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Biological agents for synthesis of nanoparticles and their applications

Chetan Pandit [a], Arpita Roy [b,*], Suresh Ghotekar [c], Ameer Khusro [d], Mohammad Nazmul Islam [e], Talha Bin Emran [f], Siok Ee Lam [g], Mayeen Uddin Khandaker [g,*], David Andrew Bradley [g]

[a] Department of Life Sciences, School of Basic Sciences and Research, Sharda University, Greater Noida, India
[b] Department of Biotechnology, School of Engineering & Technology, Sharda University, Greater Noida, India
[c] Department of Chemistry, Smt. Devkiba Mohansinhji Chauhan College of Commerce and Science, Silvassa 396 230, University of Mumbai, Dadra and Nagar Haveli (UT), India
[d] Research Department of Plant Biology and Biotechnology, Loyola College, Chennai, Tamil Nadu, India
[e] Department of Pharmacy, International Islamic University Chittagong, Chittagong 4318, Bangladesh
[f] Department of Pharmacy, BGC Trust University Bangladesh, Chittagong 4381, Bangladesh
[g] Centre for Applied Physics and Radiation Technologies, School of Engineering and Technology, Sunway University, 47500 Bandar Sunway, Selangor, Malaysia

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ABSTRACT

In terms of cost-efficiency, biocompatibility, environmental friendliness, and scalability, green nanoparticle (NP) synthesis is a novel field of nanotechnology that outperforms both physical and chemical approaches. Plants, bacteria, fungi, and algae have lately been used to produce metals and metal oxide nanoparticles as an alternate method. The development of alternative strategies to restrict the growth of hazardous bacteria, as well as the building of resistance by germs to various antibiotics, led to the introduction of nanoparticles as novel antimicrobial agents. Metal oxides have been found to form oxide monolayer structures for drug delivery when they react with a transporter's surface. Metal oxide nanoparticles have emerged as biomedical materials in recent years, with applications in immunotherapy, tissue treatment, diagnostics, regenerative medicine, wound healing, dentistry, and biosensing platforms. Biotoxicology and its antimicrobial, antifungal, and antiviral characteristics were hotly contested. Metal oxide nanoparticles have tremendous applicability and commercial value, as evidenced by important discoveries in the realm of nanobiomedicine in terms of locations and amounts. This paper describes the production of nanometal oxides from various green materials, as well as their applications.
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1. Introduction

Nanobiotechnology is a novel concept and area of nanotechnology that has attracted worldwide interest. Green nanotechnology is the ideal approach to minimize the effects of nanomaterial manufacturing and application while also reducing the risks of problems associated with other methods (El Shafey, 2020; Rzayev et al., 2021; Ramalingam et al., 2021; Murthy et al., 2021). Fig. 1 shows the biological synthesis of nanoparticles (Patra and Baek, 2014). Chemical conditions, reaction circumstances e.g., temperature and pH which can change the structural attributes of nanoparticles such as size and shape. Nanotechnology is the utilisation of nanoparticles that have a very small size and a much larger surface area than its bulk form (Arasu et al., 2019; Roy, 2021; Savunthari et al., 2021; Kaur and Roy, 2021). Nanomaterials have a variety of properties, including chemical, optical, and thermal capabilities (Al-Dhabi and Valan Arasu, 2018). Several bulk materials possess different properties when studied at the nanoscale. One known reason for this phenomenon is because of their higher aspect ratio. For different nanoparticles, this can result in a variety of characteristics. As a response, nanomaterials have considered as potential alternative for use in a variety of biological applications (Valsalam et al., 2019a,b; Abd Elkodous et al., 2019). Due to their biocompatibility, anti-inflammatory and antimicrobial action, effective drug delivery, bioactivity, bioavailability, tumor targeting, and biological absorption, NPs are frequently utilized in biological, medical and environmental applications (Magdalane et al., 2018; Valsalam et al., 2019a,b; Al-Dhabi et al., 2019; Salem and Fouda, 2021; Khalith et al., 2021).

* Corresponding authors.
E-mail addresses: arbt2014@gmail.com (A. Roy), mayeenk@sunway.edu.my (M. U. Khandaker).

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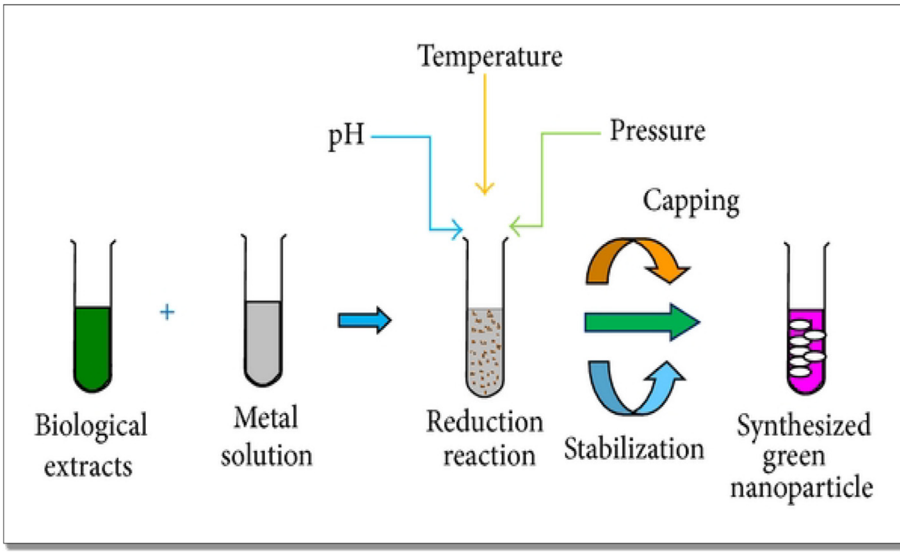

Fig. 1. Biological synthesis of nanoparticles (Patra and Baek, 2014).

Nanoparticles have potential applications and have gained considerable interest in different fields such as medicine, materials chemistry, information technology, agriculture, biomedical, optical, catalysis, electronics, environment, energy, and sensors (Arokiyaraj et al., 2015; Kalaiselvi et al., 2016; Surendra et al., 2016a,b). These metal oxide nanoparticles include copper oxide, zinc oxide, iron oxide, titanium oxide, magnesium oxide, cerium oxide, zirconium oxide, etc (Helan et al., 2016; Surendra et al., 2016a,b; Roy and Bharadvaja, 2019; Roy, 2021, Ahmed et al., 2021a,b). Ultimately, our aim is to provide a strategy for "green" synthesis and associated components that will help researchers working in this area while also serving as a useful reference for readers interested in the subject in general (Singh et al., 2018). Green synthesis methods utilize biological agents such as viruses, bacteria, fungi, algae, and plants for the synthesis of nanoparticles. Bacteria, fungi, and viruses that are used for the synthesis of nanoparticles are nonpathogenic in nature because they should not interfere with the application of synthesised nanoparticles (Raina et al., 2020; Ahmed et al., 2021a,b). The aim of this review is to provide a summary of various green synthesised metal oxide nanoparticles and their potential role in applications.

2. Methods of nanomaterial synthesis

Nanoparticles have been extensively investigated because of their remarkable properties, which are influenced by their structural shape, and many studies have used chemical and physical techniques to synthesize nanoparticles. The 'top-down' and 'bottom-up' techniques to nanoparticle synthesis are shown in Fig. 2. Nanoparticles are made by dissolving bulk materials into small particles in the top-down technique such as lithography, sputtering, mechanical [e.g., milling, grinding], chemical etching, thermal evaporation, pulsed laser ablation, and photo reduction (Chang et al., 2013; Hou et al., 2019; Bukka et al., 2019). The main advantages of top-down approach are the cost and controlled shape and size of the product (Mijatovic et al., 2005). This method provides consistency in terms of particle shape, size, and geometry, and provides a monodisperse population with improved yields, allowing the scale-up of manufacturing. It also improves encapsulation efficiency and drug stability (Aryal et al., 2019). Top-down approaches are good for producing structures with long-range order and for making macroscopic connections. The top-down technique, on the other hand, has a key flaw i.e., surface structure is incomplete. In the bottom-up approach, wet-chemical processes [e.g., chemical reduction or oxidation of metals ion] solid-gel chemistry, co-precipitation, microemulsion, chemical vapour deposition [CVD], hydrothermal, pyrolysis, radiation induced, solvothermal, and electrodeposition procedures are used (Mazari et al., 2021). Bottom-up synthesis, known as self-assembly, involves putting together nanoparticles from tiny components including molecules, atoms, and smaller particles (Thiruvengadathan et al., 2013). These are, though, damaged by the usage of possibly dangerous and harmful ingredients, more expensive, ecotoxicity, high consumption levels and long response time by-products. Most chemical methods use harmful reducing agents such as ethylene glycol, sodium borohydride [NaBH4], sodium citrate and hydrazine, but these methods result in poor particle sizes and size distribution regulation, necessitating the use of additional capping agents such as polymers [e.g., polyethylene glycol, poly[vinylalcohol], ascorbic acid, and polyvinylpyrrolidone [PVP] (Mukherji et al., 2018), and dendrimers, surfactants [e.g., sodium dodecyl sulfate, cetyl trimethylammonium bromide [CTAB], phospho lipids, and gemini surfactants were required in steric stabilization to prevent nanoparticle agglomeration (Talib, 2016). The stabilizing and reducing agent adsorption on the nanoparticle surface is then cleared with a high heat decomposition process, which may limit the active site of the particle, resulting in a reduced surface area and lower product reactivities (Kango et al., 2013). Thermal annealing is also required to achieve good crystalline sample. The high cost and toxic qualities of this synthetic approach may restrict its use on a large scale. Furthermore, the products developed by this technique have poor efficiency (Hu and Zhu, 2015).

Biosynthesis is a green technique that involves metal atoms creating clusters and eventually nanoparticles, and it synthesised from the bottom-up method. Chemical reduction is related to the biosynthetic idea, although green materials are used instead of expensive and toxic chemicals to synthesise nanoparticles. Researchers used adverse reaction monitoring to distinguish between biochemical reduction of nanoparticles utilising green synthesis and a traditional wet-chemistry technique were used (Sharma et al., 2019). The cytotoxicity and phytotoxicity of green nanoparticles were significantly lower than those of wet chemical nanoparticles, demonstrating that green nanoparticles are harmless and can be employed broadly in biomedical applications, nota-

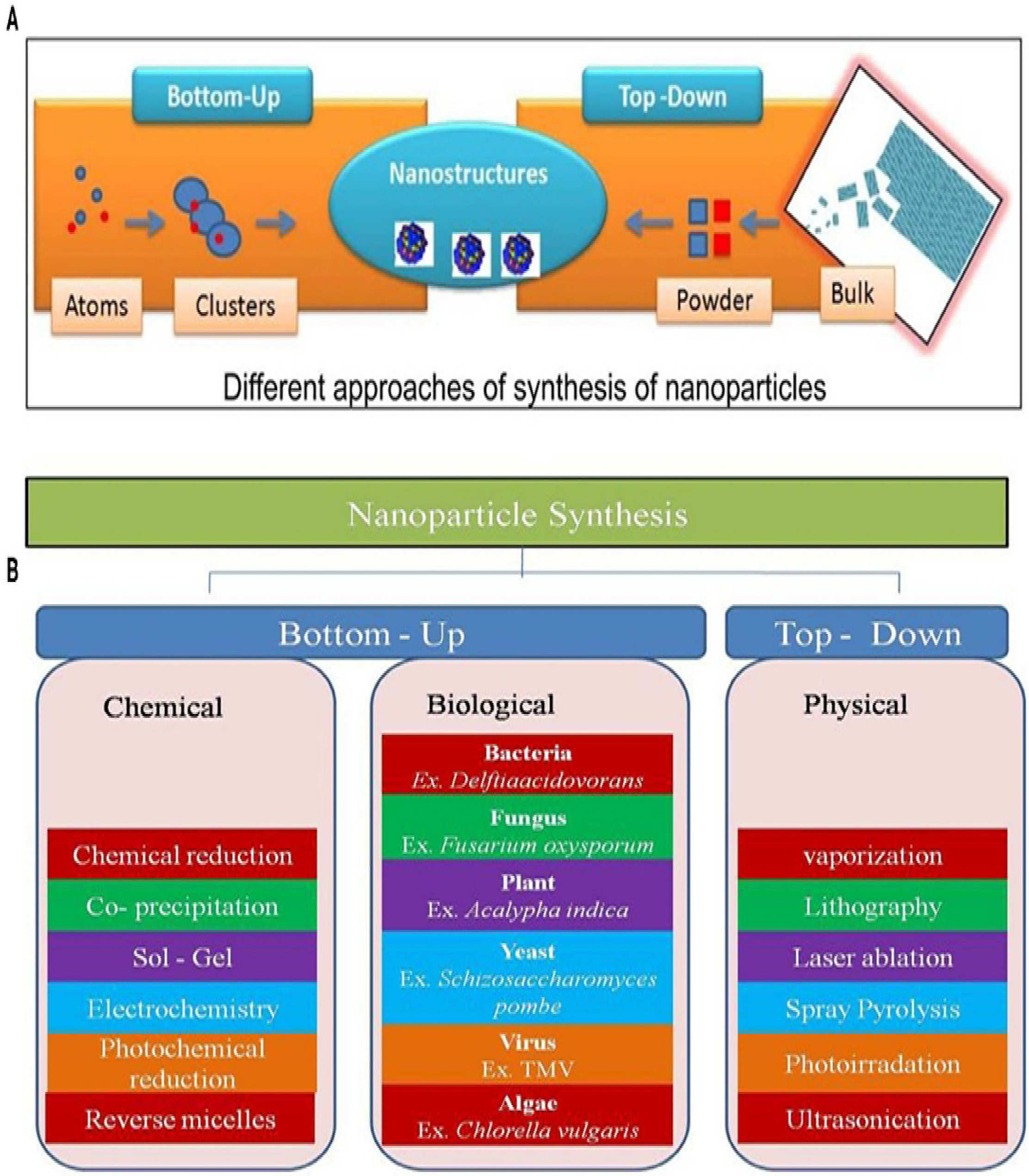

Fig. 2. Method of synthesis (Zhang et al., 2020).

bly in melanoma research (Shankar et al., 2021). As a result of these factors, as well as an increasing awareness of the significance of biosynthesis had been lauded as an auspicious eco-friendly alternative that seems to provide finest methodology or outputs among core green chemistry approaches (Fig. 3). Plants, algae, fungus, yeast, or bacteria are few biological agents present in nature. The structure and appearance of synthesised nanoparticles are significantly determined by the nature of biological entities. The diverse spectrum of biological entities has resulted in a fascinating array of nanoparticle shape and sizes, with the entities serving as a blueprint for nanoparticle development Fig. 3.

Nagajyothi et al. (2014) produced gold (Au) nanoparticles of diverse shapes from *Lonicera japonica* flower extract, including face-centered cubic, quasi-spherical, trilateral, and hexagonal structures, with size of 8.01 nm for Au nanoparticles. Algae & seaweed are two more reducing agents that have newly surfaced. The brown algae *Cystoseira baccata* was used to make Au nanoparticles, which are thought to have great potential in the treatment of colorectal cancer. Platinum (Pt) salts and protein concentrations both influence the form and size of Pt nanoparticles in biogenic production. Fungi such as *Neurospora crassa* or *Fusarium oxysporum* are also being discovered as a viable "scale-up" approach for the synthesis of PtNPs. Similarly, metal nanoparticles were biologically produced using extracts from plants, with phytochemical components present that act as capping agents (Jan et al., 2021). Studies demonstrate the wide variety of biological entities found naturally and provide a number of advantages. By altering parameters such as plant extracts, boiling duration, acidity, extract ageing effects, and temperature synthesis of nanoparticles can be done. Biogenic synthesis is ideal due to the existence of numerous biomolecules, cost effectiveness, good stability, lack of toxic chemicals, and simple and safe operation procedures (Sharma et al., 2019).

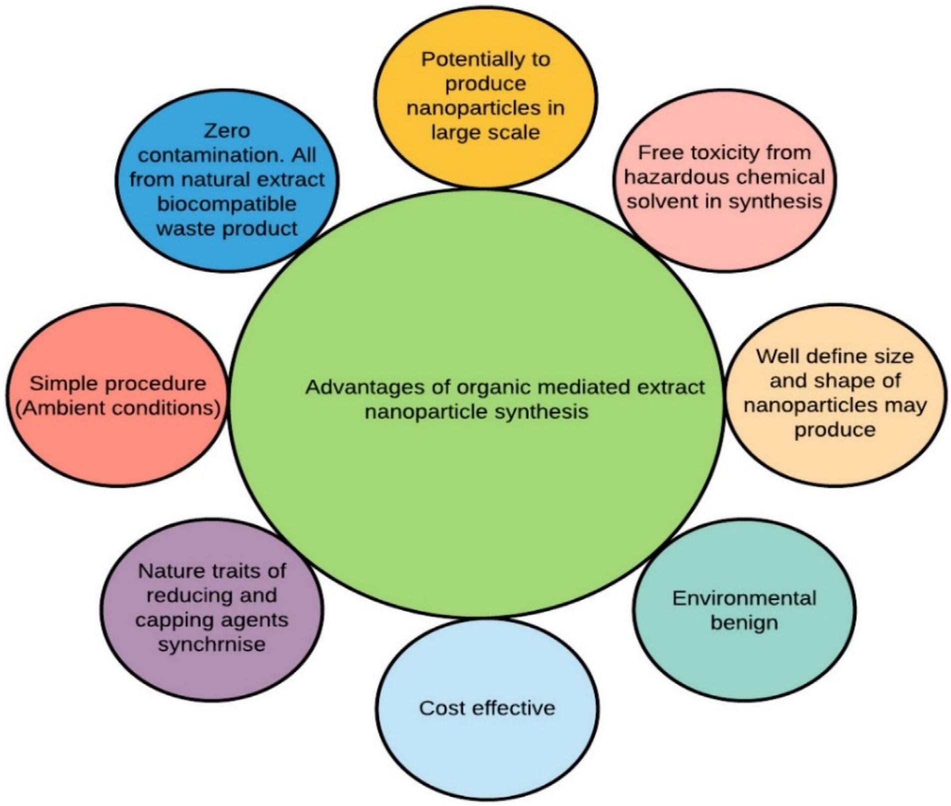

Fig. 3. Advantages of biogenic synthesis.

3. Viral synthesis of nanoparticles

Viruses are used to produce artificial nanocrystals such as cadmium sulphide, silicon dioxide, ferrous oxide, and zinc sulphide, which is a unique approach. Semiconductor nanoparticles such as zinc sulphide and cadmium sulphide are of interest in green chemistry, or ways in generating them are being intensively investigate in electronics industry. Using entire viruses to make nanomaterials has been investigated for the past several years (Zeng et al., 2013). The outer capsid protein of the virus plays a useful role in nanoparticle formation by generating a metallic ion-binding surface with high reactivity (Pokorski and Steinmetz, 2011). On the surface of the tobacco-mosaic virus [TMV], there are 2,130 capsid protein. All peptides can be used as notches connections to deposit or fabricate three-dimensional vessels for a variety of medical purposes (Royston et al., 2008). When Au and Ag salts were added in modest amounts of TMV before adding *Nicotiana benthamiana* or *Hordeum vulgare* plant extracts, size of the synthesised nanoparticles was reduced. Due to the comparatively modest production of free nanoparticles at greater TMV concentrations, it increased their quantities as compared to individuals who did not get the viral supplement. TMV was also employed as a bio-template for nanowire metallization (Love et al., 2014). Unlike in absence of virus, presence of pathogen not only reduced length of biosynthesized NPs, and moreover significantly increased their synthesis.

4. Bacterial synthesis of nanoparticles

Industrial applications such as environmental remediation, genetic modification, and bioleaching have all employed microbial species (Gumulya et al., 2018). Microbes can decrease metal ions, creating them promising options for nanoparticle production (Table 1). Metallics and other nanoparticles are made using a range of bacterial species. Prokaryotes and actinomycetes are widely used in the synthesis of metals / metal oxide nanoparticles (Gobinath et al., 2021). Bacterial derived nanoparticle has been utilised because they are relatively easy to control. *Pseudomonas proteolytica*, *B. indicus*, *B. amyloliquefaciens, B. cecembensis*, *SH10 Phaeocystis antarctica*, *Geobacter* spp., *B. cecem, Enterobacter cloacae, B.licheniformis*, *Klebsiella pneumoniae*, and *Morganella psychrotolerans* are some of them used in the production of Ag nanoparticles. Titanium dioxide nanoparticles were generated by *Lactobacillus* sp. and *B. subtilis* (Khan and Fulekar, 2016). Au nanoparticles are generated by *Rhodopseudomonas capsulata*, *Pseudomonas aeruginosa*, *B. subtilis*, *E. coli DH5*, and *B.licheniformis* (Srinath et al., 2018), whereas cadmium nanoparticles were previously synthesied by *E. coli*, *Rhodopseudomonas palustris* and *Clostridium thermoaceticum* (Sweeney et al., 2004). Microbes could be oppressed as a biological catalyst for the synthesis of inorganic constituents, a bio-scaffold for mineralization, or an active participant in the production of nanomaterials. During an incubation phase, bacteria can generate extracellular or intracellular nanomaterials in broth medium. As a by-product of this process, bacterial biosynthesis of nanoparticles is a feasible, versatile, and suitable option for large production (Kalishwaralal et al., 2008). The biosynthetic procedure for generating nanoscale oxides of metal is still relatively unknown. The primary reason for this is that most of the enzymes involved in biosynthesis are unknown (Tsekhmistrenko et al., 2020). Although biological synthesis has been shown to manufacture nontoxic oxides of metal, it involves careful cell culture, which makes size, shape, and crystallinity difficult to control (Castro et al., 2014).

5. Fungal synthesis of nanoparticles

Production of nanoparticles using fungus has been a focus of study due to its application in a broad range of sectors, like antimi-

Table 1
Bacterial synthesis of nanoparticles.

NPs	Organism	Size (nm)	Application	References
Ag	*Pseudomonas* sp.	20–70	Antibacterial	Banu and Balasubramanian, 2014
	Bacillus thuringiensis	43.5–142.9	Larvicidal action	John et al., 2020
	Ochrobactrum anhtropi	38–85	Antibacterial	Kalishwaralal et al., 2008
	Bacillus spp.	77–92	Antimicrobial and antiviral	Elbeshehy et al., 2015
	Pantoea ananatis	8.06–91.31	Antibacterial	Monowar et al., 2018
	Bacillus brevis NCIM 2533	41–68	Antibacterial	Saravanan et al., 2018
	Bacillus mojavensis BTCB15	105	Antibacterial	Iqtedar et al., 2019
	Actinobacter	13	Antibacterial	Wypij et al., 2017
	Sinomonas mesophile	4–50	Antimicrobial	Manikprabhu et al., 2016
	Bacillus brevis	41–68	Antibacterial	Gan et al., 2018
	Bacillus methylotrophicus DC3	10–30	Antimicrobial	Wang et al., 2016
Cu	*Shewanella loihica*	10–16	Antibacterial	Lv et al., 2018
Au	*Micrococcus yunnanensis*	53	Antibacterial and anticancer	Jafari et al., 2018
	Mycobacterium sp.	5–55	Anticancer	Camas et al., 2018
TiO2	*Aeromonas hydrophila*	28–54	Antibacterial	Jayaseelan et al., 2013
ZnO	*Halomonas elongata IBRC-M 10,214*	18.11	Antimicrobial	Taran et al., 2018
	Sphingobacterium thalpophilum	40	Antimicrobial	Rajabairavi et al., 2017
	Staphylococcus aureus	10–50	Antimicrobial	Rauf et al., 2017

crobials and electronics (Pantidos and Horsfall, 2014). The ability of the *Fusarium oxysporum fungus* to synthesize Ag nanoparticles with diameters ranging from 5 to 15 nm has been confirmed, and they have been covered with mycological proteins to make them stable. Studies have reported internal synthesis of Ag and AuNPs, and sulphide of cadmium, molybdenum, and zinc nanoparticles and intracellular productions of Ag, Au, cadmium sulphide, molybdenum sulphide and zinc sulphide nanoparticles (Al-Mubaddel et al., 2017). They are superior abiotic factors for the production of metals and their oxide nanoparticles because they include a variety of intracellular enzymes. Competent fungus may create larger quantities of nanoparticles than bacteria (Gudikandula et al., 2017). Due to the occurrence of enzymes, peptides, and reductive elements on the surface of cells, fungi have a significant advantage over other species (Narayanan and Sakthivel, 2011). Enzymatic reductions (reductase) in cell walls or inside infectious cells are the most likely technique for the creation of metal nanoparticles. Furthermore, infectious enzymes increase the quantity of synthesized nanoparticles and speed up the reductive abilities for stable nanoparticle production (Mohanpuria et al., 2008). Extracellularly synthesized nanoparticles are often considered to be less or non-toxic (Rai et al., 2011). Pt nanoparticles of diameter ranges from 15 to 30 nm were generated extracellularly at room temperature using *Fusarium oxysporum* extract. Castro-Longoria et al. observed that using the *Neurospora crassa* fungus to make Ag nanoparticles needed a particular temperature and that resulting particles was quasi-round with a diameter of 20–110 nm. Overall, these investigations shown that fungal extracts may be used to stabilise and reduce Pt nanoparticles (Castro-Longoria et al., 2012). Pt nanoparticles were produced biologically using the fungus *Neurospora crassa* and it was intracellularly produced with sizes from 4.5 to 35 nm. They may also produce spherical nanoagglomerates with dimensions ranging from 20 to 110 nm. Pt nanoparticles were synthesised using all feedstock and extracts from *N. crassa*. Single-crystal nanoagglomerates are found in the Pt nanoparticles synthesised from *N. crassa* extract (Pantidos and Horsfall, 2014). Pt nanoparticles were also shown to be synthesised by *Fusarium oxysporum* both extracellularly and intracellularly, but under ideal quantities when produced intracellularly. Magnetite [common ferrous oxide] nanoparticles were found to be synthesised intracellularly by the phytopathogenic fungus *F. oxysporum* and the endophytic fungus *Verticillium* sp. Table 2 summarises different types of nanoparticles synthesised by several fungal species.

6. Algae synthesis of nanoparticles

Algae are organisms which have been shown to assimilate heavy metals from the environment as well as synthesis metallic nanoparticles (Fig. 4). *Fucus vesiculosus*, a brown alga, is now being researched for its potential to bioreduce and biosorb Au [III] ions (Mata et al., 2009). Reduced tetrachloroaurate ions were utilised

Table 2
Fungal synthesis of nanoparticles.

NPs	Organism	Size(nm)	Applications	References
Ag	*Candida glabrata*	2–15	Antibacterial	Jalal et al., 2018
	Trichoderma longibrachiatum	10	Antimicrobial	Elamawi et al., 2018
	Fusarium oxysporum	21.3–37	Antibacterial	Ahmed et al., 2018
	Aspergillus terreus	16–57	Antibacterial	Singh and Vidyasagar, 2018
	Ganoderma sessiliforme	45	Antibacterial, antioxidant, and anticancer	Mohanta et al., 2018
	Rhodotorula glutinis	15.45	Antifungal, cytotoxic, and dye degrading	Popli et al., 2018
	Aspergillus sp.	5–30	Antibacterial and cytotoxicity	Mohmed et al., 2017
	Arthroderma fulvum	15.5	Antifungal	Siddiqi and Husen, 2016
	Penicillium aculeatum Su1	4–55	Drug distribution and antimicrobial	Ma et al., 2017
	Trichoderma harzianum	20–30	Antifungal	Guilger et al., 2017
	Fusarium oxysporum	34–44	Antibacterial	Hamedi et al., 2017
Au	*Cladosporium cladosporioides*	60	Antibacterial and antioxidant	Joshi et al., 2017
	Pleurotus ostreatus	10–30	Antimicrobial, anticancer	El Domany et al., 2018
ZnO	*Fusarium keratoplasticum A1-3*	10–42	Antibacterial, cytotoxic, and textile-loading	Mohamed et al., 2019
	Aspergillus niger G3-1	8–38	Antibacterial and cytotoxic	
	Aspergillus terreus	10–45	Antibacterial and cytotoxic	Fouda et al., 2018
Al2O3	*Colletotrichum* sp.	30–50	Antimicrobial	Suryavanshi et al., 2017

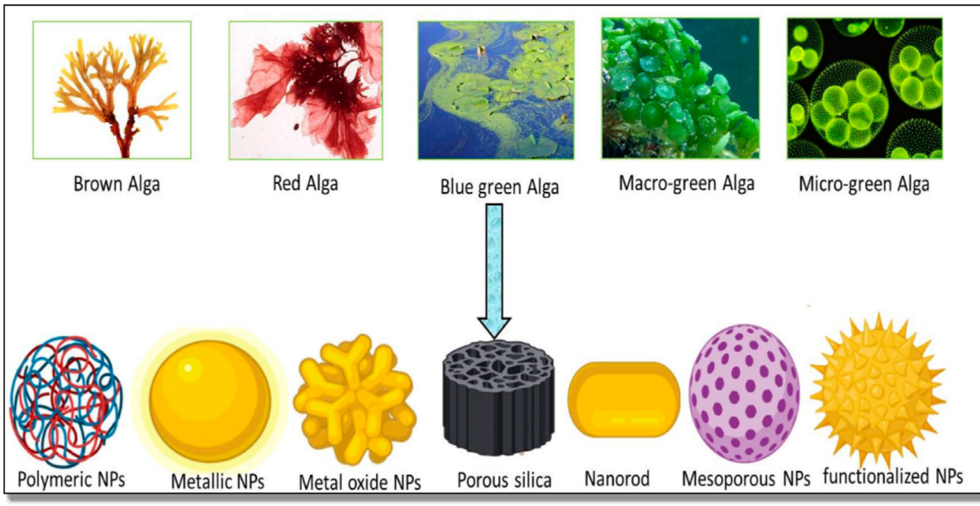

Fig. 4. Synthesis of nanoparticles from different algae (Chaudhary et al., 2020).

to generate Au nanoparticles from dried algal cells of *Chlorella vulgaris* (Luangpipat et al., 2011). Because algae absorb metals and reduce metal ions, they're termed "bio-nano factories" and they able to synthesise metallic nanoparticles from both live and dead dry biomass. Microalgae are photosynthetic microorganisms that form colonies and filamentous that belong to various divisions such as Chlorophyta, Charophyta, and Bacillariophyta. They make up a significant portion of the planet's biodiversity. Bioreduction with *Fucus vesiculosus* could be used as a more ecologically acceptable alternative to recover Au from microelectronic scrap leachates and dilute hydrometallurgical mixtures. *Phaeodactulum tricornatum* is a phytoplanktonic alga with CdS nanocrystals with phytochelatin coatings were made in response to the findings (Scarano and Morelli, 2003). Proteins in the algal extract act as a stabiliser, reducer, and shape-control modifier, among other things (Yenumula and Nagadesi, 2018). *Sargassum wightii*, an ocean alga, also generated extrinsic Au, Ag and Au/Ag bi-metallic nanoparticles. Using *S. wightii*, Singaravelu et al., (2007) found the fast formation of extrinsic Au nanoparticles ranging in sizes from 8 to 12 nm. *Kappaphycu salvarezii*, *Fucus vesiculosus*, *Tetraselmisko chinensis*, *Chondrus crispus*, and *Spirogyra insignis* are among the algae that were reported in the synthesis of Au and Ag nanoparticles. Because they were made from living *Euglena gracilis* microalgal cells that was already cultivated in either mixotropic [light-exposed and cultivated as in carbon-rich organic culture medium] as well as autotropic (non-light-exposed as well as grown in an organic carbon-rich culture mediums) environments (Dahoumane et al., 2016), Au nanoparticles synthesised possess dynamics, outputs, and solubility. Algae are easier to work with, less poisonous, and less damaging to the air; manufacturing may be done at room pressure and temperature, and in simple watery conditions with a neutral acidity. Several algae species are used for the synthesis of nanoparticles (Table 3).

7. Plant synthesis of nanoparticles

Plants contains wide range of bioactive compounds which includes alkaloids, flavonoids, terpenoids, steroids, etc which act as a reducing agent in the synthesis of nanoparticles. Plants including *Acalypha indica*, *Ficus benghalensis*, *Zingiber officinale*, *Plumbago zeylanica*, *Centella asictica*, *Parthenium hysterophorus*, *Sapindus rarak*, *Passiflora foetida*, etc (Verma et al., 2021; Ikram et al., 2021; Peralta-videa et al., 2016; Wang et al., 2016; Roy et al., 2021a, Roy et al., 2021b) have recently been used to synthesise various types of nanoparticles (Table 4). Plant extracts have greater benefits than microorganisms for synthesis of green nanoparticles because it's one-steps process, nonpathogenic and cost-effective process (Fig. 5) (Roy and Bharadvaja, 2017a,b; Nagore et al., 2021; Mittal and Roy, 2021). It aids in the elimination of hazardous by-products while also assisting in nanoparticle size fine-tuning. Extract from *Camellia sinensis* were utilised in making iron oxide NPs with spherical and irregular cluster configurations. Zinc oxide nanoparticles were made from leaf extracts of *Acalypha indica*, *Hibiscus rosa-sinensis*, *Coriandrum sativum*, *Calotropis gigantea*, and *Coriandrum sinensis*. Titanium oxide nanoparticles were made using extracts of *Jatropha curcas* or *Eclipta prostrata*. Oxides of copper were generated by leaf extracts of *Aloe barbadensis* and *Aloe sylvestris* (Jeevanandam et al., 2016). Peralta-videa et al. (2016) reported synthesis of plant based metallic nanoparticles and its

Table 3
Algal synthesis of nanoparticles.

NPs	Organism	Size (nm)	Application	Reference
Ag	*Portieria hornemannii*	60–70	Antibacterial	Fatima et al., 2020
	Padina sp	25–60	Antibacterial and antioxidant	Bhuyar et al., 2020
	Ulva lactuca L.	31 ± 8	Anticancer	González-Ballesteros et al., 2019
	Gelidium amansii	27–54	Antimicrobial	Pugazhendhi et al., 2018
	Anabaena flos-aquae	5–25	Anticancer and cytotoxic	Ebrahimzadeh et al., 2020
Au	*Ulva lactuca L*	7.9	Anticancer	Vaali-Mohammed et al., 2017
	Cystoseira baccata	8.4	Anticancer	González-Ballesteros et al., 2017
ZnO	*Sargassum muticum*	30–57	Anticancer	Sanaeimehr et al., 2018
CuO	*Botryococcus braunii*	10–70	Antimicrobial	Arya et al., 2018
	Sargassum polycystum	–	Antimicrobial and Anticancer	Ramaswamy et al., 2016
Fe3O4/Ag	*Spirulina platensis*	30–50	Anticancer	Salehzadeh et al., 2019

Table 4
Plant synthesis of nanoparticles.

NPs	Plants	Size (nm)	Application	Reference
Ag	*Morus alba L.*	80–150	Antibacterial	Razavi et al., 2020
	Panax ginseng	5–15	Anticancer and antiviral	Sreekanth et al., 2018
	Dolichos lablab	4–16	Antimicrobial and anticancer	Kahsay et al., 2018
	Alternanthera bettzickiana	5–15	Antimicrobial and anticancer	Vaali-Mohammed et al., 2017
	Thymus vulgaris	30	Anticancer and antioxidant	Heidari et al., 2018
Au	*Camellia sinensis*	10	Antibacterial	Onitsuka et al., 2019
	Nigella arvensis	3–37	Antibacterial, antioxidant, cytotoxicity and catalytic	Chahardoli et al., 2018
Cu	*Morus alba L.*	50–200	Antibacterial	Razavi et al., 2020
	Crotalaria candicans	30	Antibacterial	Lotha et al., 2019
Se	*O. tenuiflorum*	15–20	Medical and pharmaceutical	Liang et al., 2020
	Zinziber officinale	100–150	Antimicrobial and antioxidant	Menon et al., 2019
Pt	*Taraxacum laevigatum*	2–7	Antibacterial	Tahir et al., 2017
Pd	*Morus alba L*	50–100	Antibacterial	Razavi et al., 2020
	Couroupita guianensis Aubl.	5–15	Antibacterial and cytotoxicity	Gnanasekar et al., 2018
ZnO	*Aloe socotrina*	15–50	Drug delivery	Fahimmunisha et al., 2020
	Olive leaves	40.5–124	Antibacterial	Ogunyemi et al., 2019
	Tecoma castanifolia	70–75	Antioxidant, antibacterial, and anticancer	Sharmila et al., 2019
	Passiflora caerulea	30–50	Antibacterial	Santhoshkumar et al., 2017
TiO2	*Trigonella foenum graecum*	20–90	Antimicrobial	Subhapriya and Gomathipriya, 2018
	Artemisia haussknechtii	92.85	Antimicrobial and antioxidant	Alavi and Karimi, 2018
FeO	*Skimmia laureola*	56–350	Antibacterial	Alam, et al., 2019

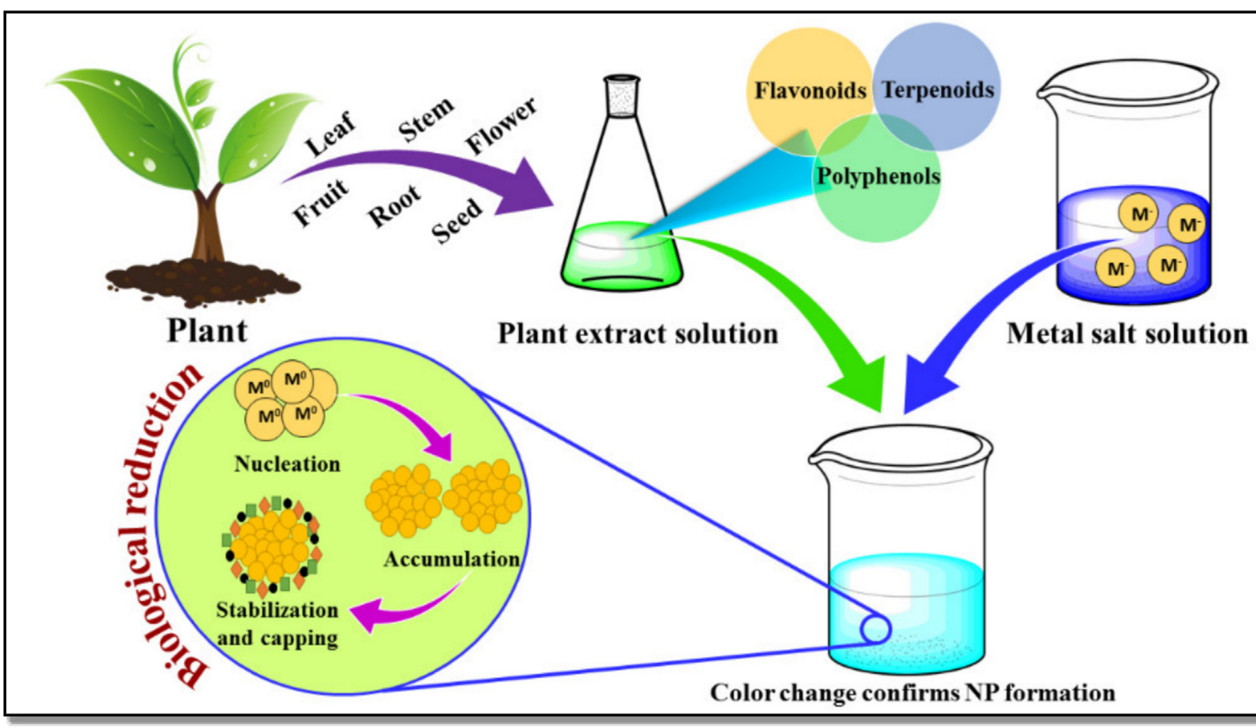

Fig. 5. Plant synthesis of nanoparticles (Dikshit et al., 2021).

applications. Metals from their constituents are reduced and stabilised by macromolecules and phytonutrients [phenolics, flavonoid, ethyl alcohol, terpenes, and phenolic acids] present in plant extracts. These macromolecules are split into two group: [i] redoxed intermediaries for metals reductions, or [ii] capped agent for non-agglomeration and post-surface modification of nanoparticles. Furthermore, the produced nanoparticles are free of pollutants and suitable for physiologically mediated applications (Naseer et al., 2020). A number of experiments employing diverse plant components to synthesise ZnO with different characteristics have been reported. Herbal extract from plant like *V. trifolia*, *O. basilicum L. var. purpurascens Benth*, *S. chirayita*, *C. alata*, *C. roseus*, *S. multiflorus*, *A. indica*, *E. crassipes*, and *A. betulina* has been utilised to synthesise spherical shaped ZnO nanoparticles for antibacterial and biomedical purposes (Gupta et al., 2018). Ikram et al. (2021) reported synthesis of selenium nanoparticles from different plants and their potential applications.

8. Factors affecting synthesis of nanoparticles

Toxicity is an important factor in considering when using nanoparticles for biomedical applications to ensure that they are safe and effective (Fadeel and Garcia-Bennett, 2010). In certain studies, metal nanoparticles have been shown to be dangerous to people. Metal nanoparticles' toxicity is governed by their size and surface load. It is mandatory to recognize potential health hazards related to nanoparticles. It is critical to investigate small cellular changes in DNA injury and oxidative stress in human tissues in order to rule out probable genotoxicity. Chemical inertness is another important consideration when utilising nanoparticles for implants. Oxides of iron, zinc and titanium are utilised commonly and may be made and altered through carbon derivatives that permit them all in order of binding to antibodies, drugs, and ligands for attention (Amiri et al., 2019). The function of nanoparticles could aid by noncovalent interaction between surface metal ions or ligands and hydroxyl groups (Arranz-Mascarós et al., 2020).

For biomedical applications, metals oxide nanoparticles ideally had the following characteristics:

[1] chemical stability,
[2] wear and scratch resistance,
[3] biocompatibility, and
[4] nontoxicity.

The heat required for production of nanoparticles is significantly connected with the stability of nanoparticles (Yu and Xie, 2012). Different factors, such as reaction time, reactant concentrations, pH, and temperature, may be used to control the morphological features of nanoparticles [Table 5]. Such characteristics are critical for understanding the impact of environmental variables on NP synthesis, as they can play a key role in optimizing metallic NP production using biological methods (Roy and Bharadvaja, 2019).

However according to previous research, the higher the volume of extract used, the faster the rate of synthesis because more chemical constituents are accessible in the solution to bind with the precursor and lead to quick bio-reduction and nanoparticle stabilisation. The proportion of the volume of green extract to the concentration of nanoparticle precursor used must correspond to attain an ideal state for green manufacture of nanoparticles. Yield of nanoparticles is mostly determined by the volume of extract used in the synthesis process. The findings show that the volume and kind of extract used in nanoparticle manufacturing have a significant impact on their morphological aspects and biological activity.

9. Applications

Nanotechnology's benefits are rapidly expanding in a variety of sectors. Many new technologies use nanoparticles, including sun protection and moisturizers, desalination, inks, sun filters, blemish clothing, agribusiness and pharmaceuticals, finished fabrics, or wound treatments are all examples of products that are manufactured (Diallo and Brinker, 2011). Nanoparticle's characteristics have sparked a lot of interest in biomedical research. Drug delivery, theranostic, cancer treatment, antibacterial, and implants & wound healing are some of the biological applications of nanoparticles (Murthy et al., 2020).

9.1. Antimicrobial activity

The antibacterial characteristics of NPs are complex and encompass a variety of processes. As a result, the mechanism of antibacterial activity is yet unknown. At low concentrations, nanoparticles have been demonstrated to have antibacterial action. ZnO nanopowders have an inferior inhibitory and microbial concentration than zinc acetate, according to various publications. ZnO nanopowders are operative in contradiction to Gram positive and Gram-negative microbes. Azam et al. (2012) examined antimicrobial efficacy of oxides of copper, zinc, and iron nanoparticles against Gram positive and Gramnegative microorganisms. Different probable processes have been assigned in the literature, including [i] oxidative strain due to ROS formation (Li et al., 2012), [ii] disbanding of NM resulting in the creation of zinc ions and [iii] internalisation in these nanometals in nuclei, all of which result in cell apoptosis. The major process is the generation of reactive O2 species [ROS], which are linked together with particle diameter, surface area, and crystalline nature (Cui et al., 2018). The interaction of nanoparticles with bacteria generally results in harmful effects, which are then oppressed for antimicrobial applications in trades like foods and agriculture. On the other hand, growing problems of antibiotic resistance strain caused by transmission of antibiotic resistance genes across bacteria may address through employing bactericidal nanoparticles as a replacement for some traditional antibiotics (Nikolova and Chavali, 2020).

Table 5
Factors affecting biological synthesis of metal nanoparticles.

S. No.	Factors	Metal nanoparticles' impact on biological synthesis
1	Reactant concentration	Shape of synthesized nanoparticles
2	Reaction temperature	Generates nanoparticle's size, shape, yield, and stability
3	Reaction time	Size and form of the nanoparticles created
4	pH	Size and form of the nanoparticles created

9.2. Drug delivery

Noble metal nanoparticles with unique and adjustable optical characteristics, such as Ag and Au nanoparticles, have substantially assisted in the development of targeted drug delivery methods. Liposomes could be used as drug delivery carriers in addition to the traditional forms of nanocapsules for delivery of delicate biological molecules. The idea of green synthesis has been extended to drug distribution, resulting in the field of "green nanomedicine," which attempts to make medication delivery safer in the clinic by using nanoroutes (Das and Chatterjee, 2019). Nanoparticles are the most commonly used targeted agents because of their comparative comfort in manufacturing, firmness, and control of conjugation chemistry. Targeted ligands may not have the specificity or affinity. Biotin [vitamin H] has been frequently utilised for nanoparticle conjugation because of its strong affinity for streptavidin (Pramanik et al., 2016). Folic acid [vitamin B9] has a high attraction for endogenous folate receptor, it has been calculated for the use in malignancies with high levels of folate receptors (Carron et al., 2018). Many additional task-specific polysaccharides, short peptides, antibodies, and tiny compounds have been developed and used in the same way. Despite the fact that many drug delivery arrangements are being successfully deployed during recent ages, there are still certain issues that require solved or improved technologies in order to carry medicines to the intended destinations. As a result, nano-based drug delivery arrangement is presently investigated to aid in creation of more complex drug delivery methods (Patra et al., 2018). Cell-released biological nanoparticles also know as extracellular vesicles are one of the developing drug carriers with high complexity. Extracellular vesicles based drug delivery exploits intrinsic mechanisms for molecular transport in the body. By integrating extracellular vesicles biology and manufacturing with clinical insights from synthetic nanoparticles is likely to substantially advance the field of drug delivery (Witwer and Wolfram, 2021).

9.3. Theranostic applications

Theranostics is a pretty recent branch of medicine that blends tailored therapy with diagnostic testing. It is a method of obtaining diagnostic images and administering a therapeutic dose of radiation to a patient using particular biomarkers found in human body. Recent researches in nanomedicine technology had made it feasible to combine drug delivery methods with 154 creations of single agent and integrated target therapies or diagnostic capabilities (Iyer et al., 2013). Another common theranostic agent is SPION. The FDA has given its approval for the use of SPION as an MRI contrast agent. SPION can be guided magnetically to relevant tissues by synthetic magnets. This technique is operative in cancer medications. According to studies, SPIONs loaded with DOX are effective rather than taken up breast cancer cells which are resistant to DOX [1 M DOX-resistant MCF-7] than free medicine. Lower drug doses and less side effects are the benefits of this method (Wang et al., 2013).

9.4. Cancer therapy

Despite the availability of medicines, cancer takes the lives of millions of people every year. Furthermore, due to the use of existing antineoplastic drugs, the longevity of patients is vulnerable to unfavorable side effects. As a result, the creation of novel NP-based medicines has received a lot of interest because they are more effective, have fewer side effects, and target cancer cells. The enormous surface area of NPs, which allows the mixing of high pharmacological doses, may be responsible for these actions (Khan and Fulekar, 2016). ZnO NPs are ideal anticancer agents because of their unique biocompatibility, selectivity, simple manufacturing method, and ability to dissolve at low pH. ZnO nanomaterial trigger angiogenesis of human malignant melanomas skin cell line via caspase 3 pathway, according to Alarifi et al. (2013). Ye et al., (2016) dprofuced ZnO-Gd-DOX nanoparticles in diagnosis and to treat mouse tumours in-situ, demonstrating improved therapeutic efficacy [DOXIL], in contrast to the FDA-accepted marketable DOX medicine, DOX-liposome vaccination. Several forms of nanoparticle drug carriers have been investigated in cancer therapy, including polymeric micelles, liposomes, dendrimers, and metallic NP, to reduce the adverse effects of traditional anticancer medications and improve the anticancer medication efficacy of particular treatments (González-Ballesteros et al., 2019).

9.5. Wound healing and implants

Patients are traumatised by bacterial adherence and multiplication in biomedical implants. Implants that have become infected can cause bone resorption and must be removed. Antimicrobial coatings on grafts that work autonomously or synergistically with the given antibiotic to prevent bacterial contagion have been the subject of research. Biocompatibility, antiinfective effectiveness, durability, and mechanical stress resistance were taken into account when deciding whether or not an antibacterial coating should be employed. Titanium is a material that is frequently utilised in biomedical implants. Titanium-coated implants provide a biocompatible surface for cell adhesion and growth (Damiati et al., 2018). Anti-infection coating materials for medical implants have also been demonstrated to be successful using alumina [Al_2O_3], ZnO, and CuO NPs (Zhang et al., 2019; Maimaiti et al., 2020). Metal oxide NPs are used in polymeric nanofibers as well as hard tissue repair to improve the overall characteristics of wound dressing materials made from composite skin tissue engineering. Increased growth factor synthesis, fibroblast proliferation, and extracellular matrix creation all contribute to wound healing and re-epithelization. ZnO NPs have been found not to enter the skin and to dissolve slowly as ions in an aqueous solution (Holmes et al., 2016). However, ROS synthesized by metal oxide NPs have a signalling and regulatory role in tissue engineering. ROS have been shown to have antibacterial properties in wound healing, as well as a role in tissue wound-to-leucocyte communication (Grandvaux et al., 2015).

9.6. Biosensing

Nanobiosensors operated by affixing a ligand to a receptor, which triggers a signal transducer response. On the basis of their detecting mechanism [signal measurement], some nanobiosensors are used into electrochemical, piezoelectric, optical, semiconductor, and calorimetric categories, and all of these convert data into electrical impulses. Electrode materials are important in the development of excellent power electrolytic detection devices that use a variety of sophisticated analytical methods to identify target molecules (Zhu et al., 2015). Nanobiosensors for the detection of tiny molecules can be enzyme based, geno-sensors, immunosensor, cytosensor, and biosensor. Small compounds are examined using electroanalysis. The presence of H_2O_2, glucose, or dopamine is detected by small molecule electroanalysis. Fe_2O_3 NPs shaped like cubes were used as a glucose biosensor material with high sensitivity and rapid reaction for non-enzyme catalytic oxidation under hydrothermal conditions.

9.7. Bioimaging

ZnO NPs are excellent for bioimaging applications because they have potential biocompatibility, are simple to produce, and are cost-effective. ZnO NPs have improved physicochemical properties and may be absorbed by tissues and cells, making them ideal for imaging. Conventional azo dyes and fluorescent dyes are used to generate extrinsic luminous characteristics, which have a variety of limitations. Low intensity and short wavelength luminescence, photobleaching, and restricted particle size management capabilities are the primary problems connected with the characteristics and structure of ZnO in terms of bioimaging applications. There is instability in water and overlapping of the absorption spectrum of live creatures due to the very wide emission band of ZnO (Reineck and Gibson, 2017). ZnO nanometals are altered in a variety of ways, including nanocomposites and doping, due to the limits of bare ZnO. Li et al. (2015) made multi-colour ZnO NPs with hexadecyltrimethoxysilane [hydrophobic layer] and aminopropyltriethoxysilane [hydrophilic layer], resulting in ZnO.@HDS.@APS nano-composites with ten-fold increased luminoscence intensity and no photo-bleaching after 24 h. Zhang et al. (2012) were also able to create monodispersed silica-coated ZnO NPs with hydrophilic amino groups on the surface.

9.8. Vaccines

Conventional vaccines based on live-attenuated pathogens possess risk of reversion to pathogenic virulence while inactivated pathogen vaccines frequently lead to a weak immune response. Vaccines based on nanoparticles is a new approach which has shown great potential to overcome limitations of conventional vaccines. This is due to recent advances in chemical and biological engineering, which allow the design of nanoparticles with a precise control over the size, shape, functionality and surface properties, leading to enhanced antigen presentation and strong immunogenicity (Al-halifa et al., 2019).

10. Future perspectives and challenges

Green nanoparticle synthesis is predicted to grow in popularity, allowing for nontoxic production and use of environmentally friendly nanoparticles. Novel green nanoparticle synthesis methods are likely to emerge as a result of contributions from a variety of fields, including physics, chemistry, and biology. Despite the fact that there are a number of obstacles to overcome, the sector has a lot of promise. Through different studies and data validation, understanding the exact mechanisms may lead to the long-term development of green nanotechnology.

The following are the key problems that were encountered during the green synthesis of nanoparticles:

- Stability of high-yielding NPs are linked to variables including pH, salt content, contact duration, and temperature. These variables vary depending on the biological entities utilised.
- To determine characteristic of individual component in nanoparticles which are biologically manufactured, the compounds present in organic material filtrate should be thoroughly examined.
- Green technique of synthesis of a certain size and form need additional optimization research. Furthermore, synthesis of NPs with specific physicochemical properties needs additional research, particularly for biological applications.
- Another issue in commercialising NPs is scaling up production using environmentally friendly techniques.
- More research is needed on the mechanistic element of making NPs using green methods.

11. Conclusion

The 'green' production of metals and their oxide nanoparticles had been a significant field of research in last ten years. Biocomponents such as bacterium, fungi, plants, algae, even viruses are often used to synthesise a variety of nanoparticles. This review focused on synthesis of metal oxide nanoparticles from different biological sources and their applications in various fields. Use off more secure, and credible reducing, sustainable, and capping agents, as well as avoidance of hazardous compounds like sodium borohydride and diazane [N_2H_4], is required for green synthesis of nanoparticles. Biomedication, biotechnology, biomaterials, biosensing, pharmaceuticals, etc are just a few of the uses for green synthesised nanoparticles. Immunoassays, delivery of healing medicines, tumour treatments, chemotherapeutics, and sterile agents, as well as bandages, pharmaceuticals, and consumer products, might all benefit from green nanoparticle production. As a result, a deeper knowledge of green chemistry as a method of synthesising nanoparticles opens up new possibilities. Essentially, using green technology to produce metal and metal oxide NPs has a widespread range of applications, including antibacterial and anticancer activity, phytopathogen management, and bioremediation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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