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A review on green synthesis of metallic nanoparticles and it's *In vivo* studies

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Abstract

Nanotechnology has made significant advances into medicines. It has changed medication design and delivery methods by producing nanoparticles that can cross relatively impenetrable barriers like the blood brain barrier. New eco-friendly chemical synthesis techniques have created a new area of potential for nanomedicine, and several metallic nanoparticles have been produced utilizing natural plant extracts (leaf, stem, peel, bark, fruits). The main aim of this articles was to review the approaches, synthesis methods, characterization, and different applications such as extract solution and *in vivo* activities. updates on the usage of biogenic nanoparticles as pharmacological agents and their hypothesized mechanism of action. Despite the obstacles, we are optimistic that green nanoparticles will soon be a viable therapeutic candidate.

Keywords: green synthesis, metal nanoparticles, *in vivo* studies, nanopharmacology

Introduction

Nanotechnology is defined as the manipulation and production of materials and devices on the size of atoms or tiny groups of atoms. The "nanoscale" is measured in nanometers, or billionths of a metre (the prefix derives from the Greek word "nanos," which means "dwarf"), and materials made at this scale typically display unusual physical and chemical characteristics owing to quantum mechanical processes. Nanomedicine is use of nanotechnology to healthcare, illness diagnosis, treatment, and prevention. Nanotechnology encompasses a broad range of topics with sizes ranging from 1 to 100 nanometers. Nanotechnology has many uses in the area of medication delivery. By reducing the deposition of the active agent at non-targeted areas, nano drug delivery methods can minimize drug consumption and adverse effects. Ayurveda is a comprehensive system of Indian medicine that dates back thousands of years. medicine's ancient holistic approach. As preparations, many plants, metals, and nonmetals are utilized. Ayurvedic medicine is a form of primary medicine. Numerous metal mixtures known as Bhasma have been utilized in medicinal practice since the Ayurvedic description. It is the 8th century AD, Metals or minerals should be cooked at elevated temperatures for therapeutic purposes, according to Ayurveda's Puta system. melting and then quenching at particular intervals in suitable media such as herbal juices or decoctions The Bhasma (burned) These procedures are used repeatedly to get metals [1]. UV-visible FTIR, SEM, TEM, X-ray diffraction and particle size analysis revealed that these bhasma are found nanometer dimension. These bhasma may be considered as nanomedicine and are free from of toxicity in therapeutic doses. A nanoparticle is a tiny entity that acts as a single unit in terms of transport and characteristics in nanotechnology. Particles are further divided into categories based on their diameter. The diameter of coarse particles varies between 10,000 and 2,500 nanometers. The size of fine particles ranges from 2,500 to 100 nanometers. Nanoparticles are ultrafine particles with sizes ranging from 1 to 100 nanometers. [2] The two names for the same thing are due to the fact that they were initially referred to as "ultrafine particles" in the 1970s and 1980s, when the first thorough basic research utilizing "nanoparticles" was done in the United States and Japan. However, the new word "nanoparticle" had acquired acceptance in the Western World before the National Nanotechnology Initiative was created in the 1990s. Nanoparticles' size-related properties may or may not differ significantly from those of tiny particles or bulk materials [3]. Despite the fact that most molecules are tiny enough to fit into the above framework, nanoparticles are rarely used to describe them. Natural nanoparticles (1-100 nm), are found in aquatic surface and ground water as suspended particles less than 25 nm. In biological systems, examples include DNA, and complex nanostructured proteins such as polysaccharides, viruses, and bacterial exudates that control a range of biological activities [4].

Nanomedicine is associated with pharmaceutical formulations of nanoscale sized particles to develop better drug molecules and technologies for early diagnosis and treatment of diseases with the objective to enhance the efficacy and specificity so as to improve the life span and quality of patient lives [5]. Nanopharmacology is a holistic branch of science involving the amalgamation of chemistry, engineering, biology, and medicine, and evaluates the interactions of nanoparticles with the living systems to render the creation of safer and efficient formulations. Over the last decade, nanoparticle-based delivery modalities such as peptides, carbon nanotubes, nano diamonds, liposomes, quantum dots, graphene, and metal-based nanoparticles have shown huge therapeutic potential by enhancing the pharmacokinetics of the drug and site-specific delivery. The main aim of developing these nanostructures is to understand the disease pathology and thereby enhance the therapeutic index of patients. Therefore, these methods of revolutionizing the conventional drugs into nanodrugs give us the solution to the looming threat to patient's resistance to chemotherapy and antibodies [6].

Nanofabrication Techniques

In General, there are two types of techniques or approaches in nanotechnology to produce nanoparticles or nanostructures [7]

A. Top-down approach

A top–down approach corresponds to using nanofabrication tools that are controlled by external experimental parameters to create nanoscaled structures/ functional devices with the desired shapes and characteristics starting from larger dimensions and reducing them to the required values. A. Reducing the size of bulk materials to nanosize; it refers to making nanostructures by templating, and accomplishing size reduction by physical methods. (Table.1)

B. Bottom-up approach

Building organic and inorganic materials into defined nanostructures, atom by atom or molecule by molecule, often by self-assembly.

The last decade has seen amazing advances in nanofabrication techniques (both top–down and bottom–up) that have revolutionized developments of advanced nanomaterials with unprecedented functional properties. Extension of existing nanofabrication techniques will facilitate rapid development of microelectronic circuits with nanometer scale features. Outside the field of microelectronics, new nanofabrication techniques that take advantage of the combination of top–down and bottom– up approaches must be developed for new products and technologies applied in different research areas ranging from biology and medicine to materials science and electronics. Top–down methods that have been covered in this review include lithography-based techniques. While optical lithography remains a popular technique in the microelectronics/nanoelectronics arena, and the feature size below 50 nm is achievable using the current infrastructure, the technique remains very expensive. In this regard, one viable approach for optical lithography processes could be less-dependencies on the state of- the-art very expensive clean room operations [8]. The bottom–up method has tremendous promise in realizing very complex nanostructures that are difficult to achieve by the usual top–down processes. Complex technologies will need combination of nanoscale materials with competing properties in a single system for viable material solutions to some of the most difficult technological challenges. Bottom–up nanofabrication techniques such as self-assembly, vapor-deposition or sol–gel processes provide unique opportunities in combinatorial nanomaterials fabrication. A continuation of the use of these techniques is anticipated in the future for the fabrication of multi-component nanomaterial systems such as nanocomposites. The bottom–up approach has enormous potential for the fabrication of extremely complex nanostructures, which are difficult to accomplish using traditional top–down approaches. For feasible material solutions to some of the most challenging technological issues, complex technologies will require the integration of nanoscale materials with conflicting characteristics in a single system. In combinatorial nanomaterial production, bottom–up nanofabrication techniques such as self–assembly, vapor–deposition, and sol–gel processes provide unrivalled potential. It is predicted that the usage of these approaches will continue in the future for the production of multi-component nanomaterial systems, such as nanocomposites, in the creation of nanomaterial systems [9].

The exciting progress to date suggests that the field of nanofabrication will not only continue to advance its current frontiers and respond to the needs of the electronics industry but is also uniquely positioned to take on new challenges in the development of novel biomedical and energy-related technologies. In biomedicine, for example, developments in nanofabrication tools will allow production of ever smaller and more sensitive diagnostic and therapeutic probes to accommodate an enormous number of biological structures and functions. The ability to construct sophisticated surfaces with functional chemicals and in controlled chemical environments will enable understanding and mimicking of biological systems and processes. Synthetic organic chemists will continue to focus on methodologies to construct the complex molecules that cater to pharmacological targets inspired by natural products. The fact that DNA has a considerably smaller one dimension (less than 10 nm in half pitch) than the existing semiconductor industry appears to be the most important motivating element for pushing for future advancements in DNA nanoelectronics manufacturing. Nanoelectronics fabrication, on the other hand, entails a large number of complex unit procedures and requirements. These must not only be compatible with the CMOS process but also fulfil strict requirements such as line edge roughness and throughput in order to be included into certain manufacturing processes. However, despite the energizing and quick speed of growth in this direction, this burgeoning field is still very much in its early stages. There are several critical concerns to be addressed, ranging from core unit operations to overall integration and integration of systems. New nanostructured devices are developing as sensitive bioanalysis platforms, and their optical and electrical characteristics are distinct from those of conventional devices due to their nanofabrication. Dual optical switches for DNA sequence analysis based on fluorescence quenching and simultaneous Raman scattering of gold nanoparticle aggregates, Raman "hot spots" within synthesized dimers of silver cubes or spheres that improve sensitivity by factors of 20 million, and bioelectrical "noses" based on human olfactory receptor-coated SWNT-FET (field effect transistor) that improve sensitivity by factors of 20 million are examples. Furthermore, nanofabrication has enabled the understanding and manipulation of a large number of complex processes in bio-targeting, ranging from drug delivery to bone-inspired biomedical scaffolds to eye-tissue regeneration, as well as self-organization and responsive behavior, amongst other applications. As new materials and nanofabrication tools become accessible, biomedicine will become more reliant on more and more ways of nanofabrication, which will allow the development of new approaches to be developed. In the field of nanotechnology, the biosynthesis of metal and metal oxide nanoparticles utilizing biological agents such as bacteria, fungi, yeast, plant, and algae extracts has gained prominence. Plants and their parts contain carbohydrates, lipids, proteins, nucleic acids, pigments, and a variety of secondary metabolites that work as reducing agents to make nanoparticles from metal salts without releasing any hazardous by-products [10] Similarly, biomolecules such as enzymes, proteins and bio-surfactants present in microorganisms serve as reducing agents. For instance, in many bacterial strains, bio-surfactants are used as capping and/or stabilizing agents [11]. Extracellular synthesis of Ag NPs involves trapping metal ions on the cell's outer surface and reducing them in the presence of enzymes or biomolecules, whereas intracellular production takes place within the microbial cells. It has been proposed that extracellular synthesis of nanoparticles is inexpensive, favors large-scale manufacturing, and necessitates less complicated downstream processing. As a result, the extracellular technique is preferred to the intracellular method for the creation of nanoparticles. have shown that further processes, such as ultrasound treatment or interactions with appropriate detergents, are required to release the produced silver nanoparticles. Furthermore, the rate of biosynthesis of Ag NPs, as well as their stability, play an important role in industrial production [12].

Table 1: Various nanofabrication techniques

1.	Physical methods	a. Arc discharge method b. Electron beam lithography c. Ion implantation d. Inert gar condensation e. Mechanical grinding f. Milling g. Spray pyrolysis h. Vapour-phase
2.	Chemical Methods	a. Coprecipitation method b. Chemical reduction of metal salts c. Electrochemical method (electrolysis) d. Microemulsion method e. Pyrolysis f. Phytochemical (irradiation) method g. Sono-chemical method h. Sol-gel process i. Solvothermal synthesis
3.	Biological Methods	a. Using plant andtheir extracts b. Using microorganisms c. (Virus, bacteria, fungi and actinomycetes) d. Using algae (micro- seaweeds) e. Using enzymes and biomolecules f. Using industrial and agricultural wastes

Plants and plant extracts have acquired appeal in green synthesis because to their rapid development, single-step approach, cost-effective procedure, non-pathogenicity, and ecologically benign nature. Plant-based green synthesis is typically faster than that of other microbes such as bacteria and fungi. As a result, the utilisation of plant extract in green synthesis has generated several studies and study. Depending on the composition of the plant extract, it was discovered that metal NPs might be produced in a metal salt solution in a short period of time at room temperature. Following the selection of the plant extract, the primary influencing criteria are the extract concentration, temperature, metal salt, and pH [13]. The important point is the active agent found in this component, which allow stabilization and reduction, and the biomolecules that create stable NPs. Biomolecules, e.g., amino acids, polysaccharides, alkaloids, and proteins are the key compounds that affect reducing and capping NPs Several significant parameters influence nanoparticle synthesis, characterization, and use. The pH of the solution, temperature, extract concentrations, raw material concentrations, size, and, most significantly, synthesis processes are all elements to consider. Despite the benefits of organic green synthesis, controlling the polydispersity of NPs is a serious difficulty. To address this problem, optimise the reaction conditions by altering the pH, temperature, incubation duration, irradiation, salt content, and redox state. For example, pH is an important element in the green synthesis of nanoparticles. In the case of plants, pH fluctuations impact the charge of phytochemicals, which affects the reduction and biding of Ag during the synthesis process. Green technology is typically used to produce nanoparticles at temperatures below 100 °C. Furthermore, particle size and porosity influence the attributes of green synthesised silver nanoparticles [14]

Characterization of Nanomaterial

It is essential to understand and regulate nanoparticle production and applications in order to understand and control nanoparticle characterization. Some of the techniques used to characterised nanoparticles include scanning and transmission electron microscopy (SEM, TEM), X-ray photoelectron spectroscopy (XPS), Fourier transform infrared spectroscopy (FTIR), atomic force microscopy (AFM), dynamic light scattering (DLS), powder X-ray diffractometry (XRD), and ultraviolet–visible spectroscopy (UV–Vis). It is possible to resolve many characteristics such as particle size, shape and crystallinity as well as fractal dimensions, pore size and surface area by employing these methods. The utility of AFM over traditional microscopes such as SEM and TEM. The value of TEM is that it checks 3D pictures, allowing particle height and diameter to be measured. It is necessary to compute the volume. The particle size distribution is represented by the grape Additionally, dynamic light scattering was used to identify.in addition to that, Crystallinity is determined by X-ray diffraction, and UV–visible light is utilized to determine Colour. The use of visible spectroscopy is employed to verify sample formation. Plasmon resonance is displayed in this way [15].

a. Size

Size is an extremely essential way to describe nanoparticles. it describes whether it is a big particle, its dispersion, and whether it operates on a nanoscale or micron scale Electron microscopy is a new form of microscopy. Primary way to ascertain particle size distribution. We measure particles and clusters using Transmission Electron Microscope (TEM) and Scanning Electron Microscope (SEM). Particles and clusters are measured using Scanning Electron Microscope (SEM) and Transmission Electron Microscope (TEM) pictures, whereas bulk materials are assessed using transmission electron microscope (TEM) images. Laser diffraction techniques are used to determine the solid phase. These numbers are applied to measure the volume of liquid and particle interactions. Since use imaging methods to investigate gases a Scanning Mobility Particle Size (SMPS) is used, which offers faster and more precise measurements than other approaches [16]

b. Surface area

The surface area of nanoparticles is very important in the identification of these particles. The surface area to volume ratio of a nanoparticle has a significant influence on the efficiency and characteristics of the particle. The BET (Brunauer–Emmett–Teller) analysis method is the most often used method for estimating the surface area of a surface. A simple titration approach is required for the surface area measurement of particles in the liquid phase, however it is a time-consuming and labor-intensive procedure. Because of this, nuclear magnetic resonance (NMR) spectroscopy is employed. The surface area of nanoparticles in the gaseous phase has been evaluated using a modified SMPS and a differential mobility analyser, according to the researchers [17].

c. Composition

The purity and effectiveness of a nanoparticle are governed by the chemical or elemental makeup of the particle itself. The presence of higher concentrations of secondary or unwanted components in a nanoparticle Its efficiency may be reduced, and secondary reactions may occur. as well as contaminants throughout the process X-ray photoelectron spectroscopy X-ray photoelectron spectroscopy (XPS) is frequently used to determine the composition Some procedures, such as mass spectrometry, are considered to be scientifically valid. Both atomic emission spectroscopy and ion chromatography are used in this study. include chemical digestion of the particles, as well as mechanical digestion Analytical methods involving wet chemistry The particles that are present in the gaseous phase The samples are collected either by filtration or electrostatic collection, and the analysis is carried out using spectrometric or wet chemical methods [18, 19].

d. Morphology of the surface

The shapes and surface structures of nanoparticles play an important role in utilizing their characteristics. Spherical, flat, cylindrical, tubular, conical, and irregular shapes are some of the shapes available. has crystalline or amorphous surfaces, and uniform or imperfections on the surface The surface is generally determined by electron microscopy imaging techniques like TEM & SEM The particles in the liquid phase are deposited on a surface and analyzed, whereas the particles in the gaseous phase are deposited on a surface and analyzed. For imaging with electron microscopy, they are captured electrostatically or by filtration [20].

e. Charge on the surface

A nanoparticle's interactions with the target are determined by its surface charge, or charge. A zeta potentiometer is commonly used to monitor surface charges and their dispersion. a solution's stability For the charge, a Differential Mobility Analyzer (DMA) is used. Nanoparticles in the gaseous phase are determined. The charge of nanoparticles in gaseous phase is determined using a Differential Mobility Analyzer (DMA) [16].

f. Crystallography

Crystallography is the study of the arrangement of atoms and molecules in crystal solids. The structural arrangement of nanoparticles is determined using a powder X-ray, electron, or neutron diffraction technique [21].

g. Surface hydrophobicity

The precise measurement of the surface hydrophobicity of nanoparticles is required for the safety assessment of these materials. However, it is true that hydrophobicity plays a role in defining the biological and environmental destiny of nanoparticles and the potential toxicity of these particles. One option is to utilize the usual water/octanol method, in which case you would mix the particle solution in a beaker with the two phases separately. If the particles are hydrophobic, they will most likely separate at the interface, making it impossible to determine the concentration of the particles in the two phases but how do you determine how hydrophobic the particles are (i.e., how much of their polar component of the surface free energy is absorbed by water). Water contact angle measurements, rose bangle (dye) binding, and hydrophobic interaction chromatography etc method to evaluate hydrophobicity [22].

h. Concentration

It is possible to calculate the amount of air or gas required for the procedure by observing the concentration of nanoparticles in the gaseous phase of the solution. Performance or efficiency of a system is governed by the number of nanoparticles present in a given unit volume of air or gas, as well as the size and dispersion of those particles. A Condensation Particle Counter is a type of instrument that is often used to compute concentrations (CPC).

Pharmacological Activities of Nanoparticles

Several recent studies have concentrated on silver, gold and metallic nanoparticles, in addition to zinc oxide, copper oxide, zirconium oxide, iron oxide, and yttrium oxide. All of these materials have shown evidence of activity against bacteria and cancer, as well as possible mechanisms of action. In this study, it was shown that the bottom-up production of smart metal nanoparticles (NPs with desirable modifications that have been controlled in size, shape, and morphology) increases selectivity and biological activity toward targeted cells while causing no harm to normal cells. Aspect of NPs that deserves special mention is their selectivity. It is this feature that will enable NPs to be utilized as medication replacements in biological applications in the near future. The generation of reactive oxygen species (ROS) that cause cell component and membrane damage, the interaction of released metal ions with proteins that causes inhibition of enzyme activity and physiological processes, as well as a nonoxidative mechanism, are some of the proposed mechanisms for the antimicrobial and anticancer activity of metal nanoparticles that cause cell component and membrane damage [23]. Nanopharmacology is a holistic branch of science involving the amalgamation of chemistry, engineering, biology, and medicine, and evaluates the interactions of nanoparticles with the living systems to render the creation of safer and efficient formulations. Over the last decade, nanoparticle-based delivery modalities such as peptides, carbon nanotubes, nano diamonds, liposomes, quantum dots, graphene, and metal-based nanoparticles have shown huge therapeutic potential by enhancing the pharmacokinetics of the drug and site-specific delivery. The main aim of developing these nanostructures is to understand the disease pathology and thereby enhance the therapeutic index of patients. Therefore, these methods of revolutionizing the conventional drugs into nanodrugs give us the solution to the looming threat to patient's resistance to chemotherapy and antibodies [24]. According to recent research, the majority of nanomaterials have antibacterial activity that can be attributed to at least one of the following mechanisms: inhibition of cell wall/membrane synthesis, disruption of energy transduction, production of toxic ROS, photocatalysis, enzyme inhibition, and reduced DNA production [25].

Metal nanoparticles are also known to possess antioxidant properties. Generally speaking, antioxidant agents are enzymatic and non-enzymatic compounds that have the ability to control the production of free radicals. This group of free radicals has been discovered to be responsible for the development of cellular damage, which includes brain damage, cancer, and atherosclerosis. They are produced by reactive oxygen species (ROS) such as hydrogen peroxide, superoxide dismutase, and hydrogen radicals, among other substances. Several biomolecules, including proteins, lipids, fatty acids, glycoproteins, phenolics, flavonoids, terpenoids, and sugars, have been shown to have a significant impact on the development and production of free radicals. When compared to other synthetic commercially available materials such as ascorbic acid and other antioxidants, the antioxidant efficacy of silver nanoparticles was shown to be much greater. A number of chronic illnesses, including diabetes, cancer, AIDS, nephritis, and metabolic disorders, have been shown to benefit from the antioxidants' scavenging properties. The extract from biosynthesized metal nanoparticles contains a high concentration of phenolics and flavonoids. Oxidative stress caused by reactive oxygen species (ROS) is a critical component of NP antibacterial activity. Superoxide radical (O), hydroxyl radical (OH), hydrogen peroxide (H2O2), and singlet oxygen are the four forms of ROS (O2). Short-term stress responses produce O and H2O2, which may be decreased by endogenous antioxidants such as superoxide and catalases. Singlet oxygen (O2) is responsible for a large portion of the physiological damage produced by ROS [26]. Under normal circumstances, bacterial cells maintain a balance between the creation and clearance of ROS, but when ROS production is excessive, the intracellular redox status changes and promotes oxidation. Oxidative stress is a major contributor to changes in bacterial membrane permeability, which may lead to cell membrane damage. Nano silver ions activate oxygen, producing reactive oxygen ions and hydroxyl radicals that may inhibit or kill bacterial cell growth. Similarly, by causing oxidative stress inside bacterial cells, nanoparticles may cross, interact, and ultimately destroy bacterial membranes [27]. Nanotechnology is a cutting-edge field of contemporary material science study. This branch of study is growing rapidly and has a significant influence on biotechnology and biomedical research. Nanoparticles have unique features due to their form, size, and dispersion. There are several ways to synthesise nanoparticles, including reduction in solution, radiation induced, electrochemical, microwave-assisted, and lately green chemistry. In addition to being eco-friendly and compatible with medicines and other biomedical uses, using biological materials to synthesise nanoparticles has a number of advantages over using hazardous chemicals. Aside from being less hazardous than certain physicochemical techniques, biosynthesis of nanoparticles may generate vast numbers of nanoparticles that are uniform in shape, size, and composition. Compared to other physicochemical techniques, biological synthesis may generate nanoparticles of better specified size and shape.

Plant extracts have been employed for metal ion reduction since the early 1900s, although the nature of the reducing agents involved in this approach is still unknown. Plant or whole plant extracts, as well as plant tissue, have been used to reduce metal ions for over 30 years due to their simplicity. Plant extracts are considerably easier to employ than whole plant extracts and plant tissues for the creation of nanoparticles. Metal nanoparticles may be made from a wide range of plant species. Plant extracts include biomolecules that can convert metal ions to nanosized materials using single-step green manufacturing techniques. Metal ion bioreduction involves plant-based biogenic reducing agents. Water-soluble plant metabolites (flavonoids, terpenoids, alkaloids, and phenolic chemicals) and co-enzymes involved in metal ion bioreduction are examples of these. This is because various plant extracts contain variable amounts of organic reducing agents, making comparison difficult. Some researchers believe plant extracts can be utilised as reducing and stabilising agents in the creation of nanoparticles. It is easy to extend and may be more cost-effective than other methods based on microbial processes and whole plants. Live plants, as well as plant extracts, have been proven to produce nanoparticles. Plant extract-mediated reduction commonly includes both water-soluble extract and a water-soluble metal salt solution. The reaction occurs at room temperature and takes minutes or seconds to complete. Metal nanoparticles are distinguished from their bulk counterparts by their high surface energy, spatial confinement, and reduced shape. Due to their unique properties, nanoparticles have found use in sectors such as catalysis, agriculture, electronics, biological research, and even ground water purification. Gold, silver, copper, iron, zinc, and other metal nanoparticles are used in food packaging, wound dressings, medicine delivery catheters, and other applications due to their antibacterial characteristics. Silver nanoparticles are known to be utilised in biomedical research due to their potent antibacterial characteristics; zinc and titanium nanoparticles are known to be used in cosmetics. The second use of biological nanoparticles is to create biosensors for various substances found in the environment and agriculture. Aside from that, nanoparticles are used to transmit genes to plants and identify cells in medicine. Alternative uses for metal nanoparticles are still being developed and researched, but they include magnetically responsive drug delivery, optical imaging, and photothermal therapy. Because of the unique physicochemical properties of nanoparticles and their extensive usage in research, the scientific community has opted to invest heavily in developing a novel nanoparticle manufacturing method. Other physicochemical techniques pollute the environment by releasing heavy metals into the environment during synthesis. Green nanoparticle synthesis approaches are developing as new trends in nanoparticle synthesis due to its various advantages such as non-toxicity, reproducibility, scalability, and specified shape. The toxicity of plant latex encapsulated silver nanoparticles against human lung cancer cells was studied and shown to be dosage dependant. Further study revealed that plant latex can both stabilise silver nanoparticles in water and transport them to target cells. Further studies verified this. Gold nanoparticles of 2 nm size were successfully manufactured and incorporated into the cancer drug Paclitaxel. TGA indicated that over 70 paclitaxel molecules may be coupled to a single gold nanoparticle. This type of biomolecule can be used to carry large biomolecules like nucleic acids (DNA/Nonpeptides) and proteins. Similarly, gold nanoparticles combined with VEGF antibodies may be used to treat B-chronic lymphocytic leukaemia. Although gold and silver nanoparticles have several applications in biomedicine, their toxicity is an essential aspect to consider. It is thought that chemically produced gold and silver nanoparticles are more dangerous than biologically produced gold and silver nanoparticles. However, using gold and silver nanoparticles produced by spontaneous bio reduction may be a less harmful and more friendly choice. The ligand chemistry of nanoparticles impacts their biocompatibility as well as their composition. They exhibit larvicidal action against filariasis and malaria vectors, as well as plasmodial pathogens and cancer cells. Anti-inflammatory activity is required for wound healing. T cells, B lymphocytes, and macrophages are all engaged in the anti-inflammatory process, which produces cytokines and interleukin chemicals. T cells, B lymphocytes, and macrophages produce these chemicals. Endocrine systems generated inflammatory mediators including enzymes and antibodies. Primary immune organs generate cytokines, interleukin-1, and interleukin-2 (IL-1 and IL-2). These inflammatory mediators have been linked to biochemical reactions as well as regulating disease development. Gold and platinum nanoparticles made from plant extracts have been found to significantly improve wound healing and tissue regeneration, implying that they are used to naturally reduce inflammation. Using AgNPs as antimicrobial preservatives in food has been linked to digestive issues in people. AgNP interactions with healthy cells (epithelial, mucous membrane, etc.) and cancer cells (squamous, liver, or colon cells) through the gastrointestinal tract may result in anti- or pro-oncogenic activity. The causes of carcinogenesis are unclear, however the use of AgNPs as anticancer drugs is growing rapidly in the research and development sector. The most commonly used AgNPs disrupt the proliferative system and cell cycle of cancer cells, suppressing cancer cell growth.

Table 2: *In-vivo* pharmacological activity of green synthesis of nanoparticles

S.no	**Botanical name of plant and family**	**Plant part**	**Plant extraction solvent**	**Type of nano-Particles**	**Characterization**	**Name of *In-vivo* studies**	**Ref.**
1	*Tamarindus indica (Fabaceae)*	Seed	Aqueous	Gold	UV/Vis FTIR AFM	Sedative and analgesic activities in rat	28
2	*Moringa oleifera (Moringaceae)*	Leaf	Aqueous	silver	UV/Vis TEM Zeta sizer	Anti-leishmanial in rat	29
3	*Eucalyptus procera. (Myrtaceae)*	Leaf	aqueous	silver	UV vis SEM XRD DLS	veterinary rabies vaccine potency rat	30
4	*alpinia officinarum (Zingiberaceae)*	Rhizome	aqueous	silver	UV-Spec, FTIR, XRD, TEM and SAED analysis	antioxidant, antiapoptotic, anti-inflammatory properties in rat	31
5	*Fritillaria cirrhosa (Liliaceae)*	whole plant	aqueous	Gold	UV-VIS, HRTEM, XRD and FT-IR	anti-diabetic activity on Streptozotocin induced rats	32
6	*Nigella sativa (Ranunculaceae)*	Seeds``	70% ethanol.	silver	UV–Visible SEM	neuroprotective agents	33
7	*Andrographis paniculate (Acanthaceae)*	Stem	Aqueous& ethanol	silver	UV-Vis FTIR hydrodynamic size zeta potential TEM XRD	*In vivo* Cytotoxicity Assay in rat	34
8	*Solanum torvum (Solanaceae)*	Leaf	Aqueous	Zinc	UV–Vis FTIR DLS/Zeta Potential SEM TEM XRD	Sub-chronic toxicity study	35
9	*Hypericum hookerianum*	aerial parts	ethanolic	Gold	UV–Vis FTIR	Antiparkinsonian in Mice	36

	(Hypericaceae)				SEM analysis and EDAX analysis:		
10	*Capparis spinosa* *(Capparaceae)*	Fruits	methanol (80%)	Copper	UV–Vis FTIR XRD SEM	In Mice	37
11	*Ziziphora clinopodioides* *(Lamiaceae)*	Leaf	aqueous	cobalt	UV–Vis FTIR XRD SEM TEM	Wound healing in rat	38
12	*Hylocereus undatus* *(Cactaceae)*	Fruits	aqueous	Gold	UV–Vis FTIR SEM AFM	Toxicity and wound healing in Mice	39
13	*Catharanthus roseus* *(Apocynaceae)*	Leaf	aqueous	Sliver	UV–Vis FTIR XRD SEM TEM	Wound Healing in BALB/c mice	40
14	*Azadirachta indica* *(Meliaceae)*	Leaf	aqueous	Sliver	UV–Vis XRD SEM FTIR TEM DLS	Wound Healing in BALB/c mice	41
15	*Melia azedarach* *(Meliaceae)*	Leaf	aqueous	silver	UV–Vis XRD SEM FTIR TEM DLS	*In vivo* cytotoxicity in Mice	42
16	*Curcuma longa* *(Zingiberaceae)*	Root	aqueous	gold	UV–Vis FTIR SEM TEM	Breast cancer activity in mice	43
-17	*Ziziphora clinopodioids* *(Lamiaceae)*	Leaf	aqueous	silver	UV–Vis, XRD, FESEM-EDX, AFM, and TEM	Cutaneous Wound Healing Analysis in Rat	44
18	*Petroselinum crispum* *(Apiaceae)*	Whole plant	aqueous	silver	TEM, UV-vis, FTIR. TEM	Anti-inflammatory activity	45
19	*Acorus calamus* *(Acoraceae)*	rhizome	Aqueous	silver	UV–Vis FTIR TEM DLS	*in vivo* toxicity in rats	46
20	*Mangifera indica* *(Anacardiaceae)*	Leaf	Ethanolic	silver	UV–Vis FTIR TEM SEM XRD	*In vivo* anti-tumor activity of biogenic AgNPs in EAC model	47
21	*Cassia roxburghii* *(Fabaceae)*	Leaf	Aqueous	Gold	UV–Vis FTIR HR-TEM XRD	*in vivo* toxicity in rats	48
22	*Morinda citrifolia* *(Rubiaceae)*	fruit	Aqueous	silver	UV–Vis FTIR SEM	Antitumor And Toxicity Studies	49
23	*Citrullus colocynthis* *(Cucurbitaceae)*	fruits	Aqueous	gold	TEM	F Cysts or trophozoits of G.lamblia in Mice	50
24	*Madhuca longifolia)* *(Sapotaceae)*	Bark	Hydroalcoholic	gold		anti-melanoma activity in mice	51
25	*Momordica charantia* *(Cucurbitaceae)*	fruits	Aqueous	Zinc Cerium sliver	FTIR SEM XRD	*In vivo* sub-acute oral toxicity study, streptozotocin-induced diabetic Wistar rats	52
26	*Chamaecostus*	leaves	Aqueous	Gold	UV-Visible	*In vivo* toxicity studies, Type 2	53

	cuspidatus *(Costaceae)*				SEM TEM XRD	Diabetes and Wound-Healing Effects. In rat	

- ultraviolet–visible = (UV/Vis), FTIR =Fourier transform infrared AFM= (atomic force microscopy)

Challenges and Future Perspectives

Nanotechnologies offer both benefits and drawbacks. On the one hand, the use of nanotechnologies in medicine aids in the development of precise solutions for illness prevention, diagnosis, and therapy. It has the ability to harm and even destroy cancer cells, as well as cause cardiovascular and neurological problems, diabetes, and other diseases. Nanotechnology, on the other hand, has already generated concerns about its possible toxicity. According to certain studies, nanoparticles induce symptoms similar to asbestos fibers. Specialists even discuss the likelihood of DNA damage leading in subsequent cancer development as a result of nanotechnology use. The existence of flaws in nanomaterials can have a negative impact on their performance, as well as impair their fundamental features. Examples of such materials include carbon nanotubes, which are among the most powerful materials yet discovered. Impurities, discontinuous tube lengths, flaws, and random orientations of carbon nanotubes, on the other hand, can significantly reduce the tensile strength of carbon nanotubes [54].

(a) Another significant issue is the development of cost-effective methods for the production of nanomaterials. Quality nanoparticles are often created requiring specialized instruments and severe conditions, which makes large-scale manufacturing of these materials impossible. This is particularly important when it comes to the synthesis of 2D nanomaterials. Most of the technologies that have been used for large-scale manufacturing are low-cost, and these processes typically result in materials that contain flaws and are of poor quality in the first instance. The regulated synthesis of nanomaterials is still a difficult task to accomplish.

For example, achieving chiral selectivity, conductivity, and precisely regulated diameters in carbon nanotube production is a critical problem in this field [55]. In order to attain the theoretically estimated properties stated in the literature, it is necessary to get structurally pure nanomaterials from a variety of sources. More concentrated efforts are necessary in order to create novel synthesis techniques that overcome the difficulties associated with traditional synthesis methods. Agglomeration of particles at the nanoscale level is a fundamental problem that has a significant impact on performance in related domains. When nanomaterials come into contact with one another, they tend to clump together. Agglomeration may occur as a result of physical entanglement, electrostatic interactions, or a high level of surface energy, among other factors. Due to the van der Waals interactions that occur between 550 CNTs, they group together and form bundles, which makes it difficult to align or adequately distribute them in polymer matrixes [56]. For the same reason, the basal planes of graphene sheets are responsible for graphene aggregation because of the interactions between them and van der Waals forces. A severe agglomeration has resulted in a reduction in the large surface areas and other distinctive properties of graphene. Because of these difficulties, the practical application of high-throughput electrode materials or composite materials for a variety of applications is hampered [57]. By constructing 3D structures, it is possible to adapt the efficiency of nanomaterials to specific requirements. Several nanomaterials, such as graphene, have been tested in 3D structures to see whether they can improve their inherent characteristics. 3D structures of 2D graphene have been shown to exhibit high specific surface areas and rapid mass and electron transport kinetics, as well as high specific surface areas. In part, this is owing to the combination of the remarkable inherent characteristics of graphene with the 3D porous structures that have been developed [58]. The integration of graphene and carbon nanotube assemblies into three-dimensional structures has emerged as the most actively researched field of nanotechnology research. Developing porous structures for other nanomaterials has the potential to improve their catalytic performance by increasing the availability of the nanomaterial inside the structure. 2D ultrathin materials are an exceptional family of nanomaterials with intriguing theoretical characteristics; nevertheless, with the exception of graphene, there has been relatively little experimental examination of these materials. The production of 2D ultrathin materials, as well as their stability, are two of the most difficult problems connected with them. A greater emphasis is expected to be made in the future on their synthesis and practical application in practise. It is becoming more common in industry to use nanomaterials, and there is an increasing demand for nanoscale material manufacturing at faster rates. The discovery of novel nanomaterials with intriguing properties will continue, and additional areas will be identified in the future, as nanotechnology research continues to expand its frontiers.

It is impossible to ignore one of the most severe issues about nanomaterials, which is their toxicity, which is still little known, and which is a big worry when it comes to their usage in various applications such as environmental, residential, and industrial settings. In this case, it is uncertain if nanoparticle-based compounds are responsible for the cell's toxicity to some extent [59]. The scientific community must make concerted efforts to close the information gap that exists between the fast creation of nanomaterials and the potential toxicity of these materials in living organisms.

Understanding the interaction of nanoparticles with cells, tissues, and proteins in a precise and systematic manner is essential for the safe design and commercialization of nanotechnology [60]. The developments in the field of nanotechnology will have a significant impact on the future of sophisticated technologies. Thanks to the progress of nanomaterial-based engineering techniques, the dream of clean energy generation is becoming more and more feasible.

These materials have demonstrated encouraging results, paving the way for the development of new generations of hydrogen fuel cells and solar cells, as well as serving as effective catalysts for water splitting and exhibiting exceptional hydrogen storage capacity. In the realm of nanomedicine, nanomaterials have a bright future ahead of them. Nanocarriers can be utilized to transport therapeutic compounds to the patient's body.

Conclusion

With the advancement of nanotechnology and other fields of nanotechnology, nanoparticles are now being employed in a variety of healthcare systems. Because of the utilisation of drug delivery systems and nanosensors, nanomedicine has already proven to be effective in treating chronic infections and SARS-like diseases, among other applications. Preventive medicine, diagnosis, therapy, immunisation, and scientific inquiry are all areas where nanomedicine and its components have the potential to make a major difference. Biosensors based on different nanomaterials, such as quantum dots, can be used to detect illness and make a medical diagnosis. When compared to other creatures' metal nanoparticles, it has been demonstrated that plants' metal nanoparticles are far more stable. More quickly than fungi or bacteria, plants (and especially plant extracts) can decrease metal ions. Through the employment of nano systems such as polymeric, liposomes, lipid, and metallic nanoparticles, and micelles for drug encapsulation, nanotechnology provides advantages and assists in the overall enhancement of pharmacological therapeutic properties. Antiviral nanoparticles can interfere with COVID-19's binding, entry, replication, and budding, among other functions. Toxicological concerns about inorganic nanoparticles are one of the factors preventing their widespread usage. These factors should be further investigated and modified. Biogenic nanoparticles (Biogenic NPs) are ecologically friendly, can be manufactured rapidly, are biocompatible, and have well-defined size and shape. To overcome these limitations of nano drugs and apply this approach to large-scale production, long-term research is required. There is a need for long-term research in order to overcome these limitations and adapt this method to mass production.

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