Review Article

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Green-synthesized nanoparticles and their therapeutic applications: A review

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Abstract: Antibiotic-resistant microorganisms are a rising issue when it comes to human health. Microbial pathogens that cause harmful infections are quickly becoming resistant to the antimicrobial action of traditional antibiotics. Nanotechnology, an innovative sector being an indispensable part of healthcare and research, has in-depth and extensive applications. Nano-compounds have been promising antimicrobial agents, anti-cancerous mediators, vehicles for drug delivery, formulations for functional foods, identification of pathogens, food and drug packaging industry, and many more. However, the chemical synthesis of nanoparticles (NPs) has certain drawbacks such as causing toxicity and other adverse effects. For more than a decade, the use of NPs that are conjugated or green-synthesized has gained popularity due to the twofold action of metallic NPs mixed with biological sources. In contrast, NPs synthesized using plant or microbial extracts, conjugated with biologically active components, appear to be a safe alternative approach as they are environmentally friendly and cost-effective. Such environmentally safe techniques are referred to as "green nanotechnology" or "clean technology" and are feasible alternatives to chemical methods. Furthermore, NPs conjugated with natural biomolecules have improved bioavailability and have minimal side effects, as they are smaller in size and have higher permeability in addition to being reducing and stabilizing agents possessing excellent antioxidant activity. NPs serve as potential antimicrobial agents due to their affinity towards sulphur-rich amino acids, adhere to microbial cell walls by means of electrostatic attraction, and disrupt the cytoplasmic membrane along with the nucleic acid of microbes. They possess anticancer activity owing to oxidative stress, damage to cellular DNA, and lipid peroxidation. The green-synthesized NPs are thus a promising and safe alternative for healthcare therapeutic applications.

Keywords: alternative approach, anticancer, antioxidant, drug delivery, eco-friendly

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1 Introduction

Currently, the most widely used technology for translational research has been nanotechnology. This branch has gained immense popularity with the development of metallic nanoparticles (NPs) that employ eco-friendly biological constituents. Green-synthesized NPs have been formulated with nanostructure sizes ranging from 1 to 100 nm, which were synthesized using biological approaches along with techniques involving chemistry, physics, engineering, and computational sciences [1,2]. With wide applications, these biological NPs are considered one of the most promising arenas with varied applications, such as in catalysis, biomedical, environmental, cosmetics, drug delivery, food, health care, optics, and space industries [3,4]. Generally, two strategies are applied to synthesize NPs: the top-down method breaks down larger structures into smaller particles by applying physical, chemical, and biological approaches, while the bottom-up method uses atomic levels for NP synthesis by involving various chemical, physical, and biological reactions to form larger nanostructures (Table 1) [5].

The NP synthesis involving physical and chemical strategies widely uses chemicals with potential hazards, such as the prominently used reducing agents, stabilizers, and solvents that help to prevent colloidal agglomeration. Hence, these chemically synthesized NPs limit their use in biomedicine and other clinical uses due to their carcinogenic and toxic effects on cells [6]. This led researchers to the expansion of an eco-friendly, biologically active, reliable, and clean technique to synthesize NPs [7,8].

Green NPs that implement unicellular and multicellular biological cells such as bacteria, actinomycetes, fungi, plants, viruses, and yeasts have gained attention [9–13]. Green NPs with varied shapes, sizes, and physiochemical properties have been excellent biological systems for NP usage. The most important microbial NP synthesis is to successfully use their potential metabolites such as enzymes, polysaccharides, vitamins, and biopolymers to be used in various applications. These microbes are considered to be one of the best potential biofactory resources for synthesizing various NPs such as gold, platinum, copper, silver, palladium, cadmium, and magnetite. NPs with unique biological, physical, and chemical characteristics have gained immense interest in innumerable applications ranging from biosensors, antimicrobials, optical devices, memory schemes, medical imaging, drug delivery, and hyperthermia of tumours [14].

Table 1: Types of NPs synthesis with their properties and applications

Name	Shape	Properties	Applications	Reference
Nanobubbles	Bubble-like structure at room temperature	Selective drug/ligand delivery to target cells	Gene therapy and cancer treatment	[15]
Liposomes	Shaped like a vesicle with a hollow aqueous core, within a phospholipid layer	Can be used for both hydrophilic and hydrophobic nanodrugs	Can be used as an IV, IM, or topical; it gets degraded in the GI tract	[16]
Superparamagnetic iron oxide NPs (SPIO NPs)	Oval or spherical	They can be coated with silica and have magnetic properties that would help in the absorption of light	Diagnosis of cancer using contrast MRI, treatment of cancer using photothermal therapy and magnetic hyperthermia, drug delivery	[17]
Dendrimers	Complex spherical structures that are highly branched	Has an appearance that resembles trees	Antimicrobial properties (such as against *Pseudomonas*, MRSA, etc.), imaging, vaccination, treatment of cancer	[18,19]
Cadmium selenide (CdSe) NPs	Cubic crystal structure	Photostability, luminescence	Imaging, sensing	[20]
Pt NPs	Polyhedral (octahedral, tetrahedral, cubic, etc.)	Catalytic property	Biocatalyst, sensing	[21,22]

1.1 Green-synthesized NPs using biological components

NPs synthesized chemically and physically using top-up and bottom-up methods require greater energy and manufacturing processes and involve bulk substrates. Further, characterization, low yields, and processes using solvents and chemicals require operative parameters generating greenhouse gases that have toxic effects on both atmosphere and human health [23] (Figure 1). Green-synthesized NPs are eco-friendly and can be prepared by a single-step reduction method that utilizes relatively low energy for their reactions to occur and is found to be highly efficient [24,25]. The activities of the metal oxides were increased when they were synthesized using plants, because biomolecules from diverse sources of plants have strong strengthening reducers and function as stabilizers when combined with numerous kinds of proteins, tannins, phenolic compounds, terpenoids, flavonoids, etc. These sources

Figure 1: Advantages of green-synthesized NPs over conventional physical and chemical methods.

help to release metal ions that enter the cells and interrupt the metabolic processes. NPs conjugated with natural biomolecules are easily absorbed in human cells with fewer adverse effects and have been shown to be more effective. Simultaneously, they function as reducing and stabilizing agents, with reduced size and more penetrating capability, demonstrating good therapeutic action. Green-synthesized NPs are a superior choice in terms of therapies because of their unique properties that include the larger surface area, strong mechanical abilities, nanosize, high porosity, dispersibility, hydrophobicity, and hydrophilicity. Various NPs have been successful in inhibiting the growth of various microorganisms, both pathogenic and non-pathogenic, and act as a potential anti-microbial agent and an antioxidant as observed by various studies. Hence, the current review is focused on the gaps where green NPs have shown significant results in research and application in various fields of medicine. Some of the topics covered in this review include various applications of green nanotechnology in treating cancers, target drug delivery, biosensors, gene therapy, magnetic resonance imaging, and antimicrobial agents [26] (Figure 2).

1.2 Green synthesis and mechanism of NPs using microorganisms

The best choice for NP synthesis is basically the solvent system such as water or the natural extract from the component itself. Ionic liquids are the best choice as they are made up of ions with less than 100°C melting point, and are also referred to as “room temperature ionic liquids.” These ionic liquids are either hydrophobic or hydrophilic

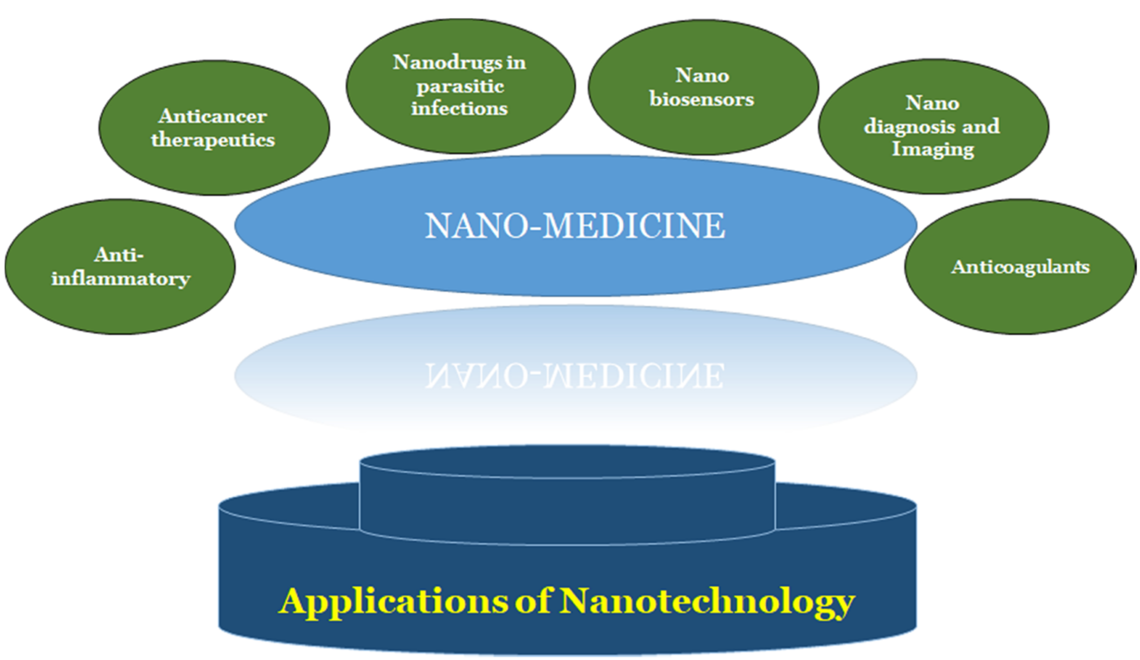

Figure 2: Various applications of nanotechnology in different fields of nanomedicine.

based on the presence of anions or cations. Further, they serve as reductants and protective agents for the synthesis of various NPs such as Ag, Au, Al, and Pt [27]. The NP synthesis in microbes involves both intracellular and extracellular processes and uses various metals and metal oxides [28]. The microbial NP synthesis is also mediated by a biochemical mechanism during cellular detoxification by altering the enzymatic catalysed reduction or precipitation reactions with soluble inorganic or toxic ions. Microbial cells bind to the target toxic metal ions from the environment and convert them into an elemental metal through enzymes. In the extracellular process, the microbes trap these ions onto the cell surface, reducing them by enzyme-catalysed reactions. During the NP synthesis, the metal ions are reduced in the extracellular process by their enzymes, proteins, components of the cell walls, or the organic components used in the culture media. However, the ions are transported from the surrounding intracellular enzymes of the microbes and transformed into NPs by their microbial enzymes. The process involves the electrostatic attraction between the carboxyl groups present in the microbial cells and the metal ions and, further, gets reduced by the intracellular enzymes and cofactors. The enzymes involved in both mechanisms include the oxidoreductases, such as cysteine desulfhydrase, NADH-dependent nitrate reductase, NADPH-dependent sulphite reductase, flavoprotein subunit α along with the cell transporters [29].

1.3 Microorganisms-derived NPs

1.3.1 Bacterial-derived NPs

Bacterial species have been extensively used in various applications that include bioremediation, genetic engineering, and other fields [13]. Bacterial species have been found to be utilized for the preparation of various NPs due to their characteristic properties that reduce metal ions; they are significant NP producers and relatively the process is alleviated by microbial manipulation. Several parameters such as the process involving the production of NPs, pH, temperature, particle size, time, and porosity greatly influence the potentiality of the synthesized NPs [3].

Bacterial species are extensively used for NP synthesis such as bioreduced silver nanoparticles (AgNPs) and employed for their distinctive morphologies of size and shape. Examples of such bacteria are *Bacillus amyloliquefaciens*, *Escherichia coli*, *Aeromonas* spp. SH10, *Phaeocystis antarctica*, *Bacillus cereus*, *Bacillus indica*, *Bacillus cecembensis*, *Shewanella oneidensis*, *Pseudomonas proteolytica*, *Geobacter* spp., *Arthrobacter gangotriensis*, *Corynebacterium sps* SH09, *Lactobacillus casei*, and *Enterobacter cloacae*. Gold nanoparticles (AuNPs) have been synthesized using *Shewanella oneidensis*, *Arthrobacter gangotriensis*, *Desulfovibrio desulfuricans*, *Bacillus megaterium* D01, and *Corynebacterium* sp. *SH09* [30,31].

1.3.2 Fungal-derived NPs

NPs consisting of metal/metal oxide biosynthesis have been effective in generating monodispersed NPs with definitive morphologies due to different intracellular enzymes [32]. Fungal NPs can be synthesized in larger amounts compared to bacteria with additional enzymes and proteins along with reducing compounds that are present in the microbial cell walls [33,34]. A total of 1,500 eukaryotic species of single-celled yeast have been studied and identified. Fungi are used to synthesize metal or metal oxide NPs such as silver, gold, etc. The synthesis of NPs uses the enzyme reductase present in the cell walls or inside the cells [32]. Yeasts have been used for the synthesis of nanomaterials and NPs by various researchers, of which AgNPs/AuNPs and *Saccharomyces cerevisiae* have the potential to be employed in innumerable applications [34].

1.3.3 Algae-derived NPs

Algae have the capability to accumulate heavy metals and are used for the synthesis of biogenic metallic NPs. The dried extracts of unicellular *Chlorella vulgaris* are used to synthesize NPs of various shapes with promising antibacterial activity towards pathogens like *Staphylococcus aureus* that are multidrug-resistant and are alarmingly increasing in nature [35]. The proteins of these algal extracts function as stabilizing agents, reducing agents, and modifiers for shape-controlling mechanisms [36]. A marine algal, *Sargassum wightii*, is also used to synthesize extracellular bimetallic NPs involving Ag, Au, and Ag/Au [37]. Other algal species used for the NP synthesis include *Fucus vesiculosus* [38], *Kappaphycus alvarezii*, and *Spirogyra insignis* [39].

1.3.4 Virus-derived NPs

The virus has been used to synthesize the quantum dots for NP synthesis; the viral capsid has a striking function due to its protein content that helps in the effective synthesis of NPs providing a highly reactive surface to interact with metal ions [40–43]. The tobacco mosaic virus (TMV) is used to synthesize the three-dimensional vessels that help in various pharmaceutical applications. With the prior addition of a low concentration of TMV to Au or Ag salts to the plant extracts such as *Nicotiana benthamiana* (Tobacco round leaves) or *Hordeum vulgare* (Barley), a decreased NP synthesis was seen [44]. Relatively, the TMV serves as a biotemplate to make the nanowires through metallization. However, there has been an unexplored virus potential that needs to be researched for NP biosynthesis and its applications.

1.3.5 Plant-derived NPs

The potentiality to accumulate heavy metals in diverse parts of plants and their extracts has been employed for the biosynthesis of NPs as it favours simplicity, efficiency, and cost-effectiveness as compared to conventional methods. To reduce and stabilize these metallic NPs, the "one pot" method has been employed using different plant extracts. For the green-synthesized NPs, these plants provide biomolecules like carbohydrates, proteins, and coenzymes with efficacy to reduce the metal salts like Au, Ag, ZnO, Ni, Co, and Cu for the biosynthesis of NPs. Various plant extracts used are alfa alfa (*Medicago sativa*), tulsi (*Ocimum sanctum*), lemon (*Citrus limon*), aloe vera (*Aloe barbadensis* Miller), coriander (*Coriandrum sativum*), mustard (*Brassica juncea*), lemon grass (*Cymbopogon flexuosus*), sunflower (*Helianthus annuus*), crown flower (*Calotropis gigantea*), and green tea (*Camellia sinensis*) [45–49].

2 Applications of NPs

Chemically synthesized NPs hold tremendous promise due to their ease of synthesis and wide range of applications; however, it also results in toxic side effects. Green synthesis is a promising and alternative, safe process. Biological NPs are excellent tools that have been implemented in various fields for the detection of pathogens/toxins, diagnosis, wound healing, tumour therapy, etc. (Figure 3). NPs are used to target cancers by drug delivery owing to their small size and they also mitigate the adverse effects caused due to photodynamic cancer therapy. A dye used in photodynamic therapy migrates to the skin and eyes leading to sensitivity that can be prevented by partial encapsulation of the dye in NPs [50]. Furthermore, AuNPs have been pragmatically useful in immunohistochemistry and the identification of protein–protein interactions as observed

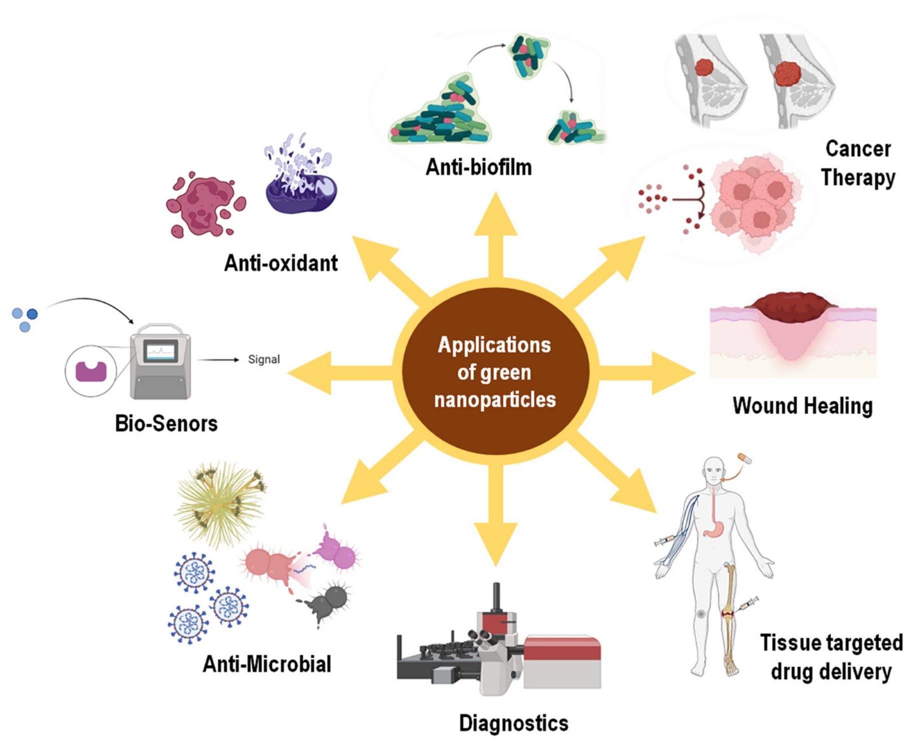

Figure 3: Applications of green-synthesized NPs derived from plants and microbes with varied biomedical applications and therapies.

in the synthesized AuNP-probe with catalytic activity for protein identification [51]. Extensive medical use of chemically made NPs has shown adverse effects that have now been shifted to safer green synthetic bio-NPs. The following section highlights the commercial, medicinal, and other significant applications of green synthetic NPs [49–53].

2.1 Nanodrug delivery systems

2.1.1 Bacteria

With the current lifestyle, there has been increase in multidrug resistant (MDR) pathogens. The use of gadgets such as mobile phones has been an indispensable part of our lives for education, communication, and entertainment with an increased rate of MDR bacteria [54]. The treatment options for these MDR strains are very limited, as seen along with the use of β-lactam drugs in the treatment [55]. Silver (Ag) NPs exhibit antibacterial properties that continuously release Ag^{2+} ions which adhere to bacterial cell membranes and cell walls with cell disruption [53–56]. On entering the cells, Ag^{2+} ions deactivate respiratory enzymes due to the production of reactive oxygen species (ROS) [57]. Accumulation of ROS damages RNA, DNA, and proteins, while Ag^{++} released from NPs binds to the sulphur and phosphorus of DNA molecules and blocks further replication and cell division, eventually leading to cell death. Ag^{2+} ions also denature ribosomes in the cytoplasm further inhibiting protein synthesis [58–60] (Figure 4).

AgNPs accumulate in the cells and alter the membrane structure, resulting in cell lysis [61]. The charges present on the surface of the NP have a substantial role in determining its interaction with the cell membrane. Cationic NPs infiltrate the cell and inflict extensive damage, while anionic NPs do not penetrate the plasma membrane but destabilize it at specific concentrations. The property of charged NPs suggests potential damage to cells as it acts as vehicles for drug delivery to cancerous cells. The denatured cytoplasmic membrane often leads to organelle rupture, eventually resulting in cell lysis. Bacterial signal transduction involves phosphorylation events, which enable them to sense, adapt, and respond to environmental changes. NPs cause dephosphorylation and the disruption of signal transduction leading to apoptosis. Ag NPs are spherical or quasi-spherical and can easily release Ag^{2+} ions due to their larger surface area [62].

In order to avoid agglomeration, capping agents are used to coat the NPs, which modifies their surface and affects their dissolution. The presence of inorganic and organic substrates in the medium also affects the NP dissolution by aggregating with them. It has been very well noted that Ag NPs release Ag^{2+} ions effectively and faster in an acidic solution as compared to neutral solutions [63]. A different mode of action by NPs has been observed in both Gram-negative and Gram-positive bacteria owing to the presence of peptidoglycan in Gram-positive bacteria, which hinders efficient penetration [6]. NPs with

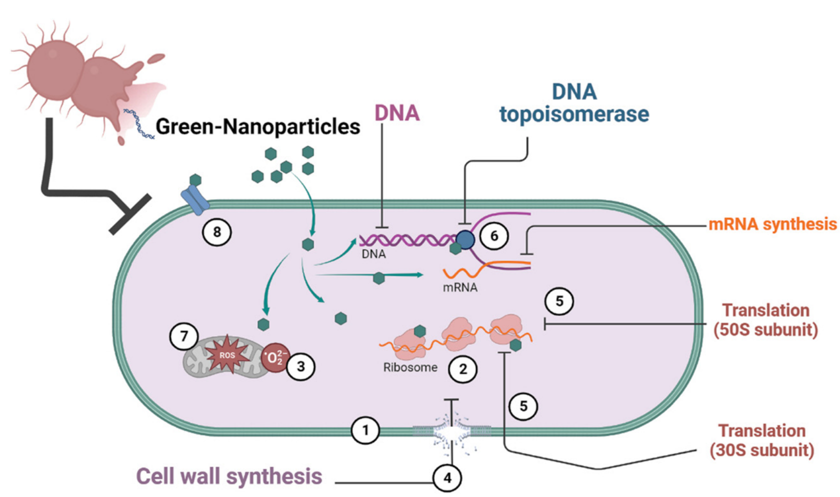

Figure 4: Mechanism of bacterial destruction by the green-synthesized NPs. (1) Metal NPs attack the bacterial cell wall and cell membrane. (2) Generates ions from the metal NPs that bind ribosomes and denatures them. (3) ROS starts to accumulate. (4) ROS with NPs ruptures the cell membrane. (5) Protein structure gets altered and damaged. (6) DNA denaturation occurs. (7) Inhibits electron transport chain. (8) Receptor sites are bounded by metal NPs causing conformational changes, which eventually, lead to cell death.

10 nm or less in size have direct cell wall permeability that enables them to enter into bacteria and cause cellular impairment, which suggests a direct correlation between the NP uptake and its antibacterial property [63–65]. Hence, Ag NPs have a greater potential as antibacterial agents, while the application of AgNPs as a biofilm inhibitor needs further investigation [66]. NPs of magnesium oxide are reported to possess anti-biofilm and anti-adhesion properties, thereby making them efficient against drug-resistant bacteria [67]. Cerium oxide (CeO_2) NPs have been noted to have potential applications. The green-synthesized NPs of CeO_2 are well known for their antibacterial and antifungal activities against various pathogens [68].

2.1.2 Fungi

Studies on antifungal activity are limited, as it has been observed that the concentration-dependent inhibitory activity is probably low due to the saturation of fungal hyphae with higher-density NPs, leading to pathogenic fungal inactivation [69]. While the studies on the effect of Ag ions on fungi are limited, reports suggest their inhibitory effect on the replication of DNA and inactivate ribosomes, enzymes, and proteins involved in ATP production [70,71]. Ag NPs synthesized with ribose sugar that acts as a reducing agent and sodium dodecyl sulphate as a capping agent showed antifungal properties against highly resistant fungi *Candida albicans* and *Candida tropicalis* [72]. Similar results against fungal infections were obtained by other researchers too [73]. Fungal cells sustained with an ion gradient, trehalose, and glucose protects the biological viability of cells from protein denaturation caused by environmental stresses such as heat, cold, high pH, dehydration, oxidative stress, and toxins [74]. NPs disrupt the membrane structure and subsequently the permeability, causing leakage of cell contents intracellularly along with damage to the membrane potential. Observations under a TEM depict the formation of pits in the fungal membrane when treated with Ag^{2+} ions leading to cell cycle arrest and death in *Candida albicans* with additional destruction of membrane and inhibition of budding [73]. Palladium NPs demonstrated effective antifungal activity against *Colletotrichum gloeosporioides* and *F. oxysporum*, although in a size-dependent manner, by disrupting cellular integrity, generating reactive species, and creating an osmotic imbalance in pathogens [75,76].

2.1.3 Viruses

While several viral diseases have been eradicated, emerging threats from novel viruses cannot be ignored due to their adaptability and mutagenic ability [77]. Hence, such viruses pose a continuous challenge to the scientific community. Enfuvirtide is one such synthetic peptide drug, permitted by US Food and Drug Administration (FDA), which targets the HIV gp41 envelope protein and prevents its fusion [78]. Under such challenging circumstances, NPs emerge as promising antiviral mediators for their exceptional physiochemical features and high surface area [79]. NPs block the attachment and entry of infectious viral particles by obstructing the multivalent interactions between viral cell surface mechanisms and host receptors on cell membranes (Figure 5) [80]. Previous studies have demonstrated the efficacy of NPs against HIV-1 [79,80], hepatitis B virus, Herpes simplex

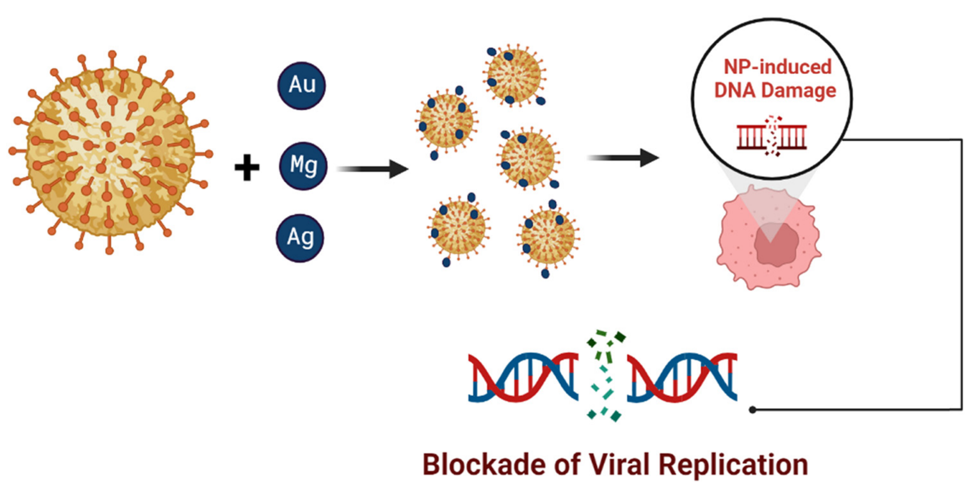

Figure 5: Metallic NPs attach to the cell surface proteins and viral genomes further stopping the replication process.

virus type 1, monkeypox virus, and influenza [81–84]. Although the interaction and efficacy of NPs against viruses were largely dependent on the size of NPs, they also interacted at specific sites. NPs also bound strongly to sulphur-containing residues of GP120 [82]. Both Ag and gold NPs have promising antiviral properties, particularly against enveloped DNA/RNA viruses.

2.1.4 Parasitic infections

NPs have been recently used alone and/or with a combination of the recommended drug in the antimalarial treatment that has helped to represent an innovative therapy [85]. AgNPs synthesized with leaf extracts of *Anisomeles indica* and *Carissa spinarum* were effective against the mosquito species such as *Anopheles subpictus*, *Culex tritaeniorhynchus*, and *Anopheles albopictus* with toxicity [86–90]. AgNPs synthesized using *Bacillus safensis* have potential activity against *Anopheles gambiae* larvae and showed 100% mortality with LC50 of 42.19 $\mu g \cdot mL^{-1}$ [91]. The *Hyptis suaveolens* and *Leucas aspera* leaf extracts were used to synthesize AgNPs that displayed larvicidal commotion against *Aedes aegypti*, *Anopheles* spp., and *Culex quinquefasciatus* [92]. A seaweed *Ulva lactuca* extract of AgNPs displayed a potential activity against *A. stephensi* with inhibitory activity against *Plasmodium falciparum* [90,93]. Leaf extracts of *Cinnamomum zeylanicum* used with the AgNP synthesis exhibited mosquitocidal activity and the NPs had greater efficacy towards larvicidal activity, as also observed with the flower extracts of *Couroupita guianensis* [91].

Trypanosomiasis, occurring in two major forms, has accounted as a severe disease in humans and includes American and African types. Sleeping sickness or African trypanosomiasis is transmitted by the vector tsetse fly, caused by haemoflagellate parasite *Trypanosoma brucei*, and affects millions of people leading to death if not treated; however, the American type is called “Chagas disease,” and is caused by *Trypanosoma cruzi* [92]. The use of NPs for the treatment of trypanosomiasis has not been much researched yet; however, there are few reports of spherical AgNPs (4–9 nm) and AuNPs (7–22 nm) that had potential activity against it [93]. The crude extract of *Callistemon citrinus* when used in the AgNP biosynthesis has antitrypanosomal activity. It has been noted that the bioactive agents derived from *Serratia marcescens* and *Chromobacterium violaceum* when used in AgNP and AuNP syntheses inhibited the growth of *Trypanosoma brucei* gambiense, however, at a lower rate [94,95].

3 Anti-inflammatory agents

Detecting NPs is difficult due to their little or no detection signals; however, it is notable that NPs are useful in delivering drugs that reduce inflammation. In certain autoimmune diseases, such as rheumatoid arthritis (RA), which is a chronic syndrome characterized by rapid progression, swelling, inflammation, and eventually, destructs joints. The available medications for the treatment, although initially beneficial, cause adverse side effects during long-term use (Table 2). An improved method of administration of the drugs would be to administer them directly at the site of inflammation. This would be an arduous and expensive task. This can be done using NPs as vectors that target and administer the anti-inflammatory drugs straight onto the inflammation sites [110]. This can be observed in several studies where NPs as encapsulated drugs containing liposomes are used to deliver drugs, such as glucocorticoids and clodronate, targeting arthritis in animal models [111]. An additional study on an RA model observed that clodronate liposomes when administered through the IV route could potentially suppress the onset of the disorder by specifically targeting the macrophages [112]. In a study done on adjuvant-induced rats, it was observed that when glucocorticoid prednisolone was encapsulated in polyethylene glycol (PEG)-coated liposomes and when these NPs were directed to rats, it was evidenced to be effective tenfold more compared to the usual approach. Symptoms were seen to have disappeared within 2 days and the rats were in complete remission after 6 days [113]. These observations show that NPs can be considered potential candidates for anti-inflammatory actions in disorders, especially autoimmune disorders.

4 Anticoagulants

The current procedures for the control and prevention of blood clots during surgical procedures, bloodlines, and treatment of thromboembolic events are majorly dependent on heparin-based anticoagulant drugs. Although effective, these anticoagulants require constant monitoring and need neutralization using antidotes [114] due to the bleeding risks associated with their administration, which is more prevalent among patients with a high bleeding risk [115]. NPs aim to overcome these associated risks by being used as anticoagulating agents. Magnetic NPs are a potential candidate in the areas of magnetic resonance imaging, drug delivery, gene transfer, and

Table 2: Synthesis of microbial-derived NPs and their application in various fields of medicine

Microorganism	Metal	Size (nm)	Shape of the NP	Applications	Reference
K. pneumoniae, *E. coli*, *Enterobacter cloacae*	AgNP	28–122	Round	Antimicrobial agents, electrical batteries, and optical receptors	[96]
Lactobacillus casei	AgNP	20–50	Sphere-shaped	Bio-labelling drug delivery, cancer treatments	[97]
Bacillus cereus	AgNP	20–40	Round	Pathogens colonization by *E. coli*, *S. aureus*, *P. aeruginosa*, and *S. typhi* is inhibited by the green-synthesized NPs	[98]
P. proteolytica, *Bacillus cecembensis*	AgNP	6–13	Globular	*P. antarctica*, *P. proteolytica*, *A. gangotriensis*, *A. kerguelensis*, *E. coli*, and *B. indicus* are inhibited by the potential AgNPs	[99]
Bacillus indicus	AgNP	—	—	Antimicrobial activity, catalysis	[100]
Shewanella alga	AuNP	At pH 7: 10–20 At pH 2: 5: 15–200 At pH 2: 20	Wedge-shaped	pH-dependent synthesis of NPs	[101]
Desulfovibrio desulfuricans	AuNP	20–50	Round	Catalysis reaction	[102]
*Rhodopseudomon*as capsulate	AuNP	10–20	Triangular	Cancer hyperthermia	[103]
Magnetospirillum magnetotacticum	Fe_2O_3NP	47	Handle-shaped cluster		[104]
Klebsiella aerogenes	Cadmium sulphide (CdS) NP	20–200	—	—	[105]
E. coli	CdSNP	2–5	Labelled with fluorescent probe	Wurtzite structures	[31]
Aspergillus flavus	AgNP	1–8	Isotropic		[106]
Aspergillus niger	AgNP	20	Sphere-shaped	Antimicrobial activity	[107]
Fusarium solani	AgNP	5–35	Round	Biolabelling, sensors, drug delivery	[108]
Aspergillus fumigates	AgNP	5–25	Circular	Coating for solar energy absorption and material for intercalation for electrical batteries	[11]
Penicillium fellutanum	AgNP	5–25	Circular	Surface coating and thin film for various applications	[109]

magnetic drug targeting [116]. In a study done in 2018, the heparin-stabilized ferrimagnetic iron oxide nanoparticles (Hep-SPIONs) were used for haemodialysis and classified as an active nano-anticoagulant. Compared to the commercial heparin widely used for medical procedures, these Hep-SPIONs showed similar anticoagulant activity and have the promising magnetic ability. This is further supported by the fact that Hep-SPIONs also exhibit significant blood compatibility without severe toxicity in an animal haemodialysis model. Since Hep-SPIONs show these considerable properties, they can be potentially used as an effective and safe treatment for a number of purifying blood procedures in the future [117].

5 Thrombolytic activity

Cardiovascular disorders, such as myocardial infarctions, venous thromboembolisms, and ischemic strokes, are a group of potentially fatal disorders with high morbidity and high mortality that are primarily caused by thrombotic occlusions of blood vessels [118,119]. Currently, these can be treated by thrombolytic drugs/therapy by the use of injections containing plasminogen activators (PAs). The use of PAs has major limitations and can have side effects such as rapid drug elimination from the body, narrow therapeutic window, and haemorrhagic risks. Nanomedicine, which is an amalgamation of medical applications and nanotechnology, can reduce the potential fatal side effects of the present thrombolytic drugs [120].

6 Anticancer therapeutics

NPs have long been studied for potential anticancer properties and, in certain studies, specific NPs have been seen to exhibit anticancer properties. In a study published in 2019, it was observed that titanium oxide nanotubes were coated with selenium NPs; the latter were seen to prevent the growth of MG-63 cancer cells. The TiO_2 tubes coated with these Se-NPs were capable of exhibiting anticancer properties along with other beneficial properties such as antibacterial properties [121]. The existing therapeutic strategies meant to tackle cancer in the form of cancer chemotherapy and cancer biology are far from being used at their optimal levels, as expected [122]. The usage of mesoporous silica NPs has been used effectively as a drug delivery vector due to their faster dissolution rate of the drugs being dissipated. This is further supported by better availability and stability within *in vivo* environments (Table 2) [123]. While graphite g-C_3H_4 has been used for various activities like remediation, energy production, microbial disinfection, and drug delivery, especially in cancer therapy has been a potential resource due to its effectiveness, surface activity, stability, and biocompatibility [124]. Green-synthesized CeO_2 NPs have also shown promising and potential activity against cancers and also for diabetes due to their stability [125].

7 Nanobiosensors

Certain organic compounds have been used as antimicrobial packaging materials such as essential oils, organic acids, and bacteriocins [126]. Nanobiosensors are used in the food industry for pathogen detection during processing [127]. Many NPs like Ag, chitosan, copper, and metal oxide NPs like zinc oxide (ZnO) or titanium oxide (TiO_2) have antimicrobial properties [128]. Conventional methods for infectious disease diagnosis are slow with low efficiency, time-consuming, and complicated processes, especially during emergencies. Microbial biosensors have made a benchmark by providing a rapid, inexpensive, and accurate for diagnosing infectious agents, hormonal imbalances, and DNA. Epinephrine was determined by immobilizing *Phanerochaete chrysosporium* ME446, a white rot fungus, using glutaraldehyde crosslinked with gelatin on a Pt electrode for NPs ranging from 5 to 100 µm in size with 1.04 µM detection limits. Epinephrine was converted into epinephrine quinone by redox reactions in fungal cells, which are catalysed by lactase enzyme, thus increasing the current flow [129]. For viral infections, as observed in rat basophilic leukaemia, mast cells form an exocytotic response within minutes of the addition of antigens that have been used to construct biosensors for pathogen detection [130]. *E. coli* SOS-EGFP was analysed to study the SOS response triggered following harmful chemicals in DNA, which was noted in DNA damage detected by the fluorescent protein controlled by a recA gene promoter [131]. Lab-on-a-chip, which works on the electrochemical system by integrating microbes onto a microfluid chip, has been fabricated as a microfluid device that enables the detection of the analyte even at very low concentrations by energetically transferring the targeted analyte to the surface of the microbial biosensors [132]. Forensic identification for recognition of body fluidic traces containing DNA and miRNA as evidential proof has been analysed using microbial biosensors [133]. These portable biosensors might be a promising array system that can help to minimize cost and increase the speed with efficiency.

8 Nanoimaging

Currently, NPs have been used as a potential tool for diagnosis purposes. The role of NPs as multimodal and multifunctional imaging at a molecular level has been an additional advantage. Further, their nanoscale size, loading capacity, and controlled release patterns with tailored surfaces have enhanced their potentiality and hence gained immense popularity and strategy for cancer diagnosis. Magnetic NPs using iron oxide have been used in magnetic resonance imaging (NMR), as drug delivery systems, cancer treatment, and therapy with magnetic fluid hyperthermia [134]. The most minute details of the critical growth of the lethal cancerous cells can be checked by imaging the sentinel lymph nodes (SLNs). Food-grade honey can be used for the synthesis of carbon NPs in SLN imaging, for its strong optical absorption in the near-infrared regions, smaller size, and rapid lymphatic transport for greater resection of the SLN and reduces the complications in axillary investigations using low-resolution imaging process [135]. Grape juice synthesized for fluorescent carbon NPs is simple, chemically free for hydrothermal treatment with less toxicity, and excellent stability has been employed as probes for cellular imaging, which might be an alternative to the traditional quantum dots [136]. These imaging probes of fluorescent NPs are the current labelling technique that can be expected in near future as new medical diagnostic tools owing to their photostable properties and brightness [137].

9 Future perspectives

Nanotechnology has been growing rapidly with an extensive range of applications in various arenas. NPs affect humans and animals and cause numerous health disorders of the lungs, kidneys, etc. However, there is still a lack of information on the risks associated with prolonged use that needs to be worked on. Green synthesis offers a safe mechanism to produce non-toxic NPs with additional beneficial effects. Green synthesis has already been applied in several fields owing to the use of natural alternatives. Nanomedicine is presently one of the most striking research areas that span the diagnosis and therapeutics options including cancer, drug delivery, etc. There is a need to generate NPs of uniform sizes, consistency in properties, biocompatible with drug loading, and release only to the target cells. Though NPs are known to have a significant advance in the field of diagnosis and therapy, their anticipation needs to be extended in other areas like treatment for parasitic infections and response in cancer therapy, which has been neglected and remains limited. The main fundamental research needs to be on the fundamental markers of NPs to allow the specific target sites of diseased tissues without altering the normal cellular functioning; emphasizing the molecular genetics of diseases will help further to signify the advanced nanomedicine, modelling cell interactions with drugs, and animal model studies. The toxicity and efficacy of these NPs need further research. An interesting upcoming area is the development of personalized healthcare that needs to be built on the concepts and mechanism by including nanodevices and nanorobots for successfully handling the near future with care; these green-synthesized NPs are potentially viable and can be a safe biomaterial.

10 Summary and conclusion

Recent years have seen a lot of increasing demand for environmentally friendly based green technology using plants and microbes. With the increasing demand for NPs synthesized from biological sources, the research has paved way for their varied applications. NPs are generally utilized for their antimicrobial properties resulting from their metal components to act against bacteria, fungi, and certain viruses. However, green-synthesized NPs being eco-friendly and low cost have different biomolecules as vital components that have gained immense popularity. The antimicrobial properties of green-synthesized NPs are employed in various industries such as in food packaging, active agents in skin care products, treatment for diseases, and drug delivery. The role of this novel nanomedical discipline has been well reported with its antimicrobial, anticancer, antioxidant, anticoagulant, antiparasitic, diagnosis, and nanoimaging properties. Although it is to be noted that overuse and extensive deployment of NPs might lead to toxicity due to the accumulation of metals and ions that are released leading to lethal effects on humans, currently, concentration usage has not been signified yet. In conclusion, green synthesis is a largely positive and quite significant venture in all fields of science where the use of biological and biodegradable resources used in the synthesis of NPs will undoubtedly lead to an eco-friendly era. However, some shortcoming challenges need to be studied, such as the extraction process, non-uniform particle sizes, environmental parameters, biological resources used, and most important application without toxicity. Improvising green-synthesized NP particles with reference to the above challenges will undeniably be a great choice in a simple, low-cost, energy saving, and substantial process. It will further help to investigate the future challenges and issues in understanding their translation to clinical trials and offer in the future development of improvised health care, especially in personalized medicines.

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