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Review Article

Green Nanoparticles in Sustainable Therapeutics and Future Sustainability

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ABSTRACT

Green nanoparticles (GNPs) are being produced from microbial and plant sources and have numerous applications in various fields. The article focuses on the NPs that provide various focal points in the many scientific and technological fields for the cutting-edge uses of nanoparticles. Due to their toxicity, cost-effectiveness, ease of use, and environmental friendliness, green NPs are extremely important. It is closely observed how important green NPs are to the development of science and technology in the context of sustainable therapeutics. The only issue with green nanoparticles is occasionally how toxic they can be. A sustainable future, which the entire world looks forward to, is directly related to green nanoparticles and their role in numerous applications.

INTRODUCTION

Recent advances in science and technology have led to amazing discoveries and innovations around the world. The fields that play a significant role in science and technological wonders are nanoscience, nanotechnology, nano-biotechnology, and green nano-chemistry. Nanoparticles are nano-sized particles with at least one dimension at the nanoscale (nm size) either individually or in the material that is made from them [1]. The rapidly emerging technique of nanotechnology, along with green chemistry, is providing safe and environmentally friendly nanoparticles. Green chemistry provides nanomaterials based on plants as the source. Due to the cutting-edge technological production of these particles, they are indispensable and superior to other materials [2]. The innovation of nanoparticles through green chemistry is reducing the poisonous effects of NPs and enhancing their remarkable and methodological properties. This compensation is done by plant metabolites, the counterparts of NPs, and other organic material combinations so that they can be more responsive [3].

Green Synthesis of Nanoparticles

Generally, there are two approaches used for the synthesis of nanoparticles; bottom-up synthesis and top-down synthesis. In bottom-up approach the smaller particles

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combine together to form nanoparticles from the atomic scale up to the nanoscale. Whereas, in top-down approach larger particles are broken down to form smaller particles of nanoscale. Physical method for the synthesis involves mostly the "top-down" approach. The most important methodologies used for physical approach are evaporation condensation and laser removal [4]. The chemical method for synthesis involves the process of chemical reduction using different reducing agents both organic and non-organic and organic solvents [5]. Although, these physical and chemical methods are toxic and have many adverse effects, they are usually carcinogenic and are toxic to the environment because of their non-degradability. And due to these adverse effects on the heath and the environment, an environmentally friendly approach is used that is non-toxic and biodegradable. This method is known as the biological method or green synthesis in which nanomaterials are produced by using green sources such as plants, micro-organisms, etc [6]. The biological method is classified as the "bottom-up" approach. The most reported nanoparticles synthesized by the biological methods are Ag (silver), Au (gold), Se (selenium), Zn (zinc), Cu (copper) and Pt (platinum) synthesized by yeast, fungi, bacteria and actinomycetes [7]. The process of green synthesis or biological synthesis involves the selection of environmentally friendly and biodegradable reducing agents, stabilizers and solvents. These biological entities are the one responsible for the synthesis of metallic NPs by transforming the metallic ions using their reducing abilities present in the proteins of these organisms either plant or microbes [8].

Plant Mediated Synthesis of Nanoparticles

The use of plant as the source of synthesis of nanoparticles is more preferred when compared to microbes because not only are plants non-pathogenic, they also have multiple pathways present for production [9]. Different type of metallic nanoparticles has been produced from plant mediated methods. Recently, silver nanoparticles are being produced by using plants because they provide a fast, single step economical process of synthesis. The plus point of using plant extract for silver NPs is that they are available in bulk and are non-toxic. and due to their vast variety of metabolic pathways the silver ions can be reduced very efficiently [5]. The first nanoparticle of platinum was synthesized by using the extract of *Diopyros Kaki*. Various organic and metabolic compounds such as cellulose and protein are present in plants, and they are used for the production on NPs. The morphology and size of these nanoparticles depend on different types of plants as well as factors such as pH, reaction time and temperature [10].

Microbes Mediated Synthesis of Nanoparticles

Microbial nanoparticle production can be either intracellular or extracellular where extracellular synthesis is more preferred as it is less time consuming and does not require extra steps for the extraction and purification of nanoparticles.

Bacteria as a Source

Bacteria has the ability to reduce metal ions into metallic nanoparticles hence, they are used as the major biological factories for the production of Ag and Au nanoparticles. Also, another reason is that they can be easily manipulated. The bacterium *Delftia Acidovorans* was used to produced pure gold (Au) nanoparticles [11].

Algae as a source

Blue green algae, also known as cyanobacteria, is eco-friendly and proves to be an efficient approach for the synthesis of nanoparticles, most commonly used because of their availability and abundance. As their growth rate is faster than plants so they can be used to produce nanoparticles in bulk [9]. The protein present in the algal extract play the role of reducing agent, stabilizer and are responsible for the shape of the nanoparticle. As of now, there are 30 strains of cyanobacteria that produce silver nanoparticles out of which only one strain is the best for the synthesis called *Cylindrospermum stagnale* [12].

Fungi as a source

The synthesis of metals or metal oxides using fungi gives very well-defined morphologies of nanoparticles, this efficiency is due to the availability of various intracellular enzymes. The best advantage of fungi over bacteria is that the fungi can produce larger number of nanoparticles. The fungus *Fusarium oxysporum* has the ability to produce gold nanoparticles both intracellularly and extracellularly with different size ranges [9].

Table 1: Biosynthesis of variable sizes of nanoparticles under different conditions using the same fungal strain of *Fusarium Oxysporum*

Fungal strain	Optimized Conditions	Size of nanoparticles	References
Fusarium oxysporum	*pH of 9 and 11* *1.5 mM of AgNO3* *Temperature of 40 and 60 °C* *Sunlight + 190.7 Lux*	*10-20 nm*	*[13]*
Fusarium oxysporum	*pH of 6* *10mM of $AgNO_3$* *Temperature of 50 °C*	*5-13 nm*	*[14]*
Fusarium oxysporum	*Biomass conc.: 4.96 gL^{-1}* *5 mM $AgNO^3$*	*25-50 nm*	*[15]*
Fusarium oxysporum	*Temperature of 28°C*	*24 nm*	*[16]*

Yeast as a source

The use of *Saccharomyces Cerevisiae* for the production of gold and silver nanoparticles has been reported. Most important in this context are the *Candida* and *Sargassum* species that are being used for the production of metal and metal oxide nanoparticles. *Saccharomyces Cerevisiae* is

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diversely being used for the synthesis of the gold and TiO_2 nanoparticles. Recently, selenium nanoparticles have also been synthesized using the same yeast strain. The yeasts reduce the selenium ions in the selenium salts that are being used as precursor, leading to the formation of Se nanoparticles. This method was not only cost effective, but also the nanoparticles synthesized this way were very stable[17].

Virus as a source

The biosynthesis of quantum dots using virus is widely studied and is of particular interest. A unique feature of virus is their capsid or protein coat which is a highly dense and reactive surface that has the capability to interact with the metallic ions. The proteins that cover the surface of the virus act as point of deposition for various materials or it can be used for drug delivery. Viruses are also being used as a template for the production of nanomaterials such as nanorods and wires [7]. These viral nanoparticles have profound applications in therapeutics and medical imaging. The properties like fluorescence and bandwidth absorption and emission point towards their role as promising tool in diagnostics.

Therapeutics applications of green nanoparticles

Following are some major therapeutic applications of green nano particles due to their versatility:

Anticancer properties of Green Nanoparticles

There are millions of people dying daily all around the globe and cancer is one of the major reasons for their deaths. Cancer is treated through many methods that can affect healthy cells and compromise normal functioning resulting adverse side effects. For safe treatment of Cancer new approach of green nanoparticles is widely researched.

Silver Nanoparticles as anticancer agent

Silver Nanoparticles (AgNPs) can be biologically synthesized by using three major green sources i.e., Bacteria, Fungus and Plants. Studies have revealed that AgNPs produced using biological sources show inhibitory action against propagation of cancerous cells. AgNPs obtained from 23 plant extracts have been toxic to breast cancer cell line MCF-7 or were used as inhibitor for growth of these cells. The size of AgNPs was recorded to be 5 - 80 nm and they varied in different shapes. Researches have shown cytotoxic effect of AgNPs against human liver cancer cells (HepG2), obtained by using medicinal plan Dandelion, *Taraxacum officinale.* synthesized Ag Nanoparticles using aqueous extract of *Commelina nudiflora L* having tendency to inhibit the growth of colon cancer cells (HCT-116) by increasing cytotoxicity properties of AgNPs. Inhibitory and cytotoxic effects of Ag Nanoparticles against lung and prostate cancer were reported using medicinal plant extract of *Pinus roxburghii.* It is confirmed that AgNPs stops the cell cycle of cancer cells at G2/M phase. An investigation on Lung epithelial cells (A549) revealed that AgNPs exhibit anticancer properties by downregulating enzyme Protein-kinase that ceases the cell cycle at G2/M phase. Using extracts of different plants such as *Teucrium polium*, *Tropaeolum majus*, *Gloriosa superba*, *Moringa oleifer* and *Punica granatum* to synthesize Ag Nanoparticles have shown anticancer properties against different cell lines of cancer cells[18].

Anticancer approach of Gold Nanoparticles

Gold nanoparticles (AuNPs) have gained significance importance over past few decades due its distinct physiochemical properties that makes them idea for the biomedical applications. AuNPs greenly synthesized from different medicinal plant extracts act as carrier for these plant molecules that possess medicinal properties. AuNPs restricts any cytotoxic effect on normal cells that are not cancerous in nature. The properties of AuNPs such as aggregation and size play an important role for eliminating cancer cells, depending upon its dosage. AuNPs exhibit unique property of conjugating with proteins resulting in increased biocompatibility[19].

AuNPs works similar as AgNPs by increasing the reactive oxygen species (ROS) inside the cells that leads to lipid, protein and DNA destruction which ultimately results in the death of cancer cell. AuNPs particles also upregulates pro-apoptotic caspase gene, which plays a significant role in diagnosis and elimination of abnormal cells from the body [20].

Anti-angiogenesis therapy of green nanoparticles

Angiogenesis or neovascularization is a physiological process which occurs throughout life and is defined as the development of new blood vessels from previously existing blood vessels, this process is deemed important for organ repair and development[18]. Looking at its history, the idea of angiogenesis was first introduced by Dr. J Folkman in the late 1900s and is regarded as the father of angiogenesis. It involves different procedures of endothelial cell growth, development, differentiation and migration (18). Several studies have pointed to the vascular endothelial growth factor (VECF) being the leading cause of the progression of angiogenesis. So, the treatment of these tumors would be by the use of anti- angiogenesis drugs, there are various conventional anti-angiogenesis drugs used but they have multiple side effects and resistance [21]. Raj Preeth synthesized copper oxide (CuO) nanoparticles from a green source using a phytochemical, sinapic acid which showed anti-angiogenesis activity on endothelial cells, which confirmed the potential of green nanoparticles in the inhibition of angiogenesis in cancer cells [22]. Green synthesis of silver (Ag) nanoparticles was demonstrated using bacterium *Bacillus licheniformis* which exhibited anti-

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angiogenesis activity by inhibiting the vascular endothelial growth factor in the Porcine retinal endothelial cells (PRECs) which led to the inhibition of capillary or vascular permeability[23].

Drug delivery applications of green nanoparticles

Drug delivery by the utilization of green nanoparticles has taken the world of healthcare and medicine by storm. The use of green nanoparticles for effective and selective drug delivery to the target site is widely used in therapeutics. The large surface area of nanoparticles enables it to carry, bind and absorb different variety of drugs to it. Large Nanoparticles are specifically engineered towards a specific target disease cell, this allows targeted drug delivery which leads to the increase in efficiency, and the management of the drug dosage. Drug delivery using nanoparticles also significantly reduces the side effects of the drug [24]. There are two major measures for efficient drug delivery systems one is slow release of drugs and the other is the delivery of drugs at target site. Green synthesized silver nanoparticles from the plant extract of ***Butea monosperma*** is used for the drug delivery of cancer drugs. These nanoparticles were loaded with the chemotherapeutic drug doxorubicin which is an FDA approved drug used for cancer treatment, these loaded drug delivery systems were given to cancer cells in vitro and exhibited high anticancer activity. This proved that green silver nanoparticles could be efferently used for drug delivery systems [18]. Used a strain of bacterium delftia KCM-006 for the biosynthesis silver nanoparticle which displayed the delivery of miconazole which is an antifungal drug. It was claimed that the drug loaded silver nanoparticles demonstrated efficient inhibition of biofilms of fungus[25].

Anti-Diabetic activity of green nanoparticles

Zinc oxide NPs were investigated against hyperglycemia in mice. Streptozotocin (STZ) was the method to induce diabetes in mice. Toxins like superoxide, peroxide destroy the β cells to induce diabetes[26]. AgNPs and ZnO NPs also have the ability to hinder the action of a-amylase and a-glucosidase enzymes. These enzymes are used to break down complex sugars into simpler ones. Using green nanoparticles, we can inhibit these enzymes from adding more sugar in the blood. When the action of the enzymes blocked by green nanoparticles the rate of adding glucose into the blood lowers down and eventually stopped[27].

Antimicrobial Activity of green nanoparticles

Recent researches have suggested that the biologically synthesized nanoparticles such as the silver Nano-particles are highly toxic against microbes and also exhibit a robust bactericidal effect on the microorganisms that show resistant against a variety of antibacterial drugs[28]. The antibacterial activity of green AgNPs against gram-positive and gram-negative strains of bacteria was exhibited by[29]. *S. aureus* and *E. coli* were used as model organisms to be tested against the bactericidal effect of green AgNPs by utilizing the method of well diffusion**.** The mechanism of antimicrobial effect of silver nano-particles on E. coli and *S. aureus* is due to the loss of replication of ability of DNA molecules and inactivation of several bacterial proteins important in the ATP production in a response to tackle the denaturation effect of the AgNPs.

Anticoagulant Activity of green nanoparticles

The components of the green synthesized nano-particles are not pernicious and thus can be utilized as anticoagulants due to their bio-compatibility. The anticoagulant potential of the AgNPs mediated from the extract of cocoa bean was examined by, equal volumes of blood from a healthy individual and silver nano-particles were mixed to observe the blood clot formation microscopically and macroscopically [30]. The anticoagulant activity of green synthesized AgNPs can be utilized in individual suffering from blood coagulation issues to maintain hemostasis. The maintenance of hemostasis can be a tough call and thus can be aided with the green synthesized AgNPs which are effective and have better and long-lasting effect than the typically used anticoagulants.

Wound healing activity of green nanoparticles

Many green nano particles have proven their ability to heal wounds. Zinc being an essential element also plays a significant role in enhancing wound healing as zinc-oxide. Its use has been observed in chronic and acute ulcer wound healing activity[31]. Green graphene quantum dots coated on Ag-NPs showed successful wound healing of Methicillin-Resistant *Staphylococcus aureus* (MRSA) produced wounds. Excision, burn, and incision wounds were observed to be healed by the use of silver green-NPs produced from cyanobacterium *Phormidium sp.* The healing activity of incision diabetic wounds were seen by use of green Ag-NPs extracted from Cyanobacteria *Synechocystis* sp. Due to high levels of hydroxyproline and better tensile strength of these green-NPs[32].

Green nanoparticles in sustainability

Sustainable therapeutics

The green NPs are playing a great role in sustainable therapeutics production. The super paramagnetic iron oxide nanoparticles are biocompatible and widely used as machinery for targeted drug delivery, cellular imaging, molecular imaging, diagnostics, and tool for reduction of formation of bacterial biofilms and other sustainable therapeutic applications. Biocompatible $Eu^{III}(OH)_3$ nano-rods, and cerium oxide nanoparticles show great effect in pro-angiogenic therapeutics. Green Fe_3O_4 can be used to kill cancerous cells in body [31]. *Andrographis paniculata*

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based green-NPs were seen to have anti-viral, anti-inflammatory, and anti-tumoral behaviors when used as therapeutic agents[33].

Sustainable future with green nano-particles

Green nano-particles are directly related to the sustainable future demands. Green-NPs are not only used in sustainable diverse medicine and therapeutics, but also in sustainable agriculture, food, business, cosmetics and industrial domains. Cleaning products which are non-toxic, eco-friendly energy production, reduced fossil-fuel consumption and sustainable business opportunities were presented by Malaysia by the use of green-NPs synthesis using green-nanotechnology for revolution [34]. Green nanotechnology is a potential tool for achieving 17 sustainable developmental goals (SDGs) by using green-NPs as renewable sources for several sustainable product formation as in industrial revolution [35]. Food quality detection and enhancement is aided by the use of nano-nutraceuticals delivery, nano-biomaterial based food control, nano-coding of plastics as intelligent packaging, nano-scale purification, nano-additives and nano-encapsulated biomaterials in food. Quantum dots-based core shells, gold nano-rods, and carbon nano-tubes based on green-NPs are used efficiently in sustainable agricultural procedures and products [36]. Due to the increased demand of natural and eco-friendly cosmetics, green-NPs are being used in cosmetics under the term of green cosmetics as seen in skin rejuvenation and anti-aging beauty masks. Bioremediation, waste-water treatments, recycling, pollution reduction and many more environmental enhancement strategies used require the use of restricted supply of resources. It is efficiently used in 'greener and cleaner environment' sustainable developmental strategies possible by the use of green nanotechnology based green-NPs[37].

Limitations

Lately, there have been a major advancement in the study of nanoparticles and its applications. Numerous studies have demonstrated the green synthesis of metallic nanoparticles using a range of biological sources, including plants, bacteria, fungi, and yeast [38]. However, a number of problems still exist that prohibit its mass production and subsequent usage such as low yield, irregular particle sizes, challenging extraction procedures, seasonal and regional raw material availability, and other problems that must be handled. To overcome these limitations some of the possibilities are as follows: To regulate the size and form of the nanoparticles, a thorough understanding of the reactants (plant extract, microbial inoculum, fermentation medium composition, etc.) and process variables such as temperature, pH, and rotating speed are mandatory. It is possible to boost nanoparticles generation and stability while reducing reaction time by altering various reaction parameters. Expanding the production of nanoparticles for commercial usage using green synthesis methods must be prioritized. By overcoming these obstacles, it could be possible to produce nanoparticles on a wide scale more effectively and economically than using conventional methods. Another crucial area that has to be researched is the extraction of green nanoparticles from the reaction mixture and subsequent purification of these nanoparticles. In addition to, a comprehensive toxicological investigation of the effects of the green nanoparticles on both plants and animals is necessary before these nanoparticles are utilized more broadly in a range of professions[38-40].

CONCLUSIONS

Nanoparticles, particularly metal and metal oxide nanoparticles, have received considerable amount of attention from the fields of therapeutics, biotechnology, and the environment. These nanoparticles should be biodegradable, environmental-friendly, and energy-efficient in order to be used in large-scale applications. Most of these requirements are met through biosynthesis process which involves the organisms such as green plants, algae, viruses, bacteria, fungi, and yeast. To further comprehend them, a thorough understanding of nanoparticles structure is mandatory in order to avoid toxicity and for sustainability as well as the green synthesis mechanism yet to be investigated. One of the potential ways to increase the effectiveness of green technologies is genetic modification of plants and microorganisms by imprinting the relevant machinery on a portion of their genome. In addition to, the ultimate reliability of green nanoparticles for the prevention, detection, and treatment of cancer is still being determined in clinical studies. Numerous innovative approaches for using green nanoparticles have been taken into consideration since they are effective and biodegradable. These environmental-friendly green nanoparticles may also be utilized in the future to treat a number of cancers for which there is no cure for the time being as they are target oriented and reduces the chances of immunogenicity. Green nanoparticles are widely used for several sustainable processes that will be used in the future. Here, the future sustainability needs based on the role of green nanoparticles in various arenas are discussed. Green nanoparticles are hence directly related to a sustainable future and have a great advantage over conventional nanoparticles usage and production.

Authors Contribution

Conceptualization: TK, A, HR, MW, SW
Writing-review and editing: AR, MS, RA, SMI, AH

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Conflicts of Interest

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