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REVIEW ON BIOSYNTHESIS OF NANOPARTICLES AND ITS ROLE IN TARGETED DRUG DELIVERY

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ABSTRACT: Bio-nanotechnology has emerged as an integration of biotechnology and nanotechnology. The nanoparticles are described as particles with sizes ranging from 1 to 100 nanometers. Nanoparticles exist in many forms such as spherical, cylindrical, platelets, tubes, etc. Nanotechnology is an area that is flourishing, creating an effect in all fields of human life. Biological synthesis employs plant leaf extract, bacteria, fungi, and enzymes to synthesize nanoparticles offers various benefits of eco-friendliness and compatibility for pharmaceutical and other biomedical applications as they do not use toxic chemicals. Drugs are entrapped in the polymer matrix particulates or solid solutions or may be bound to the particle surface by physical adsorption or through chemical interaction. The basic concept involved is the selective and effective localization of nanodrugs in appropriate concentration, and nanoparticles provide restricted access to non-target cells. Nanoparticles are mainly taken by the reticuloendothelial system after administration. Therefore, nanoparticles are useful for carrying drugs to the phagocytically active cells. It is possible to enhance drug delivery to targeted tissues by modifying the surface characteristics of nanoparticles. There are several benefits of using nanoparticles as drug delivery agents such as increased effect of drug, reduced side effects, and reduction in the number of dosages taken by the patient. However, more research is required to develop cost-effective green technology for the high production of nanoparticles and also to maintain the stability of nanoparticle entrapped drug for their applications in the treatment of various diseases.

INTRODUCTION: The term “nanoparticles” is used to explain the particles with size <100 nm. Nanoparticles (NPs) of ideal size, can be used as building blocks in nanotechnology. Several terms have been used to describe nanoparticles, including nanomaterials, nanoscale particles, nanoscale materials, nanosize particles, nano-objects, and nanostructure materials. NPs are in great demand by the scientific community because of their interesting properties and several technological applications¹.

The nanoparticles are presented as the source of new vistas of science. The unique physicochemical features, viz., size, shape and arrangement, and surface plasmon resonance (SPR) of the nanoparticles have been explored to meet the current research trends. The nanoparticles offer many applications in the biomedical field. These are although non-toxic to animal cells, their toxicity to bacterial cells makes them a safe and effective bactericidal agent².

Classification of Nanoparticles: Depending upon the composition, NPs are divided into three categories: Organic NPs, Carbon-based NPs, and Inorganic NPs. As the name indicates, Organic NPs comprise protein, carbohydrates, lipids, polymers, or other organic compounds. These include dendrimers, liposomes, micelles, and protein complexes such as ferritin.

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These types of organic NPs are usually non-toxic, biodegradable, and in some cases have a hollow core (liposomes) depicted in (Fig. 1) ³.

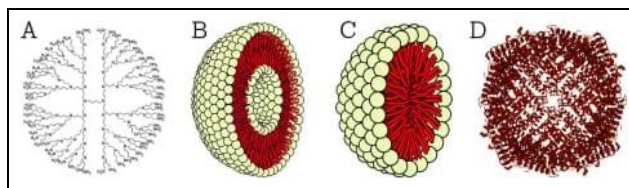


FIG. 1: TYPES OF ORGANIC NPS A DENDRIMERS, B LIPOSOMES, C MICELLES AND D FERRITIN

Inorganic NPs are neither made up of carbon nor organic materials. The typical examples include metal, ceramic, and semi-conductor nanoparticles (such as titanium oxide and zinc oxide). Metal NPs made up of metal precursors that can be monometallic. Bimetallic, polymetallic. Semiconductor NPs possess properties between metals and non-metals. Ceramic NPs are inorganic solids made of carbonates, carbides, phosphates, and oxides of metals and metalloids such as titanium and calcium ³. Carbon-based NPs made solely from carbon atoms. The examples are symmetrical closed cage-like structures called fullerenes, grapes-like aggregate structures called carbon black NPs, and discrete quasi-spherical carbon quantum dots shown in (Fig. 2) ³.

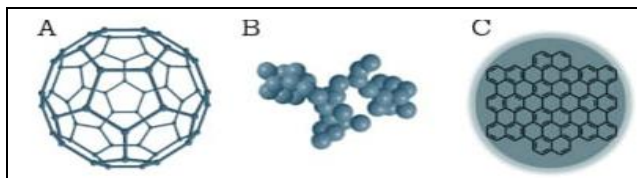


FIG. 2: CARBON-BASED NPS: A FULLERENE, B CARBON BLACK NPS, C CARBON QUANTUM DOTS

There is an ever-growing attention to inorganic nanoparticles of gold and silver, as they provide superior material properties with functional diversity. Inorganic nanomaterials have been widely used for cellular delivery due to their versatile features like broad availability, rich functionality, good compatibility, and capability of targeted and controlled delivery of drugs ⁴. In the present scenario, importance is being given to biological technologies in material synthesis for the production of a variety of nano-materials. The importance of biological synthesis is used worldwide currently because other methods are expensive, toxic, less productive, and not a green technology. Nanotechnology offers broad applications for human welfare such as in medicines, biomedical sciences, storage and drug delivery, and agriculture, etc ⁵⁻⁶. Microbial synthesis of nanoparticles is supported by the fact that the majority of the bacteria inhabit ambient environmental situations. Also, biologically synthesized nanoparticles have higher activity.

Synthesis of Nanoparticles: There are three main approaches for synthesizing NPs: physical, chemical, and biological. The physical approach is also called the top-down approach, while chemical and biological approaches are collectively called the bottom-up approach.

The biological approach is also named green systems of NPs. All the approaches are further subdivided based on the method adopted described in (Fig. 3) ⁷.

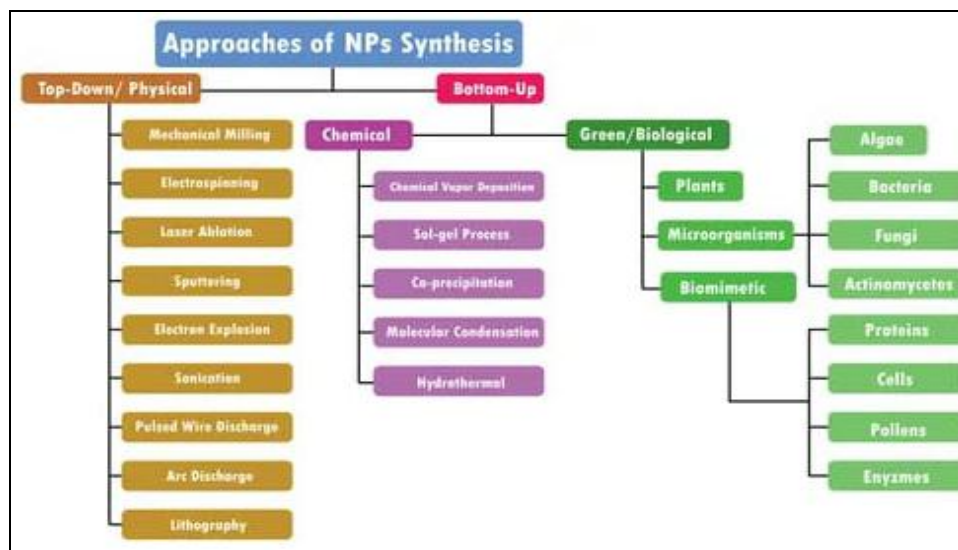


FIG. 3: APPROACHES OF NANOPARTICLE SYNTHESIS

Top-Down Approach: Bulk materials are fragmented in top-down methods to create nano-structured materials (**Fig. 4**). They are additionally known as physical approaches. The following techniques can achieve a top-down approach:

- Mechanical milling
- Electrospinning
- Laser ablation
- Sputtering
- Electron explosion
- Sonication
- Arch discharge method
- Lithography

Bottom-Down Approach: Tiny atoms and molecules are combined in bottom-up methods to create nano-structured particles (**Fig. 4**)⁸. These include chemical and biological approaches. The chemical approaches include:

- Chemical vapor deposition (CVD)
- Sol-gel process
- Co-precipitation
- Inert gas condensation
- Hydrothermal

The bottom-down approach also includes green/biological synthesis using:

- Plant parts
- Plant extracts
- Bacteria
- Fungus
- Algae
- Organic products

Physical and chemical methods are considered as traditional approaches for the synthesis of NPs. The physical method requires space for machine setup,

costly equipment's, and high temperature and pressure conditions which make them less suitable whereas the chemical approach is also known as the wet method because it involves batches of solvents that are used for stabilization or capping.

Solvents are used to ensure that they do not continue to grow past the nanoscale. Also, solutions are used for the reduction of precursor molecules. However, this approach uses chemicals that can be toxic.

Green chemistry is the desired and preferable method for the synthesis of NPs due to the use of non-toxic chemicals, large-scale synthesis, various applications, and also used in the field of medicine.

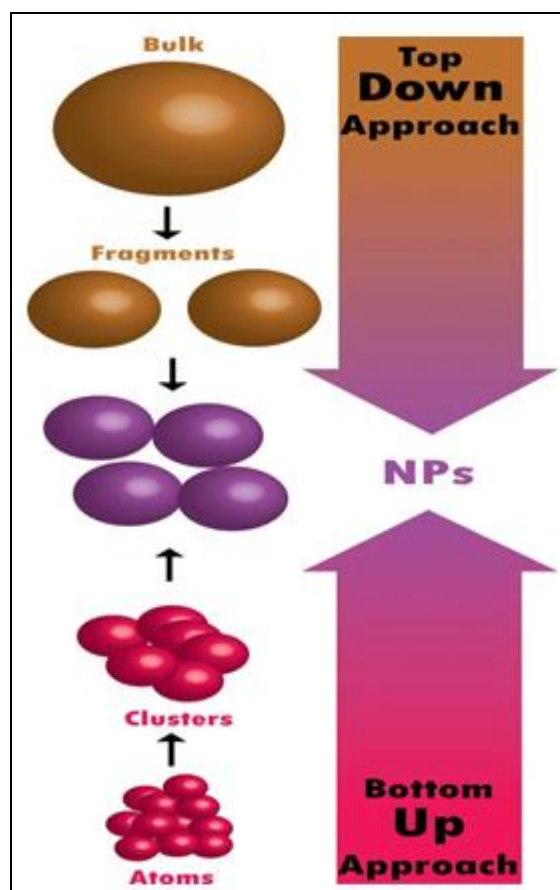


FIG. 4: TOP-BOTTOM AND BOTTOM-TOP APPROACH

Biosynthesis of nanoparticles occurs employing bacteria, fungi, *actinomyces*, and plants. It may occur either extracellularly or intracellularly⁹. There are many factors such as different temperatures, pH, and level of substrate that affect directly or indirectly the rate of nanoparticle production shown in (**Fig. 5**)⁷.

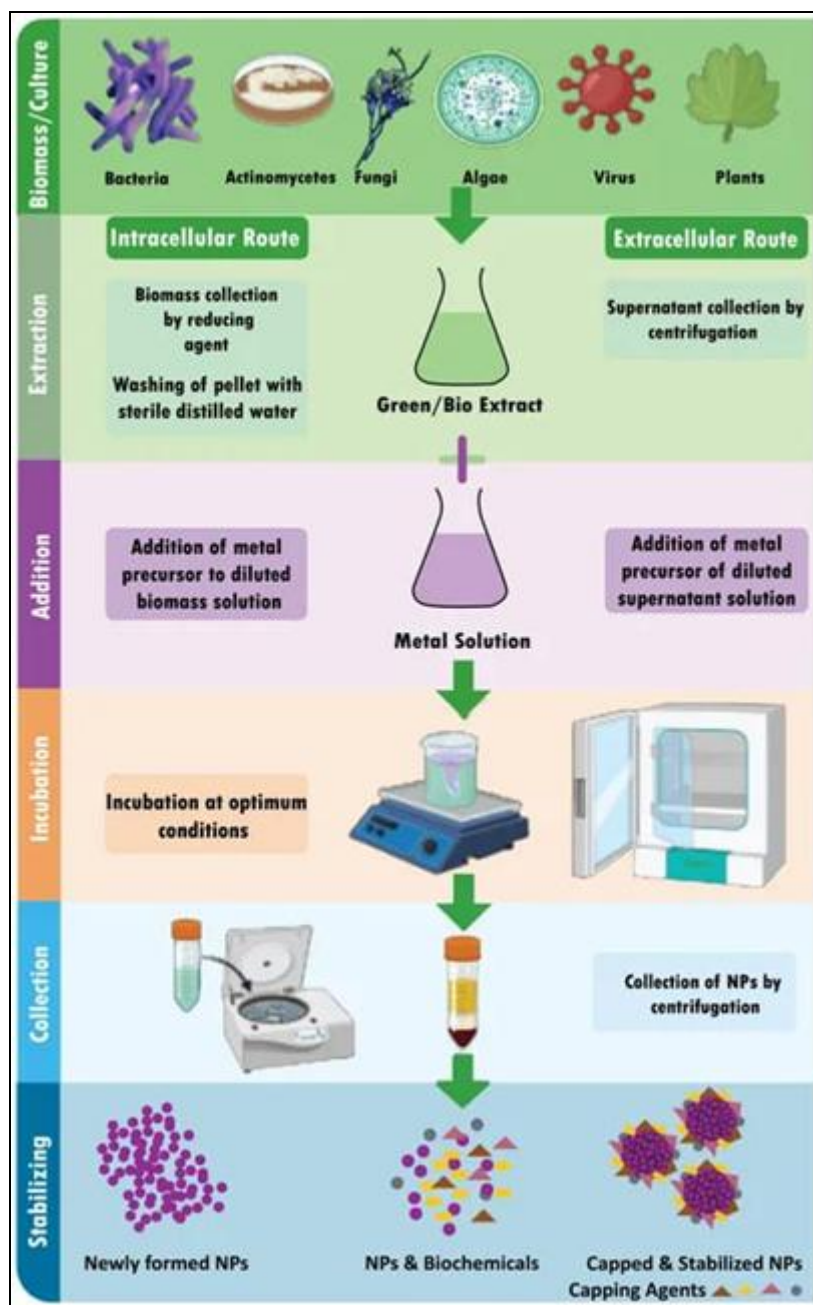


FIG. 5: SCHEMATIC DIAGRAM OF GREEN SYNTHESIS OF NANOPARTICLES

Microbially synthesized nanoparticles can be intracellularly and extracellularly synthesized based on the location where they are synthesized⁵⁻⁶. The biosynthesis of nanoparticles has emerged as an alternative to the conventional methods for the synthesis of nanoparticles¹⁰. Biological systems make nanoparticles more biocompatible, cost-effective, and eco-friendly¹¹. Several researchers have discussed the role of metal nanoparticles as an antimicrobial agent⁵. It has also reported that the antibacterial effects of copper and silver nanoparticles employing bacterial cultures such as *Escherichia coli* and *Bacillus subtilis*¹².

Metallic nanoparticles scatter optical light due to the collective resonance of electron conduction in the metal known as surface plasmon resonance (SPR) which is shown in UV absorption spectra. The magnitudes of peak and wavelength of spectral bands associated with nanoparticles are dependent on size, shape, and material composition. UV-visible spectroscopy is used for many types of chemicals with very high precision and accuracy and can be used for both quantitative and qualitative measurements⁵. Fourier transform infrared spectroscopy is useful in the detection of function groups that help in the determination of

the reducing agent responsible for the synthesis and stability of nanoparticles¹³.

Microbial Synthesis of Nanoparticles: Microbes like bacteria, fungi, actinomycetes, and algae are capable of synthesizing nanoparticles. The basis of synthesis is the reduction of metal ions to nanoparticles¹⁴. Several microbes have been reported for synthesizing metallic nanoparticles, i.e., silver, gold, etc. Silver and gold nanoparticles have many applications in several scientific areas because of their low toxicity and biocompatibility. The role of silver and gold nanoparticles in drug delivery systems is discussed¹⁵.

Biosynthesis of Nanoparticles by Bacteria: Several bacteria have been reported for the synthesis of nanoparticles such as *Bacillus*, *Escherichia coli*, and *Pseudomonas*⁷⁻⁹. They synthesize nanoparticles either intra- or extracellularly. Extracellular synthesis of metal nanoparticles has more commercial uses in diverse fields. The intracellularly synthesized nanoparticles are smaller in size and to release them additional processing steps such as ultrasound treatment or reaction with suitable detergents are necessary. Bio-matrixed metal nanoparticles could also be used as catalysts in various biochemical reactions¹⁶. Microbial production of nanoparticles depends on the localization of the reductive components of the cell. The extracellular synthesis of nanoparticles is cost-effective and synthesized in large-scale which have broad spectrum uses in bioimaging.

Biosynthesis of Nanoparticles using Fungi: Nowadays, many fungi have been studied for the synthesis of nanoparticles¹⁷. Fungi are better than plants and bacteria because the fungal mycelial mesh can resist flow pressure and agitation along with other situations in bioreactors. Also, fungi are fastidious to grow and easy to handle. The cultural and nutritional conditions are adjusted to manipulate the metabolism of fungi to obtain nanoparticles with desired properties¹⁸. The synthesis of silver nanoparticles using *Fusarium oysporum* by the action of nitrate reductase enzyme¹⁹.

Biosynthesis of Nanoparticles using Actinomycetes: Actinomycetes are gram-positive,

spore-forming actinobacteria and are considered both bacteria and fungi. They still have been classified as prokaryotes. Actinomycetes are also identified as ray fungi. Nowadays actinomycetes are also used in the synthesis of nanoparticles. It has been reported the extracellular production of monodisperse gold nanoparticles by a novel *extremophilic actinomycetes*, *Thermomonospora species*²⁰. Similarly, it has also reported that the synthesis of metallic nanoparticles using soil actinomycetes *Streptomyces* sp²¹. However, *actinomycetes* are mainly known for the synthesis of secondary metabolites, whereas, these findings would take the lead in further screening of *actinomycetes* for nanoparticle production.

Biosynthesis of Nanoparticles using Plant: Nanoparticle synthesis using plants is getting attention due to its ease, rapid rate of nanoparticle synthesis of different morphologies, and eco-friendly nature²². The production of nanoparticles by green methods, biomass, or extracts of various plants has been tried with success²³. Some of the medicinal plants have also been reported for the synthesis of metal nanoparticles²⁴. Green nanotechnology is also known as a photobiological approach that uses plants or their extracts as reducing agents in the synthesis of nanoparticles. The development of green protocols for the synthesis of nanoparticles has evolved as a novel field of science.

Characterization of Nanoparticles: Several techniques are used to determine the size, shape, and conformity of synthesized nanoparticles. A few techniques are discussed below.

Scanning Electron Microscope (SEM): The scanning electron microscope images the surface of a nanoparticle by scanning it with a high-energy beam of electrons. When an electron beam hits the surface of the specimen and interacts with atoms of a sample, signals in the form of secondary electrons, backscattered electrons, and characteristic X-rays are produced which include information about surface topography and composition of the sample²⁵.

Transmission Electron Microscopy (TEM): In TEM the crystalline sample interacts with the electron beam generally by diffraction rather than

by absorption. The intensity of diffraction depends on the orientation of planes of atoms in a crystal. This generates a deviation in the electron intensity that exposes information about the crystal structure. Along with allocation & dispersion, exfoliation, intercalation & orientation of nanoparticles can also be visualized using a TEM micrograph²⁵.

X-ray Diffraction (XRD): X-ray diffraction data gives information about the size, orientation of the crystallites, and phase composition and also helps in molecular modeling to verify the structure of the material²⁵.

Energy Dispersive X-ray (EDX) Spectroscopy: In order to determine the functional group this technique is used with SEM. The distinctive X-rays are used to recognize the composition of a sample by a technique known as Energy Dispersive X-ray (EDX) thus, giving an overall mapping of a sample²⁵.

UV-Vis Spectroscopy: Nanoparticles disperse optical light because of the collective resonance of the transmission electrons in the metal known as surface plasmon resonance (SPR). This SPR peak is shown in UV absorption spectra by these nanoparticles. The level of a peak, wavelength, and spectral bandwidth related to nanoparticles is dependent on size, shape, and material composition²⁵.

Fourier Transform Infrared (FTIR) Spectroscopy: FTIR provides information about functional groups present in the sample. The detection of functional groups leads to verifying the reducing agent responsible for the synthesis and stability of nanoparticles¹³.

Several physicochemical factors such as pH and temperature of the reaction mixture play important roles in the synthesis of nanoparticles.

Role of Nanoparticles in Drug Delivery: There are many applications of nanoparticles in scientific fields. Nowadays, nanoparticle-based drug delivery system is used to provide therapeutic agents to its target location for the treatment of various diseases. Nanotechnology is a fascinating area that facilitates quick drug delivery. Nanotechnology approaches in drug delivery overcome several limitations such as drug's low solubility and their limited

bioaccessibility after intake. Drug designing using nanoparticles has potential benefits such as the possibility to modify properties, *viz.*, solubility, drug release, diffusivity, bioavailability, and immunogenicity that ultimately lead to the development of appropriate administration routes with less toxicity and improved drug biodistribution²⁶.

Pharmaceutical nanoparticles are defined as submicron-sized (less than 100 nm in diameter) drug carriers that may or may not be biodegradable. Nanospheres are matrix systems in which the drug is uniformly dispersed, while nanocapsules are the systems in which the drug is surrounded by a unique polymeric membrane. There are several nanocarriers, such as liposomes, dendrimers, polymers, silicon or carbon materials, and magnetic nanoparticles that have been tested as drug delivery systems.

Several biopolymeric substances are utilized in drug delivery systems. Chitosan-based nanomaterials are extensively employed for continued drug delivery systems for many kinds of epithelia, including eye, pulmonary, and nasal²⁷⁻²⁸⁻²⁹. Nanoparticles provide benefits regarding drug targeting, and delivery and their potential for combined diagnosis and therapy³⁰. Drug release methods were developed to deliver or control the amount & rate. Many types of components are used in the encapsulation of many types of nanoparticles with potential uses in the detection and diagnosis of many kinds of illness³¹. Yang and coworkers prepared nanoparticles for revealing colorectal cancer (CC) cells³². Whereas, Ding and coworkers prepared Fe₃O₄ nanoparticles which are used for magnetic resonance (MR) imaging³³. Drug designing characterizes the drugs based on the knowledge of a biological target. Drug delivery systems are capable of enhancing the modified release of the active ingredients in the body.

Drug delivery systems have their own physical, chemical, and morphological properties. Apart from this, other parameters, such as the composition of the nanocarriers and other forms in which drugs are associated with them are also fundamental for understanding their drug delivery profile³⁴. There are many ways such as diffusion, chemical reaction, and stimuli-controlled drug

release in nanocarriers³⁵⁻³⁶. In the future, nanoparticle-encapsulated drugs could be able to treat many threatened diseases.

CONCLUSIONS: Nanotechnology is one of the most fascinating areas of scientific research. Several nano-sized materials are applicable to diagnose and precisely drug delivery to targets. Nanoparticle-mediated drug delivery is very effective in the treatment of cancer by delivering an accurate amount of drug to the particularly affected cancer cells with no harm to the normal cells. The role of nanoparticles in drug delivery systems will remain to be the future arena of research and development.

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