extract is prepared in an aqueous solvent or an organic solvent by heating or boiling it for a defined period. Algae solution and molar solutions of ionic metallic complexes are commonly incubated, either with continuous stirring or without stirring, for a defined duration under controlled conditions.

**Physicochemical properties of nanoparticles:**

a) **Mechanical properties:** Nanoparticles of non metallic materials are fragile and do not possess remarkable mechanical properties like plasticity, toughness, ductility, or elastic properties, whereas organic nanomaterials are flexible materials. The superior properties of nanoparticles are attributed to the diverse interaction forces between the nanoparticles and the contacting surface. The significant ones are electrostatic force, capillary forces, hydration forces, and van der Waals forces comprising Keesom force, Debye force, and London force [12].

b) **Thermal properties:** When the size of the nanoparticles decreases, the surface area to volume ratio increases hyperbolically. This higher surface-to-volume ratio allows a greater number of electrons for the transfer of heat compared to larger sizes. The superior thermal properties also result from micro convection, which occurs as a result of the Brownian motion of particles [12].

c) **Magnetic properties:** One of the notable size-dependent phenomena exhibited by nanoparticles is superparamagnetism, which is displayed in the presence of a magnetic field.

d) **Electronic and optical properties:** Metallic and semiconductor nanoparticles display certain characteristic properties like photoluminescence emission, linear absorption, and nonlinear optical properties related to the Localised Surface Plasmon Resonance (LSPR) effect and quantum confinement. Improved crystallinity and small size of biogenic nanoparticles render them superior features compared to chemical nanoparticles [12].

e) **Catalytic properties:** The application of nanoparticles, called nano-catalysis, is gaining more interest these days. When compared to bulk materials, nanoparticle catalysts show enhanced properties such as reactivity and selectivity [12].

**Synthesis of titanium oxide nanoparticles:** There are two methods of synthesising $TiO_2$ NPs.

**1) Sol-gel method [13,14]**

There are two methods of sol-gel preparation:

a) **Alcohol-based method:** Ti $(OC_2H_5)$, $Ti(OC_2H_7)_4$, and $Ti(OC_4H_9)_4$ are the major metal oxide precursors of titanium oxide nanoparticles. The metal-oxide bond in these alkoxides becomes highly polar and reactive because of the high electronegativity difference between titanium and oxygen. Addition of water leads to simultaneous hydrolysis and condensation reactions producing a gel [13].

b) **Aqueous-based process:** Precipitation and peptisation are the two major steps in the aqueous-based sol-gel process in the production of these nanoparticles. When a base is added, the inorganic metal salt rapidly hydrolyses to a gelatinous precipitate. The excess electrolyte is then washed-off. The process of the direct breakdown of a substance into colloidal particle size by the addition of a peptising agent is called peptisation [13].

2) **Hydrothermal method:** One of the suitable synthetic approaches to titanium nanoparticle manufacture is the hydrothermal method because of its several advantages like low production cost, controllability of reaction conditions, appropriate crystallisation temperature, being environmentally friendly, and low energy consumption.

Pure $TiO_2$ powder (Degussa P25, 98%) sized 25 nm, along with a crystalline structure of mixed anatase and Rutile (80:20), is used in this method. About 0.5g of titanium oxide powder is added to a 10M 40 mL NaOH aqueous solution, then stirred vigorously for half an hour. Later, this mixture can be transferred for hydrothermal treatment to a stainless steel autoclave lined with Teflon and kept at 200°C for 48 hours in a muffle furnace. Following the reaction, the white precipitate needs to be separated from the autoclave and cooled at room temperature, subsequently washed with 0.1 M HCl acid solution and deionised water. This process of acid wash should be continued until almost all the Na+ ions are removed. After removing sodium ions, the resultant white precipitate, after the centrifugation process, should be dried in an oven at 60°C and then calcined at 250°C for two hours [15].

**Properties of $TiO_2$ nanoparticles:** $TiO_2$ nanoparticles are well known for their chemically inactive nature, non toxicity, low cost, high refractive index, excellent antibacterial effects, corrosion resistance, and impressive microhardness [16]. They have impressive wear resistance, lightness, high strength, mechanical resistance, and electrical conductivity, low thermal diffusivity, and conductivity. They are white in colour and ductile in their pure form, so they can be readily customised to the required form and type [1]. Considering the non toxicity, the American Food and Drug Administration (FDA) has approved the incorporation of $TiO_2$ for use in drugs, human food, cosmetics, and food contact materials [1]. [Table/Fig-1] lists the medical applications of $TiO_2$ nanoparticles [17-19]. [Table/Fig-2] summarises the dental applications of $TiO_2$ nanoparticles [16,17,20-25]. Disadvantages are reported with titanium nanoparticles, like reduced interaction with surrounding tissue and bioactivity, which can be overcome by surface coating of this metal with biocompatible compounds [17,25].

**Synthesis of Zinc oxide nanoparticles:** The synthesis of zinc oxide nanoparticles can be categorised into conventional (physical, chemical, and biological methods) and non conventional (reactor-based) methods [26].

The synthesis of zinc oxide nanoparticles can be categorised as follows:

**1. Conventional**

a. **Physical methods:** Physical methods comprise arc plasma, thermal evaporation, physical vapour deposition, ultrasonic irradiation, and laser ablation.

| Medical applications | Characteristics |
|---|---|
| Photodynamic Therapy for cancer | TiO2, when exposed to UV light, undergoes photoexcitation and generates ROS, such as singlet oxygen, which has cytotoxic effects on cancer cells. **Selective treatment:** The ability to selectively activate $TiO_2$ in cancer cells allows for targeted therapy, minimising damage to surrounding healthy tissues. **Non invasive:** PDT is minimally invasive compared to traditional cancer treatments, offering a more targeted and localised approach [17,18]. |
| Targeted drug delivery | **Nanostructured reservoirs:** $TiO_2$ nanostructures can be employed as reservoirs for drug delivery systems. These nanostructures release drugs in a controlled manner, ensuring that therapeutic agents are delivered precisely where needed.<br>**Cancer and epilepsy:** Targeted drug delivery is especially valuable in cancer treatment, as well as in conditions like epilepsy, where localised drug release is beneficial [17-19]. |
| Cell imaging | **Antibody conjugation:** Mesoporous $TiO_2$ nanoparticles, modified with a specific antibody {Carcinoembryonic Antigen (CEA)} and a fluorescent molecule (Flavin mononucleotide; FMN), enable targeted detection of cancer cells.<br>**Minimally invasive imaging:** This technique allows for minimally invasive imaging of cancer cells, providing a non intrusive means of diagnosis [18]. |
| Biosensors for biological assay | **Electrochemical biosensors:** $TiO_2$ nanomaterials play a crucial role in the development of electrochemical biosensors for various applications such as disease diagnosis, environmental monitoring, drug discovery, food safety, and cell-capture assays.<br>**Enzyme immobilisation:** The morphology and structure of $TiO_2$ nanomaterials significantly influence the immobilisation of enzymes, thereby impacting the efficacy of biosensors [18]. |
| Genetic engineering | **Imaging tool:** $TiO_2$ serves as an excellent tool for genetic engineering, providing imaging capabilities for visualising genetic modifications. **Elimination of unwanted genes:** $TiO_2$ can be used for the elimination of unwanted genes and gene products, allowing for targeted genetic modifications in organisms [18]. |

**[Table/Fig-1]:** Medical applications of $TiO_2$ NPs [17-19].

| Applications in dentistry | Characteristics |
|---|---|
| Denture base resin | $TiO_2$ nanoparticles fill Polymethyl Methacrylate (PMMA) chain spaces, reducing porosity and increasing acrylic resin density. Silanisation of $TiO_2$ serves as a coupling agent, promoting interfacial adhesion between the polymer matrix and nanoparticles, enhancing cross-linking [17,20] The addition of 1% $TiO_2$ improves impact strength, while 5% increases micro-hardness [16]. Nanoparticles strengthen the interfacial bond with acrylic resin, resulting in improved mechanical properties [21]. |
| Denture adhesives | Titanium oxide nanoparticles in adhesives demonstrate similar water solubility, sorption, and biocompatibility as unaltered adhesives. Self-adhesive cements with these nanoparticles show superior quality. Typically, 5 to 10 wt.% of $TiO_2$ in dentin adhesives reduces the risk of cytotoxicity [22]. |
| Scaffolds in bone grafting | Nanostructured titanium dioxide ($TiO_2$) serves as a synthetic ceramic bone graft substitute due to its documented biocompatibility, superior tensile strength, high corrosion resistance, flexibility, stability, and cost-effectiveness [23]. Its high surface-to-volume ratio supports cell attachment and tissue regeneration, with increased porosity accelerating osteogenesis [24]. These qualities make titanium an ideal biomaterial for various applications, including prostheses, orthopaedic implants, and craniofacial repair, such as metal plates and meshes for fracture fixation and reconstruction procedures [1,23]. |
| Dental implants | Titanium's unique properties make it the preferred material for implants. Its nanotopography enhances cell function and osseointegration, with rough surfaces and increased free energy promoting osteoblast adhesion, maturation, and bone formation. Accelerated hydroxyapatite formation on the implant surface can occur from body fluids [17,24,25]. |

**[Table/Fig-2]:** Applications of $TiO_2$ NPs in dentistry [16,17,20-25].

- Arc plasma method: The most common method to synthesise nanoparticles is an electric arc discharge method using Zinc rod, dry air, and a carbon rod as the cathode.
- Thermal evaporation: Zinc oxide powder is mixed with graphite, a reducing agent, at a temperature of 1000-1100°C to produce ZnO nanostructures.
- Physical vapour deposition: ZnO nanowires are fabricated at a low temperature of 450°C, with an increase in diameter as the temperature rises.
- Ultrasonic evaporation: It is a natural method of fabricating nanoparticles in a solution phase operation without changing the character of the particles.
- Laser ablation: An effective method for fabricating nanoparticles using all types of materials by adjusting parameters of the laser such as duration, wavelength, temperature, etc.

b. **Chemical methods:** Chemical methods employ the precipitation method, hydrothermal method, and chemical vapour deposition technique [26-28].

- Precipitation method: A precursor solution of Zinc salt, like Zinc nitrate, is treated with a reagent, such as acid or base, under high temperature and pressure to form nanoparticles.
- Hydrothermal method: An aqueous solution of precursor chemicals is treated at high temperature and pressure to form nanoparticles.
- Chemical vapour deposition method: A transport agent, like graphite, is added to zinc and heated at high temperature, then cooled to form nanoparticles.

The solid-phase synthesis techniques involve mechano-chemical and mechanical ball milling methods. The liquid-phase techniques comprise laser ablation, exploding wire, solution reduction, and decomposition processes.

Gas phase processes include gas evaporation and spark discharge processes [29].

c. **Biological methods:** Biological methods are predominantly an eco-friendly approach, which utilise biochemical and biotechnology methods and extraction from plants, as well as animals [26,27,29].

Green synthesis of ZnO NPs is a simple extraction technique employed after cleaning appropriate plant parts like leaves, stem, fruits, flowers, roots, peels, etc., with water. Commonly involved plants are P hysterophorus, Solanum nigrum, Purnus domestica, etc., which are subjected to elution, filtration, and separation.

The resultant extract is either dried or used to react with a zinc precursor under diverse conditions of pH and temperature. The phytochemicals used include numerous bio-active compounds like polyphenols, saponins, and flavonoids, which chelate with the metal ion and also stabilise the NPs. The underlying mechanism in the production of ZnO NPs is the simultaneous reduction and oxidation of cationic zinc ion by the phytochemicals present in the extracts. Upon completing the reaction, the product is exposed to an annealing process to obtain ZnO NPs. The ZnO NPs produced by means of plant extract show higher photocatalytic, antimicrobial, and antioxidant properties compared to the NPs synthesised by fungi, bacteria, algae, and yeast [27,30].

The common sources of microbes used in the production of zinc oxide nanoparticles are Aeromonas hydrophila, Aspergillus aeneus, Pichia kudriavzevi, etc. The procedure involves selecting microbes and providing optimal conditions for cell growth. ZnO NPs are thoroughly washed with distilled water and ethanol, subsequently dried at 60°C overnight to obtain a white powder of ZnO NPs [29,31].

2. **Non conventional (reactor-based) methods:** Microfluidic reactor-based method: It is a simple method to synthesise materials on the benchtop. Compared to the conventional method, this method utilises fewer chemicals and causes less damage to the environment and health [26,27].

**Properties of ZnO NPs:** The method of preparation and the morphology determine the physical and chemical properties of zinc oxide nanoparticles [32]. Zinc oxide nanoparticles appear as a water-insoluble white powder [30]. The distinctive physical and chemical properties include a high electrochemical coupling coefficient, remarkable chemical stability, paramagnetic characteristics, extensive radiation absorption capability, and exceptional photostability.

The absence of a center of symmetry in wurtzite, along with high electromechanical coupling, results in strong pyroelectric and piezoelectric properties, making it applicable for piezoelectric sensors and mechanical actuators [27,29]. The energy band of 3.37 eV and bonding energy of 60 meV render it remarkable chemical, electrical, and thermal stability. Because of its acceptable optical, electrical, and photocatalytic properties, zinc oxide nanoparticles are applied in solar cells, photocatalysis, and chemical sensors. The low toxicity and high UV absorption enable its use in the biomedical field [32].

Summary of the medical applications of ZnO nanoparticles has been given in [Table/Fig-3] [28,32-35]. The dental applications of ZnO nanoparticles has been summarised in [Table/Fig-4] [35-38].

Research in the field of nanotechnology enables us to synthesise new materials by direct control of matter at the nanoscale. Good control over the synthetic parameters will definitely help in manipulating the physicochemical properties of ZnO and $TiO_2$ NPs, thus utilising them in various branches of science such as material science, engineering, biology, biomedicine, and dentistry.

## CONCLUSION(S)

The $TiO_2$ and ZnO NPs exhibit most of the properties displayed by an ideal oral biomaterial; hence, they are employed as antimicrobial agents, prosthetic material, and in various biomedical fields.

| Medical applications | Characteristics |
|---|---|
| Photodynamic cancer therapy | Positively charged ZnO NPs at physiological pH induces selective cytotoxicity against cell proliferation at negatively charged tumour sites [28]. |
| Bioimaging | ZnO nanoparticles, with fluorescence properties and excitonic emission, serve as bioimaging agents for cancer cells and bacteria when functionalised with specific receptor molecules. Enhancing surface modification to improve stability, fluorescence duration, and circulation can enhance their effectiveness in bioimaging applications [28]. |
| Drug delivery | ZnO NPs exhibit an isoelectric pH of-9.5, indicating a net positive charge, facilitating protein absorption through electrostatic interactions, particularly valuable in drug delivery. Their extensive surface area allows for enhanced surface functionalisation. The smaller size of ZnO NPs contributes to prolonged drug retention and decreased drug load. These nanoparticles are employed in nanocarrier systems for drug delivery, where they dissolve in acid vesicles, releasing the drug from the carrier [28]. |
| Gene delivery | ZnONps is modified to form proper vector which acts as a vehicle for effective delivery of Deoxyribonucleic Acid (DNA) into the cells for gene therapy [28]. |
| Biosensors | Used for biosensor applications due to ease of fabrication, high polymorphic nature, optical properties and high electron mobility [28]. |
| Nuerobiological applications | ZnONPs find applications as sensors for detecting neurotransmitters (e.g., acetylcholine and dopamine) in the brain, aiding in anxiety and depression studies. Additionally, they contribute to nerve guidance channels, promoting central nervous system repair by stimulating neurons and reducing astrocyte cell adhesion after injuries [28]. |
| Electronic applications | The low synthesis cost, transparency, wide band gap, crystalline nature and strong electron accepting characteristics makes them useful as a charge storage layer for electronic applications. ZnO NPs have been utilised for developing nanofloating gate memory devices and non volatile resistive switching memory device that can be used in various gadgets [28]. |
| Antibacterial activity | Enhanced antibacterial activity, particularly against gram-positive bacteria.<br>a) Their impact includes accumulation in bacterial cells, triggering zinc ion release, leading to membrane collapse, protein damage, and disruption of DNA replication [28,33,34].<br>b) Additionally, metal ion release and reactive oxygen species generation contribute to cell wall damage, increased membrane permeability, and internalisation of nanoparticles [32].<br>c) The photocatalytic activity and Reactive Oxygen Species (ROS) generation inhibit bacterial biofilm formation, increasing antibiotic susceptibility. The nanoparticles' pronounced antimicrobial activity is attributed to their high surface-to-volume ratio and surface abrasiveness [31-33]. |
| Theranostics | ZnO QDs used in photodynamic therapeutics and as diagnostic agents due to its photoluminescence property [35]. |
| Antibiotic therapeutics | Effective in maintaining the immune system against infection. ZnO 40% ointment and ZnO 10% cream. Used in medical devices, adhesives, endo dressing, cosmeceuticals and food packing due to antimicrobial properties [35]. |
| Healthcare | Protection against acne and blemishes in dermatological applications UV light protection as ZnO waxes, sunscreen lotion, cosmetic applications [35]. |

**[Table/Fig-3]:** Medical applications of ZnO NPs [28,32-35].

| | |
|---|---|
| Dental restorations and root canal therapy | Incorporation of ZnONPs into commercial composite resin could result in biofilm inhibition and increased flexural strength of the material. Because of its high polarity, these nanosize materials play a significant role in the regenerative endodontic field and disinfection of the root canal space [35,36]. |
| Dental implants | The application of mixtures of ZnO NPs and nano hydroxyapatite on to the surface of glass substrates as innovative coating materials results in decreased bacterial adhesion and enhanced support for the osteoblast to grow onto the surface coated dental implants. It is reported to have substantial antimicrobial activity and implant-bone bonding characteristics [36].<br>Coating agent on the surface of orthopaedic and dental implants and prevents biofilm formation [36]. |
| Orthodontics | ZnO NPs are used as coating for orthodontic stainless steel wires to reduce the friction between and orthodontic wires and brackets. Applications including impregnation of nanoparticles in nano-adhesives, composites and GICs because of increased antibacterial activity and reduce dimineralisation and improve remineralisation [37]. |
| Oral hygiene products | ZnO is widely used in oral hygiene products, especially dentifrices and mouth rinses, owing to its antimicrobial and antibacterial properties against Streptococcus mutans and periodontal pathogens [36,37]. |
| Denture base | Incorporation of metallic NPs such as ZnO NPs into PMMA can improve the physical, mechanical, antifungal and microbicidal properties of the resin. Incorporation of Ag and Zno NPs could significantly decrease the population of Candida albicans on the surface of PMMA base [36,37].<br>Addition of ZnO NPs at 2-2.5% by weight into silicone could improve the mechanical properties, including hardness and tensile strength [34]. Nanofillers in denture adhesive improve the bond. Incorporation of ZnO nanoparticle to the PMMA denture base increases the flexural strength of denture base [38]. |

**[Table/Fig-4]:** Application of ZnO NPs in dentistry [35-38].

Nanoparticles play a vital role in modern medicine, from diagnosis to treatment planning. Biomedical applications of these nanoparticles have gained more interest among researchers and motivated them to do more research in this emerging frontier.

## REFERENCES


[1] Mansoor A, Khurshid Z, Khan MT, Mansoor E, Butt FA, Jamal A, et al. Medical and dental applications of titania nanoparticles: An overview. Nanomaterials. 2022;12(20):3670. Available from: https://doi.org/10.3390/nano12203670.

[2] Horikoshi S, Serpone N. Introduction to nanoparticles. Microwaves in nanoparticle synthesis: Fundamentals and Applications. 2013:1-24.

[3] Tyagi S, Pandey VK. Nanoparticles: An overview of preparation. Research & Reviews: Journal of Pharmaceutics and Nanotechnology. 2016;4(2):12.

[4] Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The history of nanoscience and nanotechnology: From chemical-physical applications to nanomedicine. Molecules. 2019;25(1):112. Doi: 10.3390/molecules25010112.

[5] Murthy SK. Nanoparticles in modern medicine: State of the art and future challenges. Int J Nanomedicine. 2007;2(2):129-41.

[6] Sudha PN, Sangeetha K, Vijayalakshmi K, Barhoum A. Nanomaterials history, classification, unique properties, production and market. In. Makhlouf ASH and Barhoum A, Eds, Emerging applications of nanoparticles and architecture nanostructures. 2018;341-84. Available from: https://doi.org/10.1016/B978-0-323-51254-1.00012-9.

[7] Pal SL, Jana U, Manna PK, Mohanta GP, Pal P, Manavalan R. Nanoparticle: An overview of preparation and characterization. J Appl Pharm Sci 2011;1(6):228-34.

[8] Strambeanu N, Demetrovici L, Dragos D, Lungu M. Nanoparticles: Definition, classification and general physical properties. In: Lungu M, Neculae A, Bunoiu M, Biris C. (eds) Nanoparticles' promises and risks. Springer, Cham. 2015:3-8. Available from: https://doi.org/10.1007/978-3-319-11728-7_1.

[9] Ealia SA, Saravanakumar MP. A review on the classification, characterisation, synthesis of nanoparticles and their application. IOP conference Series Materials Science and Engineering. 2017;263(3):04-14. Doi: 10.1088/1757-899X/263/3/032019.

[10] Kandasamy S, Prema RS. Methods of synthesis of nano particles and its applications. J Chem Pharm Res. 2015;7(3):278-85.

[11] Heera P, Shanmugam S. Nanoparticle characterization and application: An overview. Int J Curr Microbiol App Sci. 2015;4(8):379-86.

[12] Joudeh N, Linke D. Nanoparticle classification, physicochemical properties, characterization, and applications: A comprehensive review for biologists. J Nanobiotechnology. 2022;20(1):262. Doi: 10.1186/s12951-022-01477-8.

[13] Ullattil SG, Periyat P. Sol-gel synthesis of titanium dioxide. In: Pillai S, Hehir S. (eds) Sol-Gel materials for energy, environment and electronic applications. Advances in Sol-Gel Derived Materials and Technologies. Springer, Cham. 2017:271-83. Available from: https://doi.org/10.1007/978-3-319-50144-4_9.

[14] AL-Hamdani AH, Abdalgaffar AN, AL-Shaikh Hussin SH, Al-Amiery AA. Synthesis of titanium oxide nanoparticle complemented with optical properties. ARPN (JEAS). 2016;11(15):9335-40.

[15] Keerthana BG, Solaiyammal T, Muniyappan S, Murugakoothan P. Hydrothermal synthesis and characterization of $TiO_2$ nanostructures prepared using different solvents. Materials Letters. 2018;220:20-23. Doi: 10.1016/j.matlet.2018.02.119.

[16] Ahmed MA, El-Shennawy M, Althomali YM, Omar AA. Effect of titanium dioxide nano particles incorporation on mechanical and physical properties on two different types of acrylic resin denture base. World Journal of Nano Science and Engineering. 2016;6(3):111-19. Doi:10.4236/wjnse.2016.63011.

[17] Kulkarni M, Mazare A, Gangadze E, Perntkova S, Kral-Iglic V, Milosevi I, et al. Titanium nanostructures for biomedical applications. Nanotechnology. 2015;26(6):062002. Doi: 10.1088/0957-4484/26/6/062002.

[18] Yin ZF, Wu L, Yng HG, Su YH. Recent progress in biomedical applications of titanium dioxide. Phys Chem Chem Phys. 2013;15:4844-58. Doi: 10.1039/c3cp43938k.

[19] Dathan PC, Nallaswamy D, Rajeshkumar S, Joseph S, Ismail S, Ajithan L, et al. A review on biomedical applications of Titanium Dioxide. Trends in Biomaterials and Artificial Organs. 2023;37(1):49-54. Available from: htpps://www. Researchgate. net/publications/ 373926218.

[20] Tandra E, Wahyuningtyas E, Sugiatno E. The effect of nanoparticles TiO2 on the flexural strength of acrylic resin denture plate. Padjadjaran Journal of Dentistry. 2018;30(1):35-40. Doi: 10.24198/pjd.vol30no1.16110.

[21] Abdulridha WA, Almusawi RA, Al-Jubouri OM, Wally ZJ, Zidan S, Haider J, et al. Studying the effect of adding Titanium Dioxide (TiO2) nanoparticles on the compressive strength of chemical and heat-activated acrylic denture base resins. Advances in Materials and Processing Technologies. 2022;8(1):1058-70. Doi: 10.1080/2374068X.2020.1838135.

[22] Al-Saleh S, Alateeq A, Alshaya AH, Al-Qahtani AS, Tulbah HI, Binhasan M, et al. Influence of $TiO_2$ and $ZrO_2$ nanoparticles on adhesive bond strength and viscosity of dentin polymer: A physical and chemical evaluation. Polymers (Basel). 2021;13(21):3794. Available from: https://doi.org/10.3390/polym13213794.

[23] Joseph S, Nallaswamy D, Rajeshkumar S, Dathan PC, Ismail S, Rasheed N. An insight into the structure, properties and applications of titanium, the magic metal. Trends in Biomaterials and Artificial Organs. 2022;36(2):139-46.

[24] Ibrahim MH, Afifi OH, Ghoneim SM, Youssef DA. The effect of titanium dioxide nanoparticles with or without platelet rich plasma on the healing of mandibular bony defects in rabbits. Tanta Dent J. 2022;19(2):68-76. Doi: 10.4103/tdj.tdj_29_21.

[25] Jafari S, Mahyad B, Hashemzadeh H, Janfaza S, Gholikhani T, Tayebi L. Biomedical applications of $TiO_2$ nanostructures: Recent advances. Int J Nanomedicine. 2020;15:3447-70. Doi: 10.2147/IJN.S249441.

[26] Zhou X-Q, Hayat Z, Zhang D-D, Li M-Y, Hu S, Wu Q, et al. Zinc oxide nanoparticles synthesis, characterization, modification and applications in food and agriculture. Processes. 2023;11(4)1193. Available from: https://doi.org/10.3390/pr11041193.

[27] Deka B, Baruah C, Babu A, Kalita P. Biological and non-conventional synthesis of Zinc Oxide Nanoparticles (ZnO-NPs): Their potential applications. J Nanotechnol Nanomaterials. 2022;3(2):79-89.

[28] Sruthi S, Ashtami J, Mohanan PV. Biomedical application and hidden toxicity of Zinc oxide nanoparticles. Materials Today Chemistry. 2018;10:175-86.

[29] Parihar V, Raja M, Paulose R. A brief review of structural, electrical and electrochemical properties of zinc oxide nanoparticles. Rev. Adv. Mater. Sci. 2018;53(2):119-30.

[30] Sharma R, Garg R, Kumari A. A review on biogenic synthesis, applications and toxicity aspects of zinc oxide nanoparticles. Excli J. 2020;19:1325-40.

[31] Mohd Yusof H, Mohamad R, Zaidan UH, Abdul Rahman NA. Microbial synthesis of zinc oxide nanoparticles and their potential application as an antimicrobial agent and a feed supplement in animal industry: A review. J Anim Sci Biotechnol. 2019;10:01-22. Available from: https://doi.org/10.1186/s40104-019-0368-z.

[32] Lakshmipriya T, Gopinath SCB. Introduction to nanoparticles and analytical devices. in nanoparticles in analytical and medical devices; Elsevier: Amsterdam, The Netherlands, 2021;01-29.

[33] Jiang J, Pi J, Cai J. The advancing of zinc oxide nanoparticles for biomedical applications. Bioinorg Chem Appl. 2018;2018:1062562. Doi: 10.1155/2018/1062562.

[34] Mokammel MA, Islam MJ, Hasanuzzaman M, Hashmi MS. Nanoscale materials for self-cleaning and antibacterial applications. Reference Module in Materials Science and Materials Engineering. 2019. Doi: 10.1016/B978-0-12-803581-8.11585-1.

[35] Jin SE, Jin HE. Antimicrobial activity of zinc oxide nano/microparticles and their combinations against pathogenic microorganisms for biomedical applications: From physicochemical characteristics to pharmacological aspects. Nanomaterials (Basel). 2021;11(2):263. Doi: 10.3390/nano11020263.

[36] Moradpoor H, Safaei M, Mozaffari HR, Sharifi R, Imani MM, Golshah A, et al. An overview of recent progress in dental applications of zinc oxide nanoparticles. RSC Adv. 2021;11(34):21189-206. Doi: 10.1039/d0ra10789a.

[37] Panahandeh N, Torabzadeh H, Aghaee M, Hasani E, Safa S. Effect of incorporation of zinc oxide nanoparticles on mechanical properties of conventional glass ionomer cements. J Conserv Dent. 2018;21(2):130-35. Doi: 10.4103/JCD.JCD_170_17.

[38] Vikram S, Chander NG. Effect of zinc oxide nanoparticles on the flexural strength of polymethylmethacrylate denture base resin. Eur Oral Res. 2020;54(1):31-35. Doi: 10.26650/eor.20200063.



**PARTICULARS OF CONTRIBUTORS:**

1. Research Scholar, Department of Prosthodontics, Saveetha Dental College and Hospitals, SIMATS, Chennai, Tamil Nadu, India.
2. Professor, Department of Prosthodontics, Saveetha Dental College and Hospitals, SIMATS, Chennai, Tamil Nadu, India.
3. Professor, Department of Pharmacology, Saveetha Dental College and Hospitals, SIMATS, Chennai, Tamil Nadu, India.
4. Research Scholar, Department of Prosthodontics, Saveetha Dental College and Hospitals, SIMATS, Chennai, Tamil Nadu, India.
5. M Tech Student, Department of Mechanical Engineering, Indian Institute of Technology, Chennai, Tamil Nadu, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**

Suja Joseph,
Professor and Head, Department of Prosthodontics, Travancore Dental College,
NH Bypass Road, Mylapore, Thattamala P.O Kollam-691020, Kerala, India.
E-mail: sjkt21@gmail.com



**PLAGIARISM CHECKING METHODS:** [Jain H et al.]

- Plagiarism X-checker: Feb 05, 2024
- Manual Googling: Apr 01, 2024
- iThenticate Software: Apr 05, 2024 (14%)

**ETYMOLOGY:** Author Origin

**EMENDATIONS:** 6

**AUTHOR DECLARATION:**

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 30, 2024**
Date of Peer Review: **Feb 20, 2024**
Date of Acceptance: **Apr 10, 2024**
Date of Publishing: **May 01, 2024**