**Nanoparticle– A Compendium on Biosynthesis, Application and Toxicological Effects**

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**Abstract**

In the last few years, attention has been focused on nanomaterials, mainly nanoparticles, due to their unique physical and chemical properties that vary from bulk components. These exceptional properties have unlocked numerous ground-breaking applications in medicine, electronics, agriculture, chemical catalysis, food industry and other fields. Finally, nanoparticles are also being produced biologically through plant- or microbe-mediated processes, a more environmentally friendly alternative to traditional physical and chemical synthesis methods. This multidisciplinary approach requires biologists and biotechnologists to understand and learn how to characterize these processes. This review article focuses on providing a comprehensive overview of the classification, characterization, biosynthesis and applications of nanoparticles. This article presents a large collection of examples of nanocomposite nanoparticles and their applications, along with comprehensive methods and techniques used for the biosynthesis and analysis of these properties. The purpose of this review is to make the various methods more accessible to readers and to help identify the appropriate method for any given nanoscience problem.

**Keywords:** Nanomaterial, Biosynthesis, Nanocomposite, Nanosciences, Toxicological effect.

**Introduction:**

A nanoparticle or ultrafine molecule is generally defined as matter between 1 and 100 nanometers (nm) in diameter. The term is sometimes used for larger particles, up to 500 nm, or for fibers and tubes less than 100 nm in two directions only. In the lowest range, metal particles smaller than 1 nm are commonly called atomic clusters.

Nanoparticles are generally distinguished from microparticles (1-1000 µm), "fine particles" (between 100 and 2500 nm in size), and "coarse particles" (between 2500 and 10,000 nm), because their smaller sizes have very different physical properties or chemical drives

**Classification:**

Based on their structure, NPs are generally placed into three categories: organic, carbon-based, and inorganic.

**Organic NPs**

This class - includes NPs composed of proteins, carbohydrates, lipids, polymers or any other organic compounds. The most prominent examples of this class are dendrimers, liposomes, micelles and protein complexes such as ferritin (shown in the figure below). These NPs are usually non-toxic, bio-degradable, and in some cases, e.g., for liposomes, have a hollow core. Organic NPs are sensitive to thermal and electromagnetic radiation such as heat and light. In addition, they are habitually formed by non-covalent intermolecular interactions, which make them more discontinuous in nature and bid passage for clearance from the body. Today, organic NPs are mostly used in the biomedical field in targeted drug delivery and cancer therapy.



# Types of organic NPs. A Dendrimers; B liposomes; C micelles; and D ferritin

**Carbon-based NPs**

This class includes NPs that are uniquely constructed from carbon atoms. Some examples of this class are fullerenes, carbon black NPs and carbon quantum dots (shown in the figure below). Fullerenes are carbon-based molecules characterized by a symmetrical closed-cage structure. C60 fullerenes have 60 carbon atoms arranged in a soccer ball shape, but other types of fullerenes such as C70 and C540 fullerenes have also been described. Carbon black NPs are grape-like clusters of highly mixed spherical molecules. Carbon quantum dots consist of discrete, semi-spherical shaped carbon NPs with sizes below 10 nm. Carbon-based NPs combine the unique properties of sp2-hybridized carbon bonds with unusual physicochemical properties at the nanoscale. Due to their unique electrical conductivity, high strength, electron affinity, optical, thermal and sorption properties, carbon-based NPs are used in a wide range of applications such as drug delivery, energy storage, bioimaging, photovoltaic devices and environmental sensing applications. To monitor microbial ecology or detect microbial pathogens. Nanodiamond and carbon nanoonions are more versatile, carbon-based NPs. Due to their exceptional low toxicity and biocompatibility, they are used in drug delivery and tissue engineering applications.



# Different types of carbon-based NPs. A C60 fullerene; B carbon black NPs; and C carbon quantum dots

**Inorganic NPs**

 This class includes carbon or organic matter. Typical examples of this category are metal, ceramic and semiconductor NPs. A metal NP is composed of a metal precursor, it can be monometallic, bimetallic or polymetallic. Bimetallic NPs can be made from alloys or designed in different layers (core-shell). Due to the confined surface plasmon resonance features, these NPs have unique optical and electrical properties. In addition, some metallic NPs also possess exceptional thermal, magnetic, and biological properties.

 Semiconductor NPs are composed of semiconductor materials, which have properties between metals and non-metals. These NPs have characteristic wide bandgaps and show important changes in their properties with bandgap tuning relative to bulk semiconductor materials. Consequently, these NPs are significant components in photocatalysis, optic and electronic devices. Ceramic NPs are inorganic materials composed of carbonates, carbides, phosphates, and oxides of metals and metalloids such as titanium and calcium. It is usually produced by heating and gradual cooling and can be found in amorphous, polycrystalline, dense, porous or hollow forms. Due to their high stability and high load capacity, they are mainly used in biomedical applications. However, it is also used in other applications such as catalysis, degradation of dyes, photonics and optoelectronics.

**Biosynthesis:**

 Biogenesis of nanoparticles by microbes is a green and environmental technology. Various microorganisms, both prokaryotes and eukaryotes, are used for the synthesis of metallic nanoparticles. Silver, gold, platinum, zirconium, palladium, iron, cadmium and metal oxides like titanium oxide, zinc oxide, etc. These microorganisms include bacteria, actinomycetes, fungi and algae. Synthesis of nanoparticles The location of nanoparticles can be intracellular or extracellular.

**Physical Method:**

**A. Physical Vapor Deposition:**

 In this method, the material of interest is usually used as the source of evaporation. Inert gas or reactive gas for effects with vapours of materials. All processes are carried out in a vacuum chamber to ensure the expected purity of the final product. Typically, high vapour-pressure metal oxides are evaporated from fibres of refractory metals such as W, Ta, and Mo in which the material to be evaporated is held. As the concentration of dispersed material near the source is high and the particle size is small (5nm) such components will prefer to achieve a stable low energy state. Smaller particle-particle interactions can lead to the formation of larger components. Therefore, they should be removed from the source as quickly as possible. This is done by running an inert gas near the source, which removes the particles near the source. In general, the dissolution rate and the pressure of the gases inside the chamber control the particle size. The vaporized atoms and molecules collide with the gas molecules and form larger particles, which condense on the cool fingers. Clusters grow when moving away from the cold finger. If clusters are formed on the inert gas atoms or molecules, upon reaching the cold finger, the gas atoms may leave the gas particles there and then escape to the gas phase. If reactive gases such as O2, N2, H2 and NH3 etc. are used in the system, the evaporated material can interact with these gases to form oxide, nitride or hydride particles. The size and shape of the vaporized material depend on the gas pressure in the deposition chamber. TiH2 particles of ~ 12nm size can be produced using gas pressures of H2 in excess of 500 K Pa.

**B. Laser Ablation:**

 In this method, the material is vaporized using high-power laser beam pulses. The setup is a high vacuum system equipped with an inert gas introduction facility and a laser beam. It is possible to synthesize clusters of any material from which a solid target can be formed. Lasers that emit UV wavelengths such as excimer lasers are necessary because other wavelengths such as IR or visible are often reflected by some metal surfaces. A powerful beam of laser vaporizes atoms from a solid source and the atoms collide with inert gas molecules and form clusters on them. They condense on the cooled substrate. This method is known as laser ablation. Single-wall carbon nanotubes (SWNT) are commonly produced by this method.

**Chemical methods**

**A. Synthesis of Colloids:**

 These are phase-separated sub-micrometer particles in the form of spherical particles, rods, tubes plates etc. These are elements suspended in some heated matrix. Metals, alloys, semiconductors and insulators of various sizes and shapes can be formed in aqueous or non-aqueous media. The synthesis of colloids is a primaeval method. M. Faraday produced gold nanoparticles by wet chemical route. Particles are so stable. Colloidal particles are synthesized in a glass reactor. A glass reactor has facilities for measuring several precursors and gases as well as temperature, pH, etc.; During the reaction. It is likely to remove products at appropriate time intervals. The reaction is carried out under an inert atmosphere to avoid any uncontrolled oxidation of the products.

**B. Synthesis of Metal Nanoparticles by Colloidal**

This process is done by the reduction of some metal salt or acid. The reaction will be, HAuCl4 + Na3C6H5O7 Au+ + C6H5O7 + HCl +3 NaCl The reaction will be carried out in water. The obtained nanoparticles show color depending on the particle size. ie (intense red color for gold metal). Similarly, nanoparticles of silver, gold, palladium and several other metals can be produced by suitable precursor, temperature, pH, duration of synthesis, etc.

C. Sol-Gel Method:

This procedure is a low-temperature process, hence less energy usage and less contamination. Sols are solid particles in a liquid. They are a subclass of colloids. Gels are unremitting networks of particles with openings filled with liquid. A sol-gel process involves the formation of sols in a liquid and then connecting the sol particles to form a network. By drying the liquid, it is possible to obtain powders and thin films. Sol-gel synthesis includes hydrolysis of precursors, condensation tailed by polycondensation to form molecules, and gelation and drying procedure by various routes. Precursors are to be chosen so that they tend to form gels. Both alkoxides and metal salts can be used. It is also likely to produce nanoparticles like nanorods, nanotubes etc. by sol-gel technique.

**Biological Methods**

**A. Synthesis using Plant Extracts:**

 The use of plants in the synthesis of nanoparticles is quite a less studied area as compared to the use of microorganisms to produce nanoparticles. There are a few examples that suggest that plant extracts can be used in the synthesis of nanoparticles. Getting gold nanoparticles from geranium plant extract is done by finely crushed leaves put in an Erlenmeyer flask and boiling in water just for a minute where it ruptures and releases intracellular material.

 The solution is cooled and decanted. This solution is added to HauCl4 aqueous solution, and nanoparticles of gold start forming within minutes.

B. Synthesis using DNA:

CdS nanoparticles can be synthesized by DNA. Cadmium acetate can be mixed with the desired medium like water, ethanol, propanol, etc. and the reaction is carried out in a glass flask with the facility to purge the solution and flow with an inert gas like nitrogen. After the addition of DNA, Na2S can be added drop-wise. Depending upon the concentrations of cadmium acetate, sodium chloride DNA nanoparticles of CdS with sizes less than ~ 10 nm can be obtained. It is found that CdS nanoparticles synthesized by this method have cadmium-rich surfaces. DNA probably bends through its negatively charged phosphate group to the positively charged (Cd+) nanoparticles’ surface. The other end of DNA is free to interact with suitable proteins. Nanoparticles prepared in this way are used as sensors of proteins.

Intracellular synthesis of nanoparticles by fungi:

This method includes the passage of ions into microbial cells to form nanoparticles in the occurrence of enzymes. In comparison to the size of extracellularly decreased nanoparticles, the nanoparticles moulded inside the organism are smaller. The size limit is undoubtedly related to the constituents nucleating inside the organisms”

Extracellular synthesis of nanoparticles by fungi:

Extracellular production of nanoparticles has more usage as compared to intracellular production since it is annulled of unnecessary contiguous cellular components from the cell. Mostly, fungi are known to yield nanoparticles outside the cell because of their massive secretory machinery, which is involved in the reduction and capping of nanoparticles.

Microbes for the production of nanoparticles:

Both unicellular and multicellular organisms yield inorganic materials either intra- or extracellularly. The capability of microorganisms like bacteria and fungi to regulate the production of metallic nanoparticles is employed in the exploration for new materials.

Applications:

**Nanoparticle applications as nanocomposites:**

 In spite of the complications with production, the use of nanomaterials grew distinctly in the early 21st century, with particularly hasty growth in the use of nanocomposites. Nanocomposites were hired in the development and strategies of new constituents, serving, for example, as the building blocks for new dielectric (insulating) and magnetic resources.

**Food packaging**

 Nanoparticles have been gradually combined into food packaging to regulate the ambient atmosphere around food, keeping it fresh and safe from microbial adulteration. Such composites use nanoflakes of clays and claylike molecules, which slow down the access to moisture and decrease gas transport across the packaging film. It is also possible to incorporate nanoparticles with apparent antimicrobial effects (e.g., nano copper or nanosilver) into such packaging. Nanoparticles that display antimicrobial activity have also been unified into paints and varnishes, making those goods predominantly useful for surfaces in hospitals and other medical accommodations and food preparations.

**Flame retardants**

 Nanoparticles were discovered for their potential to substitute extras built on flammable organic halogens and phosphorus in plastics and textiles. Studies had suggested that, in the event of a serious fire, products with nano clays and hydroxide nanoparticles were associated with fewer emissions of harmful fumes than products containing certain other types of additives.

**Batteries and supercapacitors**

 The capability to make nanocomposite materials to have extreme internal exterior areas for packing electrical charge in the form of small ions or electrons has made them particularly valued for use in batteries and supercapacitors. Indeed, nanocomposite molecules have been manufactured for numerous applications linking electrodes.

**Nanoceramics**

 A long-standing motive in materials science had been to alter ceramics that are hard and predisposed to cracking into rougher, stronger materials. By the early 21st century, researchers had accomplished that goal by integrating an active blend of nanoparticles into ceramics materials. Further new ceramics constituents that were under progress comprised all-ceramic or polymer-ceramic assortments, which shared the exclusive functional (e.g., electrical, magnetic, or mechanical) belongings of nanocomposite constituents with the belongings of ceramics materials.

**Light control**

 In the 1990s the progress of blue light-emitting diodes (LEDs), which had the capacity to harvest white light at significantly reduced costs, inspired a revolution in lighting. Blue LEDs transported a need for composite constituents that could be used to hide the diodes to alter blue light into other wavelengths (such as red, yellow, or green) to attain white light. One way of procuring the desired light is by leveraging the size or quantum effect of a small semiconducting constituent part. Light alteration in the above cases is accomplished with the submicron constituent part of inorganic phosphor constituents united into the polymer.

**Nanoparticle applications in medicine**

 The minuteness of nanoparticles is particularly beneficial in medicine; nanoparticles can not only move widely all over the body but also enter cells or be intended to bind to specific cells. Those properties have enabled new ways of attracting images of organs as well as tumours and other contaminated tissues in the body. They also have enabled the growth of new approaches to delivering therapy, such as by giving local heating (hyperthermia), blocking vasculature to unhealthy tissues and tumours, or carrying payloads of drugs.

 Magnetic nanoparticles have been used to replace radioactive technetium for tracking the spread of cancer along lymph nodes. The nanoparticles toil by misusing the change in contrast carried about by tiny units of superparamagnetic iron oxide in magnetic resonance imaging (MRI). Such constituent parts also can be used to destroy tumours via hyperthermia, in which an irregular magnetic field causes them to heat and abolish tissue on a local scale.

 Nanoparticles can be premeditated to improve fluorescent imaging or to improve images from positron emission tomography (PET) or ultrasound. Those methods characteristically require that the nanoparticle be able to distinguish a particular cell or disease state. In theory, the same idea of targeting could be used in assisting the precise delivery of a drug to a given disease site. The drug could be approved via a nanocapsule or a liposome, or it could be approved in a porous nanosponge conformation and then held by bonds at the targeted site, thereby allowing the slow release of the drug. The growth of nanoparticles to relief in the delivery of a drug to the brain via inhalation holds significant promise for the treatment of neurological disorders such as Parkinson's, Alzheimer's, and multiple sclerosis.

**Toxicological Effects of Nanoparticle:**

 Apart from their widespread use in industry and medicine, NPs and other nanomaterials have been linked to certain toxicities, which are now receiving more attention than ever before. For instance, NPs may penetrate the dendritic cells of the airway wall, which are the primary antigen-presenting cells that play important roles in coordinating the innate and adaptive immune systems. While targeting dendritic cells with nanotechnology is a promising strategy for cancer immunotherapy, studies have shown that the absorption of NPs can impair the function of these cells. The physicochemical properties of NPs also affect their interactions with dendritic cells, thus altering their immune functions in various processes such as maturation, homing, antigen processing, and antigen presentation. There are concerns regarding whether standard toxicological methods can detect any dysfunction of these cells or whether any such effects are relatively minor. As nanotechnology continues to advance, there will likely be increasing exposure to a wider range of NPs, and this will undoubtedly lead to proposals for their use.

**Table. Nanoparticle-induced toxicities in different organs.**

|  |  |  |
| --- | --- | --- |
| Brain | MNPs@SiO2 (RITC) | Silica-coated magnetic NPs activate microglia and induce neurotoxic D-serine secretion |
| IONP  | The Neurotoxic potential of iron oxide NPs in Wistar Rats |
| Carbon black nanoparticles (CBNPs)  | Exposure of carbon black NPs to chicken embryos |
| ZrO2 NP  | Breakthrough of ZrO2 NPs into fetal brains depends on the developmental stage of the maternal placental barrier and fetal blood-brain barrier |
| Silicon dioxide NPs  | Silicon dioxide NPs induced neurobehavioral impairments by disrupting microbiota–gut–brain axis. |
| zinc oxide NPs  | Crosstalk of gut microbiota and serum/hippocampus metabolites in neurobehavioral impairments induced by zinc oxide NPs. |
| Silica NPs  | Silica NPs promote α-Synuclein aggregation and Parkinson’s disease pathology. |
| Titanium dioxide nanoparticles  | Titanium dioxide NPs via oral exposure lead to locomotor activity in adult mice. |
| AgNPs  | Trolox potentiated oxidative stress in rats following exposure to AgNPs. However, AgNPs did not induce oxidative stress by themselves in the brain. |
| AuNPs  | AuNPs induced dose-dependent cytotoxicity in human neural progenitor cells and rat brains. |
| Lung | MOx NPs  | Toxicities of four different types of MOx NPs (ZnO, SiO2, TiO2, and CeO2 ) in human bronchial epithelial cells. |
| AgNPs  | The low dose of AgNPs induced early and long-lasting histological and ultrastructural alterations in rats. |
| AgNP  | Toxicity mediated by small AgNP (≤20 nm) in lung cells depends not only on the particle internalisation level but also on AgNP size and concentration, which may involve varying pathways as targets. |
| AgNP  | Low-dose AgNP exposure induced histological and ultrastructural alterations in rats’ lungs. |
| AuNPs  | Single, as well as aggregated AuNPs, show similar translocation rates across the lung barrier model. |
| ZnONPs  | High-dose (25 µg/mL) ZnO NPs caused severe cytotoxicity. |
| Heart | CdSe/ZnS Quantum dots  | Quantum dots might build up in the heart and induce some biochemical indicators. The consequence alternated and caused oxidative damage and cardiotoxicity. |
| Liver | CeO2NP  | Iron oxide NPs aggravate hepatic steatosis and liver injury. |
| Iron oxide NP  | Hepatotoxicity of graphene oxide in Wistar rats. |
| Graphene oxide  | AuNPs induced species-specific differences in their biodistribution, excretion, and potential for toxicity |
| AuNP  | AuNPs caused granulomas to develop in the mice’s livers and transiently increased serum levels of the pro-inflammatory cytokine interleukin-18. |
| AgNPs  | AgNPs intoxicated the liver by elevating the liver function markers and decreasing serum levels of albumin and total proteins. It also disturbed oxidation homeostasis and induced apoptotic reactions. |
| AgNP  | AgNPs exhibited a marked elevation in liver DNA damage. |
| AgNP  | The low dose of AgNP-induced hepatotoxicity showed early and long-lasting histological and ultrastructural alterations in male rats |
| AgNP  | In vivo study of silver nanomaterials’ toxicity concerning size. |
| Kidney  | Nano-copper particle | The nano-sized copper particle induced hepatotoxicity and nephrotoxicity in rats. |
| IONP | Surface modifications affect iron oxide NP biodistribution in rats. |
| AgNP  | Single silver nanoparticle instillation induced early and persisting moderate cortical damage in rat kidneys. |
| AgNP  | AgNPs could interact with the anatomical structures of the kidney to induce injury. |
| Reproductive System | Metal oxide NPs (MONPs)  | MONPs may induce ROS overproduction, and oxidative stress, and lead to germ cell toxicity. Eventually, the consequence of the impairment of the male reproductive system. |
| AgNPs  | AgNPs could interact with the anatomical structures of the testis and induce injury. |
| Blood | AuNPs  | Trigger platelet aggregation |
| TiO2NPs Al2O3NPs, Fe2O3NPs  | Aggregated NPs increase oxidative stress and immune response |
| Ag, Fe3O4 , CdSe/ZnS, AuNPs  | Several metallic NPs such as Ag, Fe3O4, CdSe/ZnS, and AuNPs are bio-degradable and produce a high concentration of free radicals that may trigger an inflammatory immune response. |

**Conclusion:**

 Nanoscience and nanotechnology are fields of science that are inherently transdisciplinary. With the emergence of new bio-based approaches, biologists need to understand not only the basic principles of nanoscience but also the techniques and methods traditionally used to characterize nanomaterials. In recent years, nanoparticles have become significant in many fields such as energy, healthcare, environment and agriculture due to their remarkable properties. Nanoparticle technologies have great potential to convert poorly soluble, poorly absorbed and biologically active substances into promising deliverables. However, there are concerns about the nanotoxicity of nanoparticles, especially metal nanoparticles. These particles, when ingested, can cause damage to various organs and can also adversely affect fetuses or offspring in late-stage development into adults by pregnant mothers. Therefore, despite the many useful applications of nanoparticles, the health problems associated with their uncontrolled use and emission in the natural environment must be considered. This consideration may help make the use of nanoparticles more convenient and environmentally friendly.

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