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# Green synthesis and biocompatibility of titanium nanoparticles

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## ABSTRACT

Nanotechnology (NT) is a field that is mushrooming, making an impact in all spheres of human life. Presently available literature revealed that the Titanium dioxide ($TiO_2$) synthesis using medicinal plants, microorganisms and algae and others as source has been unexplored and underexploited. NT is very important in developing sustainable technologies for the future, for humanity and the environment. The development of green processes for the synthesis of $TiO_2$ NPs is evolving into an important branch of nanotechnology. Plant mediated synthesis of $TiO_2$ nanoparticles is gaining more importance owing to its simplicity, rapid rate of synthesis of NP of attractive and diverse morphologies and elimination of elaborate maintenance of cell cultures and ecofriendliness. The nontoxic and biocompatible properties of Titania find its applications in biomedical sciences such as bone tissue engineering as well as in pharmaceutical industries. This review presents a summary of green synthesis and biocompatibility of and a concise account of the *in vitro* toxicity data on $TiO_2$ nanoparticles. Presently, the researchers are looking into the development of cost-effective procedures for producing reproducible, stable and biocompatible metal NPs.


## KEYWORDS

Titanium dioxide;
Nanoparticles
In vitro toxicity;
Biocompatible.

## INTRODUCTION

The word “nano” is used to indicate one billionth of a meter or 10 -9. Nanoparticles are clusters of atoms and their size from 1–100 nm. “Nano” is a Greek word meaning extremely small. Nanotechnology is a field that is vast in making an impact in all fields of human life. Nanobiotechnology can be used as alternative for chemical and physical methods of nanoparticles synthesis. Nano science and nanotechnology began in late 1959 with a talk entitled “*There's Plenty of Room at the Bottom”* by physicist Richard Feynman at an American Physical Society conference, held at the Cal Tech. The term Nanotechnology (NT) was coined by Professor Norio Taniguchi of Tokyo Science University in the year 1974. Nanoparticles (NP) attract greater attention due to their various applications in different fields including “nanomedicine”. NPs can be broadly grouped into two, namely, organic nanoparticles which include carbon NPs where as some of the inorganic nanoparticles include magnetic NPs, semi-conductor nanoparticles (like titanium oxide ($TiO_2$). Metallic nanoparticles are most promising and remarkable biomedical agents. Materials at the nanometer dimension are not new. NPs are common in nature, for example, life depends on many nanoscaled objects, including proteins, enzymes and DNA, and nanosized particles occur naturally in the atmosphere. Nanoparticles display unique physical and chemical features because of effects such as the quantum size effect, mini size effect and surface effect. Natural sources of nanoparticles include fires and volcanic eruptions. The nanotechnology have short to long term uses like environmental pollution cleanup, efficient and safe drug delivery mechanisms with less side effects, developments in information technology, self cleaning window glass, 'smart' fabrics which adjust to suit the temperature. Some of these technologies have already been adopted. Striving for alternative and cheaper pathways for nanoparticles synthesis, scientists contributed to the development of a relatively new and largely unexplored area of research based on the biosynthesis of nanomaterials[1] Utilizing a biological source gives an easy approach, easy multiplication, and easy increase of biomass and size uniformity antibiotic resistance is the world's major public healthcare problem. Ultra small particles (USPs, size/diameter <10 nm), so-called "ultra small nanoparticles" are reviewed[2] Applications of NPs in medical field already explored[3-6]. Scientists are looking for longer-term applications including design of additional 'smart' materials such as food packaging which changes color when the 'use by' date of its contents expires. Titanium dioxide ($TiO_2$) is a material of great significance in many fields, e.g., photo catalysis, solar cell devices, gas sensors, and biomaterials. The non toxic and biocompatible properties of Titania find its applications in biomedical sciences such as bone tissue engineering as well as in pharmaceutical industries. In medical applications the titanium pins are due to because of their non-reactive nature when contacting bone and flesh. The $TiO_2$ NPs are synthesized using various methods such as sol gel, plants, hydrothermal, flame combustion, solvothermal, fungal mediated biosynthesis etc. Recently the microorganisms such as *Lactobacillus* sp. and *Saccharomyces cerevisae* are used for the synthesis of $TiO_2$ nanoparticles[7]. As with any other man-made materials, both *in vitro* and *in vivo* studies on biological effects of NPs need to be performed In vitro model systems provide a rapid and effective means to assess NPs for a number of toxicological endpoints. They also allow development of mechanism-driven evaluations and provide refined information on how NPs interact with human cells in many ways. Such studies can be used to establish concentration–effect relationships and the effect-specific thresholds in cells. These assays are suited for high-throughput screening of an ever increasing number of new engineered nanomaterials obviating the need for *in vivo* testing of individual materials. NT is important in developing sustainable technologies for the future, for humanity and the environment. There is a growing need to develop environmentally friendly processes through green synthesis and other biological approaches.

## IMPORTANCE OF THE STUDY

Presently available literature revealed that the metal NPs synthesis using plants, microorganisms and algae as source has been unexplored and underexploited. Resistance to antimicrobial agents by pathogenic bacteria has emerged in recent years and is a major health problem. The development of green processes for the synthesis of NP is evolving into an important branch of green nanotechnology. Plants have evolved in the presence of natural nanomaterials. The reason for selecting plant for Biosynthesis is because they contain reducing agents like citric acid, ascorbic acids, flavonoids, reductases and dehydrogenases and extracellular electron shuttlers that may play an important role in biosynthesis of metal nanoparticles[8,9]. Physicochemical properties of nanomaterials, biological effects. The unusual physicochemical properties of engineered nanomaterials are attributable to their small size (surface area and size distribution), chemical composition (purity, crystallinity, electronic properties etc.), surface structure (surface reactivity, surface groups, inorganic or organic coatings etc.), solubility, shape and aggregation. Shape of the NPs has been shown to have a pronounced effect on the biological activity. Reactive oxygen species (ROS), due to their high chemical reactivity can react with DNA, proteins, carbohydrates and lipids in a destructive manner causing cell death either by apoptosis or necrosis. The most frequently affected macromolecules are those genes or proteins, which have roles in oxidative stress, DNA damage, inflammation or injury to the immune system. However, the probability of plant exposure to nanomaterials has increased to a greater extent with the ongoing increasing production and use of engineered nano materials in a variety of instruments and goods. Plant mediated synthesis of metal NPs is gaining more importance owing to its simplicity, rapid rate of synthesis of $TiO_2$ NPs of attractive and diverse morphologies and elimination of elaborate maintenance of cell cultures and ecofriendliness.

## SIGNIFICANCE AND SYNTHESIS OF $TiO_2$ NPs PARTICLES

The reason for selecting plant for biosynthesis is because they contain reducing agents like citric acid, ascorbic acids, flavonoids, reductases and dehydrogenases and extracellular electron shuttlers that may play an important role in biosynthesis of metal nano particles[10]. They life span of metal nanoparticles and speed up the rate of synthesis in comparison to microorganism's. Depending on the origin we can distinguish three types of NPs: natural incidental and engineered. Natural NPs have existed from earth formation and still occur in the environment in volcanic dusts and mineral composites. The general procedure using plants to produce metallic nanoparticles employs the dried biomass of the plants and a metallic salt, as bioreducing agent and precursor, respectively. No correlation is observed between the color development and increase in abundance exhibited by the synthesized nano metal. The green synthesis of NPs involves three main steps, including (a) selection of solvent medium, (b) selection of environmentally benign reducing agent, and (c) selection of nontoxic substances for the NPs synthesis[11]. Studies have shown that the size, morphology, stability and properties (chemical and physical) of the metal nanoparticles are strongly influenced by the condition of experiment, the kinetics of interaction of metal ions with reducing agents, and adsorption processes of stabilizing agent with metal nanoparticles[12]. Different materials can be used to make these nanoparticles, such as metal oxide ceramics, silicates, magnetic materials, lyposomes, dendrimers, emulsions and etc[13]. Several scientists already synthesized green route of $TiO_2$ NPs using *Aspergillus tubingensis*[14]. A novel, low-cost, green and reproducible bacteria, *Aeromonas hydrophila*[15], using microorganisms[16], *Annona squamosa* peel extract[17], *Eclipta prostrata* leaf aqueous extract[18].

## FACTORS AFFECTING BIOSYNTHESIS OF NANOPARTICLES

Nature has elegant and ingenious ways of creating the most efficient miniaturized functional materials. In attempts to create miniaturized structures, significant achievements have been achieved and structures of micron and nano-dimensions can now be routinely fabricated though the complexity manifested by the nature is yet a distant goal. The most important challenge in nanotechnology today is to cost effectively tailor the optical, electric and electronic property of NPs by controlling the configuration as well as monodispersity. Synthesis of nano materials with the required quality and desired properties are one of the important issues in present greennanotechnology. Different kinds of NPs can be successfully synthesized by traditionally chemical and physical methods. Temperature plays an important role to control the aspect ratio and relative amounts of gold nanotriangles and spherical nanoparticles. pH of the medium also influences the size of nanoparticles at great concern. Other than pH and temperature other factors like concentration of extract also play role in NP synthesis and reduction process of ions into metallic nano.

## ACTIVITIES OF NPs

*Solanum trilobatum* extract-mediated synthesis of titanium dioxide nanoparticles to control *Pediculus humanus capitis*, *Hyalomma anatolicum* and *Anopheles subpictus*[19], *Chlamydomonas reinhardtii*,[20] Other microorganisms[21-24], *Candida albicans*[25], *E. coli*[26].

## CHARACTERIZATION OF NPs

Characterization of nanoparticles is important task to understandand control over nanoparticles synthesis and applications and it can be done using developed and sophisticated techniques such as transmission and scanning electron microscopy (TEM, SEM), atomic force microscopy (AFM), dynamic light scattering (DLS), X-ray photoelectron spectroscopy (XPS), powder X-ray diffractometry (XRD), Fourier transform infrared spectroscopy (FTIR), and UV–Vis spectroscopy[27]. The TiO2 NPs were characterized by FTIR, XRD, AFM and FESEM with EDX.

## SEPARATION AND PURIFICATION OF NPs

Capillary magnetic ûeld ûow fractionation (MFFF) was described by[28] demonstrates that magnetic NPs can be separated not only according to size but also on material composition, HPLC and size exclusion chromatography[29,30]. NPs are successfully separated gold[31]. NPs and another important approach is centrifugation is used widely in colloid science now and Membrane filtration.

## BIOCOMPATIBILITY OF NPS (NPS)

They also serve as well defined systems for studying the structure–activity relationships involving nanomaterials. Some of the distinct advantages of in vitro systems using various cell lines include; (1) revelation of primary effects of target cells in the absence of secondary effects caused by inflammation; (2) identification of primary mechanisms of toxicity in the absence of the physiological and compensatory factors that confound the interpretation of whole animal studies; (3) efficiency, rapidity and cost-effectiveness; The cytotoxic effects for almost all kinds of metallic, metal oxide, semiconductor NPs, polymeric NPs and carbon based nanomaterials etc. have been reported. For establishing 'safe' nanotechnology it would be necessary to prove non-genotoxic nature of the nanomaterials in question. Several genotoxicity assays can be carried out *in vitro*. *In vitro* cytotoxicity studies of metallic NPs using cell lines, incubation times and colorimetric assays with different nanomaterials are increasingly being published and the techniques that can be used to assess the toxicity of nanomaterials include (1) *in vitro assays* for cell viability/proliferation using MTT, LDH assay[32,33], mechanistic assays ROS generation, apoptosis, necrosis, DNA damaging potential using ROS assay[34,35] (2) microscopic evaluation of intracellular localization include SEM-EDS, TEM, AFM, Fluorescence spectroscopy, MRI, VEDIC microscopy (3) gene expression analysis, high-throughput systems (4) *in vitro* hemolysis and (5) genotoxicity etc. The NPs are tested for biocompatibility for pulmonary[36], erythrocytes[37], endothelial cells for cardiovascular disease [38], Ovarian Cancer[39, 40] in animals spleen injury, lung inflammation[41], mouse embryonic fibroblasts[42], human monocytes[43,44] human spermatozoa[45], murine glioma cells[46], ocular use[47].

## APPLICATIONS

Nanotechnology is a field that is mushrooming, making an impact in all spheres of human life. During the current scenario nanotechnology motivates progress in all sphere of life, hence biosynthetic route of nanoparticles synthesis will emerge as safer and best alternative to conventional methods. Recently *Sesbania* Gum is used to prepare metal NPs and it is a new idea, green and low cost approach for synthesis nanoparticles[48]. Tio2 nanoparticles ($Tio_2$-NPs), approximately less than 100 nm in diameter, have become a new generation of advanced materials due to their novel and interesting optical, dielectric, and photo-catalytic properties from size quantization. photo catalyst and widely utilized as a self-cleaning and self disinfecting material for surface coating in many applications, titanium dioxide has a more helpful role in our environmental purification due to its nontoxicity, photo induced super-hydrophobicity and antifogging effect Though various biological entities have been exploited for the production of nanoparticles, the use of plants for the facile robust synthesis of nanoparticles is a tremendous. The use of nanoparticles for biomedical applications, such as drug, delivery, biosensors, cancer treatment, has been extensively studied throughout the past decade[49- 53], Toxicity of silver and other NPs are not fully understood even it is using from long time. Shape and size control of nanoparticles is easily understood with the use of plants. The nanoparticles extracted from plants are used in many applications for benefit of humans. Metal nanoparticles are applied in biology as biosensors in protein detection[54] labeling agents [55] and cancer therapeutics [56]. The Green chemistry synthetic route can be employed for both silver and gold silver nanoparticles synthesis.

## CONCLUSION

The “green” route for nanoparticle (NP) synthesis is of great interest due to eco-friendliness, economic prospects, and feasibility and wide range of applications in nanomedicine, new category catalysis medicine, nano-optoelectronics, etc. It is a new and emerging area of research in the scientific world, where day-by-day developments is noted in warranting a bright future for this field. This green chemistry approach toward the synthesis of $TiO_2$ and others have many advantages such as, ease with which the process have economic viability, etc. The characterization analysis proved that the particle so produced in nano dimensions would be equally effective as that of antibiotics and other drugs in pharmaceutical applications. The ongoing research efforts are focussed on evaluating the safety of nanomedicine and formulating the international regulatory guidelines for the same, which is critical for technology advancement. With vast technology push, there are many challenges head that need to be understood and solve in order to make the NP-based products commercially viable. This paper has reviewed recent knowledge and built a data base of bioreductive approaches to titanium oxide ($TiO_2$) NPs using different biological systems. The present review highlights the current knowledge regarding the potential sources for biosynthesis of these NPs and presents a database that future researchers can build upon. Presently, the researchers are looking into the development of cost-effective procedures for producing reproducible, stable and biocompatible metallic NPs from bioresources.

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