

How Synthesis of Algal Nanoparticles Affects Cancer Therapy? – A Complete Review of the Literature

Mostafa M El-Sheekh ¹, Samar Sami AlKafaas ², Hadeer A Rady¹, Bassant E Abdelmoaty², Heba M Bedair¹, Abdelhamid A Ahmed³, Mohamed T El-Saadony ⁴, Synan F AbuQamar ⁵, Khaled A El-Tarabily ⁵

¹Botany Department, Faculty of Science, Tanta University, Tanta, 31527, Egypt; ²Molecular Cell Biology Unit, Division of Biochemistry, Chemistry Department, Faculty of Science, Tanta University, Tanta, 31527, Egypt; ³Plastic Surgery Department, Faculty of Medicine, Tanta University, Tanta, 31527, Egypt; ⁴Department of Agricultural Microbiology, Faculty of Agriculture, Zagazig University, Zagazig, 44511, Egypt; ⁵Department of Biology, College of Science, United Arab Emirates University, Al Ain, 15551, United Arab Emirates

Correspondence: Synan F AbuQamar; Khaled A El-Tarabily, Department of Biology, College of Science, United Arab Emirates University, Al Ain, 15551, United Arab Emirates, Tel +971 3 713 6733; +971 3 713 6518, Fax +971 3 713 4927, Email sabuqamar@uaeu.ac.ae; ktarabily@uaeu.ac.ae

Abstract: The necessity to engineer sustainable nanomaterials for the environment and human health has recently increased. Due to their abundance, fast growth, easy cultivation, biocompatibility and richness of secondary metabolites, algae are valuable biological source for the green synthesis of nanoparticles (NPs). The aim of this review is to demonstrate the feasibility of using algal-based NPs for cancer treatment. Blue-green, brown, red and green micro- and macro-algae are the most commonly participating algae in the green synthesis of NPs. In this process, many algal bioactive compounds, such as proteins, carbohydrates, lipids, alkaloids, flavonoids and phenols, can catalyze the reduction of metal ions to NPs. In addition, many driving factors, including pH, temperature, duration, static conditions and substrate concentration, are involved to facilitate the green synthesis of algal-based NPs. Here, the biosynthesis, mechanisms and applications of algal-synthesized NPs in cancer therapy have been critically discussed. We also reviewed the effective role of algal synthesized NPs as anticancer treatment against human breast, colon and lung cancers and carcinoma.

Keywords: algae, metabolites, cancer therapy, green synthesis, medical applications, nanoparticles

Introduction

Cancer is one of the most dangerous diseases and causes of death worldwide. More than one million cases of cancer and half a million deaths are reported each year.^{1–3} Some of the risk variables include family history, exogenous hormones, reproductive abnormalities, geographic location and age.⁴ Currently, chemotherapy is the most widely used approach for cancer treatment. Indeed, many drugs utilized in chemotherapy have undesirable side effects on healthy cells, multidrug resistance, and poor solubility.^{5–7} Therefore, it is crucial to develop alternative therapeutic approaches to treat cancer cells without harming healthy cells.

Efficient cancer therapy and cancer treatment substitute to chemotherapy are the subjects of unrelenting research efforts these days. Nanotechnology is the science/technology to synthesize, manipulate, control and manufacture nanoparticles (NPs) having size ranging from 1 to 100 nm.^{2,8–12} Although efforts to employ nanotechnology to cure cancer and enhance the effectiveness of medications are still at the developmental stage, NPs have been widely used in biomedical applications. It has been reported that metal NPs, such as copper (Cu), silver (Ag) and zinc oxide (ZnO), could be potentially used to treat cancer cells without affecting normal cells.^{7,9}

There are two major methods used to synthesize NPs: (1) Top-down method that uses chemical and physical energy to break down larger structures into smaller components.^{3,13–15} Thermal decomposition, mechanical milling/ball milling, lithography, laser ablation and sputtering are the most common top-down approaches; and (2) bottom-up method is to generate nanomaterials from the reaction of atoms and other substances.¹⁶ Examples of bottom-up approaches are chemical vapor deposition, sol-gel process, spinning, pyrolysis, and biological synthesis.

Due to their nano-size,¹⁷ unique properties (eg, mass density)¹⁸ and surface charge,¹⁹ NPs can be linked with different ligands, such as RNA,²⁰ DNA,²¹ aptamers,²² peptides²³ and antibodies.²⁴ This will facilitate the drug transportation of the modified NP to the action site to improve the pharmacokinetic characteristics and therapeutic efficacy against cancer.²⁵ The use of NPs as an immunogenic cargo in traditional radio- and chemo-therapies has also been investigated.²⁶ For instance, the biocompatibility of NPs is linked with the unconventional artificial antigen-presenting cells (aAPCs) and in vivo repositories of immunostimulatory molecules for sustained antitumor activity.²⁷

Reactive oxygen species (ROS) can mediate apoptosis by regulating the expression of various pro-apoptotic proteins such as caspases or anti-apoptotic proteins [B cell lymphoma-2 (Bcl-2) and cellular FLICE-inhibitory protein (c-FLIP)].²⁸ Other strategies of action of NPs in inducing apoptosis in cancer cells by protein regulation, immunological interventions, transcription inhibition and site-specific cytotoxicity. There is growing evidence that proteins engaged in signaling pathways are linked to the etiology, development and oncogenic activity of cancer cells may also be regulated by NPs.^{28,29}

The apoptotic regulatory proteins can be downregulated by copper oxide (CuO) NPs.²⁹ Selenium (Se) NPs at a concentration of 5 $\mu\text{g Se mL}^{-1}$ affect the expression profile of apoptotic proteins. In addition, SeNPs can also cause alteration in the signaling pathways of the unfolded protein response (UPR).²⁹ The expression pattern of the estrogen receptor (ER)-resident Se-proteins and Se-containing glutathione peroxidases, and thioredoxin reductases significantly increased after SeNP treatment on different cancer cell lines.³⁰

SeNPs can also control pro-apoptotic proteins by activating Cx43 hemichannels.³¹ In MCF-7 cell lines that positively absorbed AgNPs, there was increased expression of -H2AX. This was followed by the release of Ag ions inside the cells and subsequently caused cell death.³¹ Gold (Au) NP conjugates can induce G1 cell cycle arrest and apoptosis induction in ER-positive human breast cancer cell lines, MCF-7.³²

In addition to its role in improving the performance of biofuel cells and production of viable biofuels,³³ nanotechnology is also involved in phyco-nanotechnology (phycochemicals produced from algae).^{10,34,35} Many algal species, including Chlorophyceae (green algae), Cyanophyceae (blue-green algae), Phaeophyceae (brown algae) and Rhodophyceae (red algae), are efficient in the synthesis of metal/metal oxide NPs.³⁶⁻³⁸ Algae are rich with secondary metabolites (alkaloids, flavonoids and terpenoids), pigments, vitamins and proteins that act as nano-biofactories.^{16,36,39} They also contain cytotoxic compounds, such as fucoidans, terpenoids, and laminarians, which have anticancer, antiproliferative, and antitumor activities.^{1,10,35,40} It is highly recommended to use algae for the green synthesis of NPs. This could be attributed to the simplicity, safety, low-cost, high energy efficiency, lack of external capping or reducing agents, and application in pharmaceutical and biomedical fields.⁴⁰

Depending on the properties of the algal species, biosynthesis of NPs can be either extracellularly or intracellularly.^{41,42} Polysaccharides, proteins, enzymes, and reducing factors present in the algal culture and precipitating reducing metallic ions to nanomaterials have been proposed in extracellular metallic NP production.^{38,41,43-45}

Henceforth, the current review highlights the potential capabilities of algae classes in the green synthesis of NPs and their role in cancer treatment. The mechanisms involved in this process along with their importance in cancer research are also discussed.

Why to Synthesize Eco-Friendly NPs?

Plants and microorganisms can produce NPs in a safe, affordable, and environmentally friendly manner.⁴⁶⁻⁴⁸ Inorganic metallic ions can be drawn in and stored by plants and microorganisms from their environment. These characteristics make living organisms reduce the environmental pollution and speed up the recovery of heavy metals from industrial waste into less hazardous forms.^{47,49,50} The features of biological agents in using their biochemical processes to convert inorganic metallic ions to metal NPs have provided new and unexplored fields of research.⁵¹⁻⁵³

Unicellular and multicellular organisms have been shown to be capable of producing inorganic external and intracellular compounds in the micro- and nano-range. Bacteria, actinobacteria, algae, molds, yeasts, plants and viruses can be used to synthesize NPs.⁵³ Each organism has varying degrees of metabolic processing capacity available to produce NPs of specific metals/metal oxides. Because not all organisms can produce NPs, careful selection of appropriate biological entities is required,^{54,55} taking into consideration that organisms with the potential to accumulate heavy metals

have better chances of producing metallic NPs.^{55–58} In addition, optimizing culture parameters of nutrition, light, pH, temperature mixing rate and buffer strength can increase the enzymatic activities of organisms to produce NPs.^{59,60}

To start the production of NPs, biomaterials are mixed with precursors of noble metal salts.⁴ When NPs are produced from their metal salt predecessors, proteins, alkaloids, flavonoids, reducing sugars, polyphenols, and other compounds present in biomaterials serve as reducing and capping agents.⁶¹ However, the process underlying NPs formation in microorganisms still needs to be fully understood.⁴⁶ In general, the potential biological pathway involved, the interactions and metabolic processes of a certain microorganism as well as the influence of environmental factors determine the ultimate size and morphology of NPs.^{46,62}

How Actinobacteria Produce NPs?

Actinobacteria can produce metallic NPs either extracellularly or intracellularly, with extracellular production being the more prevalent method.^{63–66} *Rhodococcus* sp. reduced metallic Au ions intracellularly, although AuNPs were primarily reduced on the cell wall and cell membrane (not in the cytoplasm).⁶³ During the biosynthesis process, mono-dispersed AuNPs with sizes of 5–15 nm were produced; these particles had no harmful effects on cells.⁶³ Karthik et al⁶⁵ successfully produced AgNPs by reducing silver nitrate (AgNO₃) ions using *Streptomyces* sp. LK-3. Nitrate reductase is an active enzyme in the cellular nitrogen cycle that reduces nitrate to nitrite.⁶⁷ The nicotinamide adenine dinucleotide (NADH)-dependent nitrate reductase enzyme is in charge of reducing Ag ions to metallic Ag by an electron transfer process, producing stable AgNPs as a result.

Similar nitrate reductase enzyme activity was found when reducing Au ions from aqueous solutions containing gold chloride (AuCl₄) ions.⁶⁸ During the electron transfer from NADH by NADH-dependent reductase, each Au ion receives an electron, reduced to Au, and subsequently creating stable AuNPs.^{69,70} The attributes of the produced NPs must be protected from agglomeration brought on by the high surface energy and must be prevented with appropriate stabilization.⁷⁰ Interestingly, naturally produced NPs typically have stronger antibacterial activity than conventionally synthesized NPs. The increased antibacterial activity is assumed to be associated with the synergistic proteins that are in charge of capping and stabilizing NPs.⁷¹

How Bacteria Produce NPs?

Bacteria have emerged as rapidly developing research area in green nanotechnology. Bacterial species, such as *Escherichia coli*, *Bacillus cereus*, *Acinetobacter* sp., *Klebsiella pneumonia*, *Lactobacillus* sp., *Corynebacterium* sp. and *Pseudomonas* sp. can produce metallic NPs.^{72–75} It is known that bacteria can produce metallic NPs via extracellular or intracellular methods. *Pseudomonas stutzeri* AG259 was used to produce AgNPs by NADH-dependent reductase enzyme, which provides electrons to oxidize NADH to NAD⁺.^{76,77} *Pseudomonas aeruginosa* was used to decrease Au ions, which led to the extracellular production of AuNPs.⁷⁸ Others have, however, demonstrated that biological enzymes are not involved.⁷⁸ Several variables work together to reduce the number of NPs. The first factor is dependent on the particular organic functional groups in the cell wall, whereas the second is dependent on external conditions.⁷⁹

E. coli can produce biodegradable biopolymers, ie, polyhydroxyalkanoates (PHAs), on a wide scale that have the potential to replace petrochemical-based plastics.^{80–82} Due to growing concerns about rising crude oil prices and environmental harm caused by plastics, PHAs have drawn more attention recently.^{81,82}

Bacteria have defense systems to adapt extreme environmental conditions. Such mechanisms include, but not limited to, redox state changes, efflux mechanisms, intracellular metal precipitation and accumulation, and extracellular complex formation of high metallic ion concentrations.⁸³

How Fungi Produce NPs?

Many research groups use fungi in the production of NPs. The biosynthetic capacity of fungi, including *Aspergillus* sp., *Fusarium* sp., and *Penicillium* sp., to produce both AgNPs and AuNPs has been documented.^{84–87} Fungi may also produce mono-distributed NPs of all sizes and chemical compositions.⁸⁷ In comparison to bacteria, fungi have additional characteristics that help in the production of metallic NPs. They secrete tremendous amounts of proteins and enzymes per unit of biomass, resulting in larger levels of NPs.⁸⁸

Several fungi have high intracellular metal absorption volumes, and the synthesized particles often have smaller sizes.^{89,90} During the biosynthesis of metallic NPs, the culture conditions might, however, have a substantial impact. The biomass of *Trichothecium* sp. was employed to generate extracellular NPs during the biological reduction of Au ions in stationary conditions.⁹¹ When the biomass was, however, mixed up, it tended to generate intracellular NPs.

How Plants Produce NPs?

Plants can hyper-accumulate and physiologically decrease metallic ions.^{92,93} Plants are more environmentally acceptable method for biologically generating metallic NPs and detoxifying applications. Plant extracts rich in proteins, carbohydrates, terpenoids, alkaloids and phenolics can also decrease metallic ions and stabilize them.⁹⁴

Variations in the composition and quantity of active biomolecules among plants, as well as their subsequent interaction with aqueous metal ions, are the primary contributors to the diversity of sizes and shapes of generated NPs.⁹⁵ The applied procedure for producing NPs is mixing plant extracts with a metal salt solution at room temperature. The salts are biochemically reduced, and the presence of NPs can be detected using the color change in the reaction mixture.⁹⁵

As expanded, NPs can form a variety of morphologies such as cubes, spheres, triangles, hexagons, pentagons, rods and wires.⁹⁶ The final stage of synthesis identifies the most stable and energy-efficient form of NPs. The content of plant extracts, metal salt concentration, reaction duration, pH and temperature of the reaction solution can substantially influence the quality, size and shape of the formed NPs.^{97,98}

Because plant extracts are rich in bioactive compounds, they are essential for the fabrication and stability of NPs.⁹⁴ Date pulp waste was used as an effective bio-reductant in the green production of ZnONPs for wastewater treatment as an alternative to traditional ways of NPs synthesis.⁹⁹

How Algae Produce NPs?

Some algae can also be used to biologically produce metallic NPs in addition to the accumulation of heavy metals. For instance, the dried unicellular alga, *Chlorella vulgaris*, was used to produce tetra-chloroauric ions, which were attached to the algae and reduced to produce AuNPs. It was discovered that the tetrahedral, decahedral, and icosahedral-shaped NPs accumulated close to the cell surface.¹⁰⁰ The proteins in *C. vulgaris* extract can also serve as a reducing agent, shape-controlling modifier and stabilizing agent for the production of Ag at room temperature.¹⁰¹

The brown alga *Sargassum wightii* can extracellularly synthesize Au, Ag, and Au/Ag bimetallic NPs.^{102,103} *Kappaphycus alvarezii* was also used to generate extracellular AuNPs,¹⁰⁴ and the brown alga *Fucus vesiculosus* provided biomass during the biological reduction of Au.¹⁰⁵ It has also been reported that *Tetraselmis kochinensis* has the ability to produce intracellular AuNPs.¹⁰⁶ Castro et al¹⁰⁷ have recently reported the red alga *Chondrus crispus* for the same purpose of biosynthesis of NPs. In their effort to bioremediate carcinogenic components, El-Sheekh et al¹⁰⁸ have reported that sodium alginate, *Sargassum latifolium* extract and their AgNPs are effective and cheap adsorbent agents to remove malachite green dye from aqueous solutions.

Potential Exposure and Hazard of Metal-Based NPs on Human

Metallic-based NPs are chosen for their synergistic effects, biocompatibility, and minimal cytotoxicity. The radiosensitivity effects of metallic NPs can be classified into three categories: physical, chemical and biological.¹⁰⁹ Biological impact indicates cell damage, including cell cycle effects, DNA damage and cell death. Depending on the cellular and subcellular distribution of NPs, radiosensitivity may affect specific cellular compartments, such as the cell membrane, cytoplasm, nucleus, mitochondria and endoplasmic reticulum.^{110,111}

NPs can be breathed, infused or injected into the body or the bloodstream. They can also infiltrate the body by passing through the outer layers of skin or tissue organs. For radiosensitivity, inert therapeutic NPs (eg, AuNPs) or therapeutic medicines (eg, cisplatin) can be used.^{112–114} Depending on the chosen approach and the tumor site, NPs can be delivered locally via surgical or nonsurgical procedures combined with NP/drug-loaded implants, or systemically via injection or inhalation.^{112,113}

Cobalt (Co) and Cobalt Oxide (Co₃O₄) NPs

The investigation of CoNPs as a potential anticancer treatment is a result of their antioxidant properties to enable cancer therapeutic protection. CoNPs can be a promising nanomedicine for cancer therapy.¹¹⁵ Vodyashkin et al¹¹⁶ have reported the potential application of CoNPs from water purification cytostatic agents against cancer to theranostic and diagnostic agents. CoNPs are also effective neoplastic disease treatment agent. This could be attributed to their high surface area, high mass transfer, and magnetic characteristics. They are also hazardous to tumor cells and a useful vehicle for cytotoxic medicines.¹¹⁷ Studies have demonstrated that CoNPs made using the green approach exhibit activity against cancer cells and are highly cytotoxic to cancer cells.¹¹⁸

Human lymphocytes are exposed to oxidative stress from Co₃O₄ NPs produced through thermal breakdown, which damages DNA and results in inflammatory reactions.¹¹⁹ Induction of apoptosis is brought on by oxidative stress, which significantly contributes to toxicity. It has been suggested that Co²⁺ ions released from Co₃O₄NPs induce TNF-caspase-8-p38-caspase-3 in immune cells, which is the main source of injury.¹¹⁹

In Balb3T3 cells, Co₃O₄NPs caused cytotoxicity, morphological change and genotoxicity.¹²⁰ Human peripheral leukocytes are affected in a genotoxic way by Co₃O₄NPs.¹²¹ These effects are most likely caused by the dissolution of Co²⁺ ions from NPs. Bare Co₃O₄NPs have an influence on human health because they are toxic to primary human immune cells. Surface alterations, like protein corona, could pave the way for using Co₃O₄NPs in various applications.¹¹⁹

Copper Oxide (CuO and Cu₂O) NPs

With a low dose-rate of gamma radiation, CuNPs can suppress tumor via inducing oxidative state, stimulating apoptosis and inhibiting proliferation pathway.¹²² CuNPs are also involved in optical imaging and image-guided phototherapy, for ultrasound and magnetic resonance imaging (MRI) with high spatial resolution scan.

In addition, CuONPs have been tested on the human lung epithelial cell line A549 and shown significant impact on cytotoxicity, DNA damage and ROS production.¹²² CuONPs are found to induce toxicity at the biochemical, physiological, and tissue levels in the blue mussel (*Mytilus edulis*).¹²³ The synthesized CuONPs have potential cytotoxic effects on breast cancer cells (MCF7 and MDA-MB231) and antiangiogenic effects on endothelial cells (EA.hy926).¹²⁴

Cu₂ONPs also have distinctive features in the field of nanoscale technology.¹²⁵ Taherzadeh-Soureshjani and Chehelgerdi¹²⁶ have reported beneficial cytotoxic effects of the green synthesis of Cu₂ONPs produced using the algae *Cystoseira myrica* on BC cell lines. By reducing angiogenesis and inducing apoptosis, *C. myrica* Cu₂ONPs can be used as an additional medication in cancer treatment.¹²⁶

Iron Oxide (FeO₂), Hematite (Fe₂O₃) and Magnetite (Fe₃O₄) NPs

The green synthesis of FeNPs and their effect on cancer cells have been reported. For instance, FeNPs synthesized from *Ulva lactuca* (30–40 nm) have anticancer effects against HeLa and colorectal adenocarcinoma (DLD-1) cell lines, and anti-tumor activity against glioblastoma tumors (U87-Luc and GL-261).^{127,128} FeO₂NPs have emerged as a candidate in drug delivery and cancer therapy.¹²⁹ The ROS-induced oxidative stress is associated with FeO₂NPs toxicity.¹³⁰ Important factors such as particle surface, size distribution, zeta potential and surface coating may affect their magnetic properties.

Fe₂O₃NPs and Fe₃O₄NPs also have numerous biological and industrial uses.¹³¹ Haris et al¹³² used *Oscillatoria limnetica* extract as a substantial reducing and capping agent for Fe₂O₃NPs synthesis. Previous studies have shown that Fe₂O₃NPs exert anticancer activity against human cervical carcinoma (HeLa) and MCF7 cell lines and inhibit growth and proliferation of MCF7 cells.¹³³ In vitro and in silico studies have demonstrated antioxidant effects and anticancer activities of the brown alga *Spatoglossum asperum* Fe₃O₄NPs (half-maximal inhibitory concentration (IC₅₀) = 19.24 μg mL⁻¹) against human glioblastoma cells (LN-18).⁴⁸

Titanium Oxide (TiO₂) NPs

Due to their high accumulation in cells causing modifications in gene expression, DNA damage, metabolic processes, homeostasis, inflammatory responses and lipid oxidation, TiO₂NPs can be used as anticancer agents that can lead to necrosis or programmed cell death (PCD).¹³⁴ For example, TiO₂NPs have an anticancer effect against HepG2 tumor

cells. TiO₂NPs are promising solutions to eliminate tumor growth through light irradiation and ultrasound waves caused by ROS production or ablation by heating, achieving synergistic effects, promoting cancer regression, and even reaching immunological memory.¹⁴

Silica (SiO₂) NPs

Silicon (SiO₂) NPs offer new perspectives in biosensor, drug delivery and cancer therapy. In *Calu-3* epithelial cells, amorphous SiO₂NPs (10 nm) can cause inflammation and elevated levels of ROS that cause apoptosis and reduce cell survival in a time- and concentration-dependent manner with a lethal concentration (LC₅₀) of 9.7 μg mL⁻¹ after 24 h.¹³⁵

Characterization of Algal-Mediated NPs

The characterization of algae-mediated NPs is conducted for more profound information on their synthesis and applications to comprehend the capability of NPs. Depending on the particle size dispersion, surface morphology, accumulation, zeta potential, size, delivery, wettability adsorption potential and state of the intelligent surface, isolation strategies of NPs can be determined.^{2,136,137} The most frequently used techniques for determining the size and shape of NPs are the scanning and transmission electron microscopes.¹³⁷ Due to the surface plasmon resonance (SPR), metallic NPs have exceptional optical properties that can be observed by ultraviolet-visible (UV-Vis) spectroscopy between 190 and 1100 nm.^{138,139} This radiation interacts with the metals, advancing the electronic transition from the ground to a higher energy state, and a specific SPR band is obtained for a desirable size and shape of NPs that may reach up to 2–100 nm.^{139,140}

The ingestion spectra for different materials are distinctive. AgNPs, AuNPs and ZnONPs range between 400–450, 500–550 nm and 350–390 nm, respectively.^{69,137,139–142} Depending on various features, SPR band positions may have blue- or red-shift.^{102,139,143} For instance, when the size of NPs decreases from 20 nm, SPR absorption band blue-shifts; however, if it is near 12 nm it strongly red-shifts.¹³⁹

UV-Vis diffuse reflectance spectrometer (DRS) is a comprehensive method for measuring optical retention, delivery and reflectance.¹³⁹ It is considered an excellent approach to find the band gaps of nanomaterials, which is necessary for estimating the conductance and photoactivity of the material.^{137,139,144} Based on the retention behavior of the analytes and the infrared (IR), Fourier transform infrared (FTIR) spectroscopy can recognize the functional groups of NPs; which their frequency normally ranges between 4000–400 cm⁻¹ (Table 1).¹³⁹ The correlation between the delivery spectra of the local fluid concentration and the reaction medium considers the biomolecules engaged in the interaction.^{139,145} Most normal utilitarian functional groups that attach to NPs are C=O, NH₂ and SH.^{139,143}

Other characterization approaches, such as X-ray photoelectron spectroscopy (XPS), may provide insights into the implementation of the generated NPs and their surrounding biomolecules (Table 1).^{145,167} Dynamic light scattering (DLS) spectroscopy estimates the surface charge, hydrodynamic breadth and circulation of NPs in the fluid-structure, and the zeta potential detects the particle strength.^{139,140}

X-ray diffraction (XRD) characterize and acquire accurate information regarding the composition, crystal structure, and crystalline grain size of NPs.^{68,139} The composition of NPs can be determined by comparing the position and intensity of the peaks with the reference patterns of the International Centre for Diffraction Data (ICDD) database. However, it is not suitable for amorphous materials, and XRD peaks which are too broad for NPs with a size <3 nm.¹⁶⁸ The Debye–Scherrer equation is mostly used to estimate the particle size from XRD data.^{139,169} The characterization techniques for the detection of NPs are presented in Table 1.

Mechanisms of Algal -Mediated NPs Synthesis

Algae (also known as bio-nano factories) are recognized for their ability to hyper-accumulate heavy metal ions and convert them into more malleable forms, making them superior candidates for the biosynthesis of NPs.^{5,170,171} Their downstream processing methods are well-developed and cost-effective.^{34,38} Over the last decade, there has been a lot of interest in digesting algal biomass under catalytic conditions. Microalgae are single-celled colony-forming or filamentous photosynthetic microorganisms that are classified into various categories, including Chlorophyta, Charophyta, and Bacillariophyta. AuNPs, AgNPs, and platinum (Pt) NPs have been synthesized, purified and characterized from the filamentous blue-green alga, *Plectonema organum*.¹⁷⁰

Table 1 Advantages and Limitations of the Current Techniques Used for the Detection of NPs

Technique	Definition	Uses	Advantages	Disadvantages	References
UV-Vis spectroscopy	The technique is useful to determine the concentration of NPs, provided that either a reference material is available or that the material is very well understood	UV-Vis spectroscopy is a method to detect the production and security of metal NPs in a watery arrangement. UV-Vis is an established and regularly utilized method for the quantitative investigation of nanosized NPs. UV-Vis spectroscopy can easily depict a variety of analytes, such as progress metal particles and bioconjugates of natural and inorganic NPs	For the initial characterization of the produced NPs, UV-Vis spectroscopy is a highly helpful and trustworthy approach. UV-Vis spectroscopy is quick, easy, straightforward, sensitive, selective tool for various types of NPs. It requires only a little amount of time for measurement, and, ultimately, does not need a calibration to characterize the NPs in colloidal suspensions	In general, UV-Vis spectrophotometry cannot be used to concurrently determine the concentration, size, or refractive index of NPs. It is not advised to measure them independently using UV-Vis spectrophotometry due to the inherent uncertainties	[2,146–149]
XRD	XRD is a critical instrument for fully settling the tertiary structures of translucent materials at the nuclear scale in a variety of X-ray spectroscopic modalities	XRD is a method for defining transparent size, form, and cross-section bending by long-range bonds; nevertheless, it is limited to scattering materials due to a wide-point flexible dissipation of X-ray	A wide variety of materials' structural characteristics can be analyzed using XRD. Forensic specimens, industrial materials, geochemical sample materials, and bulk and nanomaterials have all been defined and identified using XRD for a very long time	The technique is not fit for deciding the microstructures and obtaining results just from a solitary conformity/ restricting condition of the example. Another disadvantage of XRD is the low intensity of diffracted X-rays, particularly for low atomic number materials, compared with electron diffractions	[146,150–154]
DLS	DLS determines the molecular size transport of coupled NPs. Rayleigh light scattering phenomenon is used by DLS	This is a beneficial procedure for deciding the NPs shape and hydrodynamic size of tiny aggregates, polymers, and particles. DLS can examine the size distribution of tiny particles in suspension or solution on a scale ranging from submicron to one nanometer	In aqueous or physiological fluids, DLS is primarily used to determine particle size and size distributions. Typically, DLS yields bigger sizes than TEM, which may be explained by Brownian motion. To determine the average diameter of NPs dispersed in liquids, DLS is a nondestructive technology utilized. It offers the unique benefit of testing numerous particles at once, but it also has a variety of sample-specific drawback	Although it is an extremely basic and effective material method, test investigation of changing non-spherical NPs or sizes cannot be precisely estimated. Also, it gives incorrect estimations when collections are available in NPs synthesis or particle size of a somewhat little reach (1 nm–3 μ m)	[146,152,154–160]

(Continued)

Table 1 (Continued).

Technique	Definition	Uses	Advantages	Disadvantages	References
FTIR Spectroscopy	FTIR can identify changes in the overall composition of biomolecules	FTIR is used to measure the vibration and rotation of molecules affected by an infrared wavelength. Through the identification of structural variations in molecule binding, information about the existence of their interactions can be ascertained	Accuracy, consistency, and a good signal-to-noise ratio can all be achieved with FTIR. When performing spectroscopy, one can discriminate between the narrow absorption bands of functionally active residues and the massive background absorption of the complete protein by employing FTIR spectroscopy, which makes it possible to detect minuscule absorbance variations of on the order of 10^3	To prevent artefacts and fluctuations in the spectra caused by the surrounding environmental conditions and sample heterogeneity, multiple background scans and sample scans are required. For example, monitoring the sample in culture media at various temperatures can affect the sample's FTIR spectra	[146,161,162]
RS	RS Uses high spatial resolution to investigate the chemical signature of naturally occurring biological macromolecules in biocompatible circumstances	Commonly used to depict, identify, and clarify nanomaterials' vibrational and electrical designs. RS is a widely utilized method for nanostructure and nanomaterial structural characterization that gives submicron spatial resolution without the demand for sample preparation that makes it ideal for in situ studies.	One of the significant benefits of RS is that it is reasonable to examine natural examples in the fluid arrangement because water atoms are weak Raman scatters. Besides, the itemized subatomic data offered by RS can be utilized to explore compliances. Also, convergences of tissue constituents exhibit the capability of RS for identifying tissue anomalies	Weak RS can lead to long acquisition times. Not widely incorporated into current clinical workflows. Sophisticated data analysis Autofluorescence can overwhelm the Raman Signal (sample dependent)	[153,154,163,164]
EDX	EDX microanalysis method of elemental analysis is based on the production of distinctive X rays that indicate the presence of elements present in the specimens and is connected to electron microscopy	Effective for NPs detection. For example, medication distribution (mostly used to improve therapeutic performance of some chemotherapeutic agents)	EDX diffractograms can be obtained without the need of a goniometer, which is a significant benefit. The quantity of measurements can be reduced by taking advantage of EDX diffractometry's benefits. To collect enough measurement, data must be collected to calculate the stress tensor	–	[165,166]

Abbreviations: NPs, nanoparticles; UV-Vis spectroscopy, ultraviolet-visible spectroscopy; XRD, X-ray diffraction; DLS, dynamic light scattering; FTIR, Fourier transform infrared spectroscopy; RS, Raman spectroscopy; EDX, energy dispersed X-ray.

Compared to other microbial systems, algae have promising multi-purpose potential for the green biosynthesis of NPs and mass production of valuable commercial products (Figure 1).^{9,172-174} Green biosynthesis of NPs from algae can be performed in the following steps: (i) heat/boil algal extract in water or in an organic solution for a certain period of time, (ii) prepare the molar solutions of ionic metallic compounds, and (iii) incubate the algal solutions and ionic metallic compounds for a certain period of time under controlled conditions with or without stirring.^{41,175}

Algae secrete different enzymes responsible for metal bioreduction, which includes three main phases: activation, growth and termination. During the activation phase, metal ion reduction is followed by the nucleation of reduced atoms.¹⁷⁶ The growth phase, which comprises the immediate coherence of small relative NPs into stable thermodynamic particles of huge size, is followed by the termination phase that includes the final shape and size of NPs. The metal bioreduction process is affected by various factors, including pH, temperature, substrate concentration, churning and static conditions.^{177,178}

Several studies have reported that the location of the formed NPs and secondary metabolites determines whether the biosynthesis of NPs is achieved intracellularly or extracellularly.^{36,141,172} In a dose-dependent method, the intracellular biosynthesis mode involves biosynthesis of NPs depending on reductase enzymes within the algal cell.¹⁷⁹ Algae produce reducing agents during their metabolic processes, such as NADPH or NADPH-dependent reductase.^{139,180} The pathway(s) showing the extracellular and intracellular synthesis of AuNPs is illustrated in Figure 2.

Due to bioactive moieties involved in the bioreduction of the algal cell wall, biosynthesis of metallic NPs was more abundant in the cell wall than in the cytoplasm.¹³⁹ At higher pH, secondary metabolites such as proteins and residual amino acids attached to the surface, have a role in capping and stabilization of NPs via NH_2 (amine) groups.^{106,181} Vijayan et al¹⁷⁶ stated that extracellular green biosynthesis of NPs occurs when metal ions become aggregated on the algal cell surface; whereas, secondary metabolites can reduce the metal ion on the algal cell surface. Extracellular mode of biosynthesis is more popular as NPs are easily purified, but pre-treatments of washing and blending algal biomass are required.¹⁴⁵

Secondary metabolites act as reducing agents during the green biosynthesis of NPs.⁴⁶ Secondary metabolites produced by many algal species include alkaloids, phenols, flavonoids, glycosides, glutathiones, terpenoids and phenazines (Table 2).¹⁸²⁻¹⁸⁴ Other biomolecules, such as polysaccharides, lipids, polyols, phycobiliproteins, organic acids,

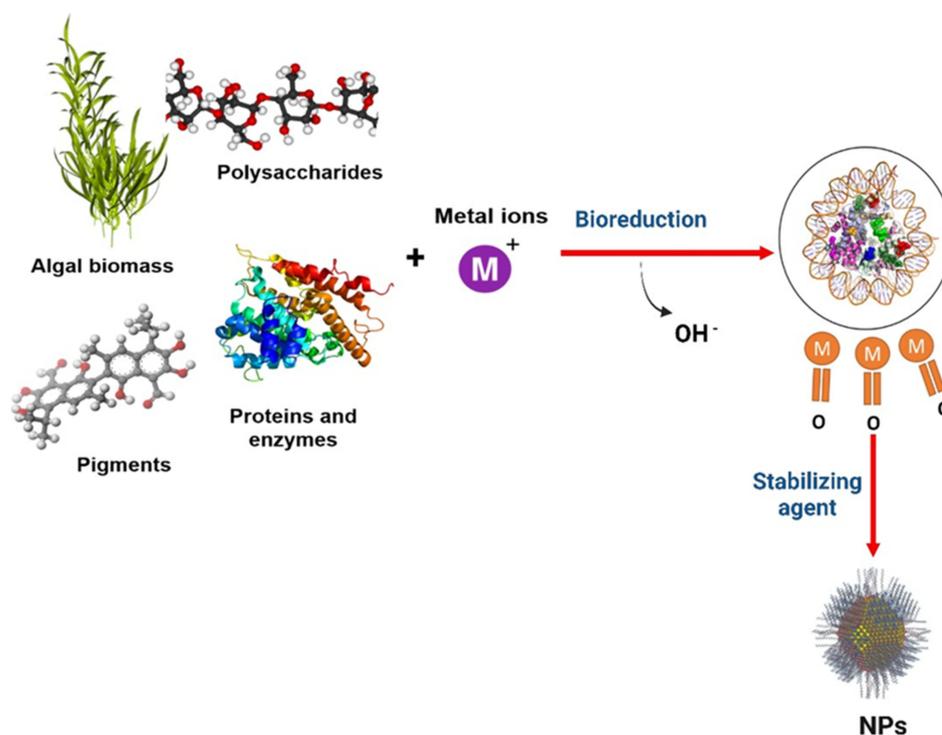


Figure 1 Green biosynthesis of nanoparticles using algae.
Abbreviations: M, metal; NPs, nanoparticles.

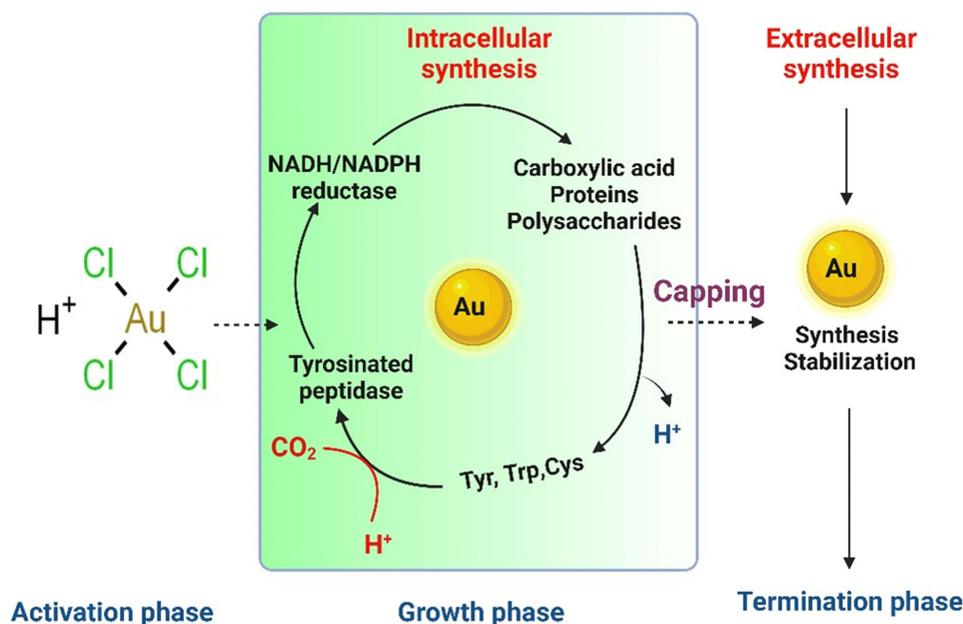


Figure 2 Intracellular and extracellular pathways for the biosynthesis of AuNPs.

Abbreviations: Au, gold; HAuCl_4 , chloroauric acid; NP, nanoparticles; Tyr, tyrosine; Trp, tryptophan; Cys, cysteine.

alcohol-based compounds and amino acids are also found in algae. The ability of algae to reduce metal ions and stabilize them into NPs in plants forms the basis of green synthesis of NPs (Figure 3).

FTIR examination on the green-synthesized AgNPs from algal extracts revealed that biomolecules containing carboxyl, amine and hydroxyl functional groups are engaged in the reduction of Au ions.²¹⁵ Thus, this has been successfully used to isolate flavonoids, terpenoids and chlorogenic acid. The flavonoid antioxidant, kaempferol, is used to generate and stabilize highly monodisperse (18.24 nm) spherical AuNPs.^{215,216} The presence of the C=O functional group in NPs has also been used to validate the potential of terpenoid fractions in the green production of ZnONPs. Furthermore, AuNPs were produced with chlorogenic acid as a reductant, and the FTIR spectra revealed an -OH functional group that was most likely involved in the synthesis.²¹⁵

Table 2 Secondary Metabolites That Act as Reducing Agents for the Green Biosynthesis of NPs

Algae type	Type of NPs	Reducing Agent	References	
Red algae	<i>Gracilaria edulis</i>	Ag	Proteins and terpenoids	[185]
	<i>Kappaphycus alvarezii</i>	Au	Polyphenolic compounds	[104]
	<i>Galaxaura elongate</i>	Au	Palmitic acid	[186]
	<i>Chondrus crispus</i>	Au	Proteins	[187]
	<i>Lemanea fluviatilis</i>	Au	Protein and organic molecules	[188]
	<i>Acanthophora spicifera</i>	Ag	Phenolic compounds, carboxylic acid, and alcoholic compounds	[189]
	<i>Gelidiella sp.</i>	Ag	Proteins	[190]

(Continued)

Table 2 (Continued).

Algae type	Type of NPs	Reducing Agent	References	
Brown algae	<i>Turbinaria conoides</i>	Ag	Carbonyl groups and polyamines	[104]
	<i>Sargassum muticum</i>	Au	Polysaccharides, proteins, and polyphenols	[181]
	<i>Ecklonia cava</i>	Au	Polyphenol compounds	[191]
	<i>Cystophora moniliformis</i>	Ag	Sulfated polysaccharides, diterpenes	[192]
	<i>Sargassum</i> sp.	Au	Amine functional groups, hydroxyl groups	[193]
	<i>Fucus vesiculosus</i>	Au	Hydroxyl groups present in polysaccharides	[105]
	<i>Sargassum muticum</i>	ZnO	Sulfate and hydroxyl groups	[194]
	<i>Turbinaria conoides</i>	Au	Fucoidan, polyphenolic, and carboxylic groups	[195]
	<i>Ecklonia cava</i>	Au	Hydroxyl and phenolic groups	[191]
	<i>Padina gymnospora</i>	Au	Fucoxanthin and flavonoids	[196]
<i>Colpomenia sinusa</i>	Ag	Polysaccharides	[197]	
Blue green algae	<i>Nostoc ellipsosporum</i>	Au	Proteins and carboxylate groups	[198]
	<i>Spirulina platensis</i>	Au	Proteins	[34]
	<i>Synechocystis</i> sp.	Au	Carboxylic groups and polysaccharides	[199]
	<i>Phormidium</i> sp.	Au	Proteins	[200]
	<i>Oscillatoria willei</i>	Ag	Tryptophan	[201]
	<i>Spirulina platensis</i>	Ag	Phytochemicals	[202]
	<i>Spirulina platensis</i>	Au-Ag	Bio-active compounds	[102]
Green microalgae	<i>Chlorella vulgaris</i>	Au	Biomolecules (amino, carboxylic, phosphate, thiol)	[203]
	<i>Pithophora oedogonia</i>	Ag	Proteins and functional groups	[204]
	<i>Caulerpa racemosa</i>	Ag	Bio-active compounds, antioxidants	[205]
	<i>Chlorella vulgaris</i>	Au	Proteins	[206]
	<i>Chlamydomonas reinhardtii</i>	Ag	Hydroxyproline glycoproteins	[207]
	<i>Tetraselmis suecica</i>	Au	Hydroxyl, nitrate and carbonyl, function groups	[208]
	<i>Tetraselmis kochinensis</i>	Au	Cell wall and cytoplasm's enzymes	[209]
	<i>Chlorella vulgaris</i>	Ag	Carbonyl groups	[210]
	<i>Chlorococcum humicola</i>	Ag	Intracellular proteins	[143]
	<i>Pithophora oedogonia</i>	Ag	Phytochemicals and proteins	[204]

(Continued)

Table 2 (Continued).

Algae type	Type of NPs	Reducing Agent	References	
Green macroalgae	<i>Ulva reticulata</i>	Au	Intracellular phytochemicals	[211]
	<i>Rhizoclonium fontinale</i>	Au	Intracellular proteins	[212]
	<i>Ulva reticulata</i>	Ag	Benzene rings, carboxylic acids, and fluoroalkanes	[213]
	<i>Ulva intestinalis</i>	Ag Au	Polysaccharides	[27]
	<i>Enteromorpha compressa</i>	Ag	Alcohols with hydrogen bonds and benzene rings	[213]
	<i>Chaetomorpha linum</i>	Ag	Peptides, flavonoids, and terpenoids	[214]
	<i>Codium capitatum</i>	Ag	Amine, peptide, and sulfate groups	[210]
	<i>Rhizoclonium fontinale</i>	Au	Intracellular proteins	[212]

Abbreviations: NPs, nanoparticles; Ag, silver; Au, gold; ZnO, zinc oxide.

Factors Affecting NPs Synthesis

Various factors influence the characterization, synthesis and application of NPs. Numerous physical factors can manage algae-mediated biosynthesis of NPs, including pH, temperature, time, static condition, and substrate concentration,^{212,217,218} as the following:

pH

pH is an important factor that affects the extent and texture of the produced NPs.²¹⁹ In general, algae require pH of 8.2 to 8.7, which is optimal alkaline for the growth and synthesis of NPs.²²⁰ Higher pH affects the reducing energy of functional groups and prevents aggregation of NPs.¹⁸⁴ The reaction of the amine groups of surface-bound protein with leftover amino acids that caps and maintains NPs is mediated by basic pH.¹⁸¹

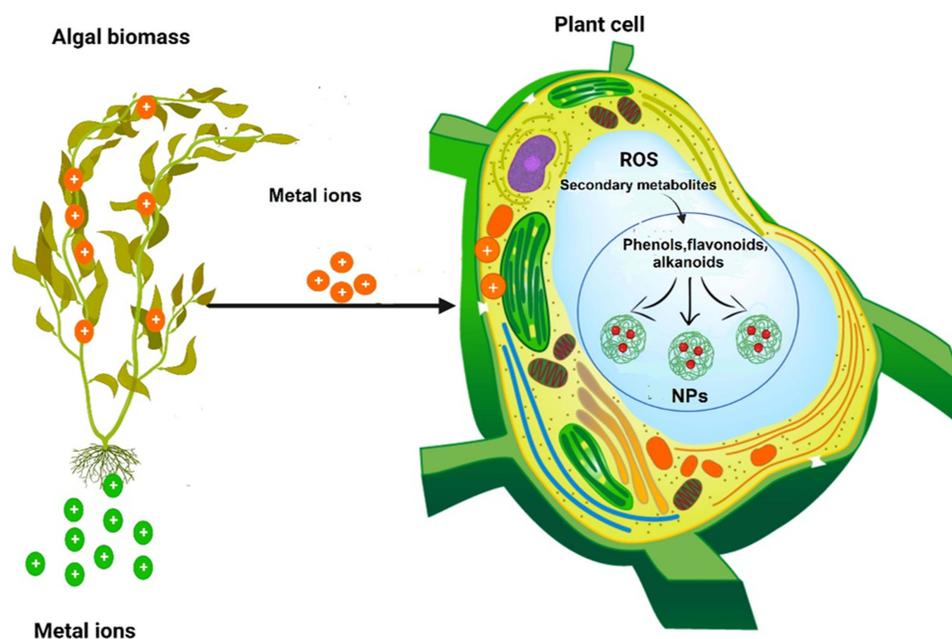


Figure 3 The role of algae in reducing metal ions and stabilizing them in plants during the green biosynthesis of nanoparticles.

Abbreviations: ROS, reactive oxygen species; NPs, nanoparticles; +, metal ion.

More functional groups bind at pH 3.0 and 4.0, and nucleate metal ions become more accessible at pH 2.0. The most attainable metal ions decrease many nucleation processes at pH 2.0, resulting in metal agglomeration.²²¹ To study the effect of pH, alterations in the UV-Vis spectra of AgNPs were generated at pH 9.0, 7.0, and 4.0. At pH 9, the color intensity of the reaction mixture peaked. Although no reaction occurred at pH 3, mono-dispersive AgNPs were formed at pH 9.²²¹

Temperature

Another important factor influencing NPs synthesis is temperature. A temperature of <100°C or ambient temperature is required for green technology. The temperature of the medium identifies the nature of NPs produced during the reaction.⁶⁹ As confirmed by UV-Vis spectra, AgNPs synthesis is affected by temperatures of 25°C, 35°C and 45°C. In this case, an increase in the AgNPs formation rate was observed with increasing the temperature.²²²

Time

The duration of the incubation of the reaction medium has major effect on the form and quality of the produced NPs in green technology.²²³ Time dependence can also be influenced by the synthesis procedure, light exposure and storage conditions.^{224,225} Thus, NPs may aggregate, compress or expand as a result of long-term storage.²²⁶

Commonly Used Green Algal-Synthesized NPs

Algae are autotrophic (eukaryotic) protists that can be unicellular or multicellular. They produce natural biomolecules and NPs of varied shapes and sizes.¹⁴³ The most widely researched algae for biosynthesis for the development of safer and more environmentally friendly NPs synthesis processes are brown, red, and green algae (Figure 4).^{143,227–229}

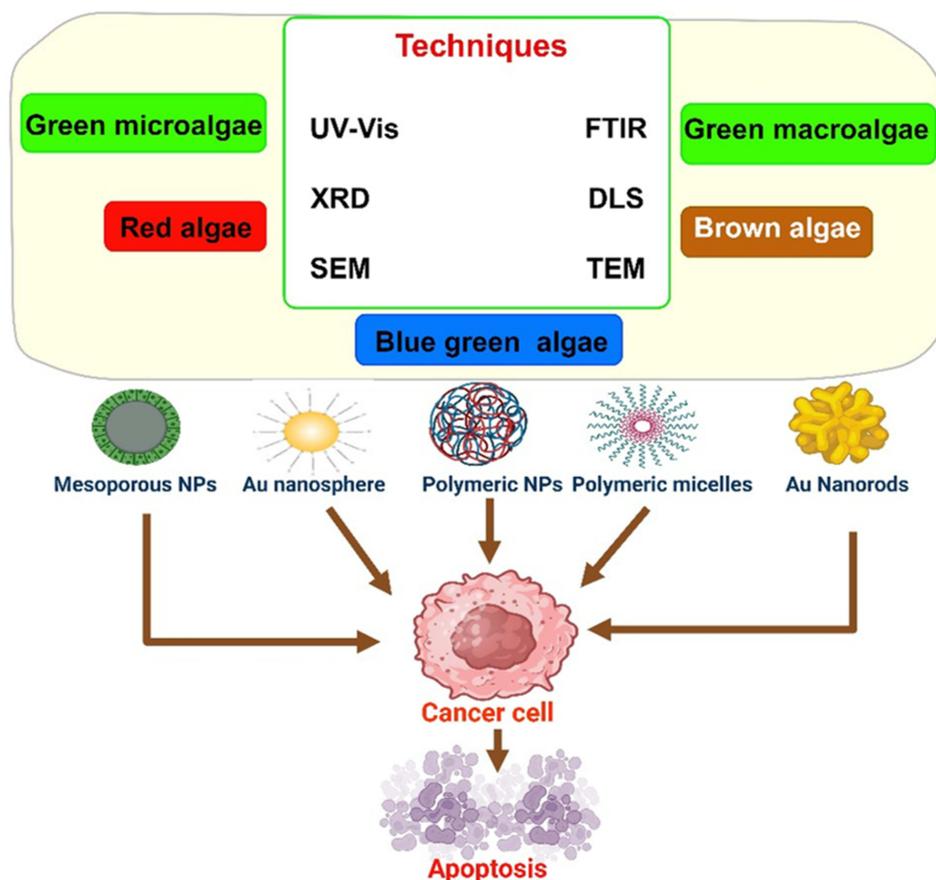


Figure 4 Algal-mediated biosynthesis and characterization techniques of nanoparticles on cancer cells.

Abbreviations: Au, gold; NPs, nanoparticles; UV-Vis, ultraviolet-visible spectroscopy; FTIR, Fourier transform infrared spectroscopy; XRD, X-ray diffraction; DLS, dynamic light scattering; SEM, scanning electron microscopy; and TEM, transmission electron microscopy.

Because algae grow quickly, are manageable and expand their biomass on average 10-fold faster than any plant species. Furthermore, they are frequently used to biosynthesize different metal/metal oxide NPs. Many strains of algae have been investigated for the green fabrication of different NPs.¹⁴³

As part of their photosynthetic process, microalgae take-up carbon dioxide (CO₂), capture sunlight and produce valuable molecules for renewable energy; thus, contributing to the “green” environment.^{228,229} Artificial photosynthesis is a chemical process that biomimics the natural photosynthesis process in order to fix CO₂ in the atmosphere. This technology is currently being researched for large-scale production. Microalgae photosynthesis can provide the same benefits as artificial photosynthesis, in addition to the possibility of a wide range of microalgal products and applications.²³⁰ Figure 4 shows algae-mediated biosynthesis and the strategies employed to synthesize a wide spectrum of NPs.

Brown Algal-Mediated Biosynthesis of Metallic NPs

Brown algae consist of about 16 orders with ~285 genera and 1800 species. Their morphology can take different sizes and forms (from the smallest threads to 60-m long sea monsters). Giant kelp plays a major role in coastal marine ecosystems.²³¹ Brown algae belonging to the order Fucales and family Sargassaceae contain important components of sterols (cholesterols, fucosterols, sulfated polysaccharides) and functional groups alginic acid, glucuronic acid, muramic acid and vinyl derivatives) may act as reducing and capping agents in biosynthesis of NPs.

Table 3 shows the different species of brown algae used to biosynthesize metal and metal oxide NPs. In general, CuNPs, AgNPs, and AuNPs are among the most frequently produced metal NPs from brown algae.^{193,195,232–234} Due to the physicochemical properties of AgNPs, which make them proper for various applications in industry and medicine, biosynthesis of AgNPs from algae has become popular and accounts for more than half of the published data.^{235,236}

Table 3 Brown Algal-Biosynthesized Metal NPs

Location of Synthesis	Algae Involved in Synthesis	NPs	Size, Shape Width and Length	Conditions of Synthesis	Characterization	Applications	References
Extracellular synthesis	<i>Polycladia mirica</i>	Se	17.48 nm and 23.01 nm in size	50°C	SEM, TEM, UV-Vis, Zeta potential, EDX, XRD, FTIR	Potent therapy effect against Ehrlich ascites carcinoma	[237]
Extracellular synthesis	<i>Turbinaria conoides</i>	Ag	Spherical, about 96 nm	1 h of darkness	SEM, FTIR, TEM, XRD	Antibacterial activities against Gram positive bacteria <i>Bacillus subtilis</i> (MTCC3053) and Gram-negative bacteria <i>Klebsiella planticola</i>	[233]
Extracellular synthesis	<i>Laminaria japonica</i>	Au	About 15–20 nm, crystalline, spherical fcc	-	XRD, FAAS, SEM, EDS, TEM, FTIR	Green chemistry and extracellular biomineralization	[232]
Extracellular synthesis	<i>Sargassum</i> spp.	Au	Longest hexagonal and triangular edges: 300–400 nm	Incubation at 37°C for 5 h with a neutral pH	XRD, UV-Vis, AFM, FTIR, AFM	Single-crystalline Au nanoplates were obtained by reducing the aqueous chloroauric acid solution with the extract of <i>Sargassum</i> sp.	[193]

(Continued)

Table 3 (Continued).

Location of Synthesis	Algae Involved in Synthesis	NPs	Size, Shape Width and Length	Conditions of Synthesis	Characterization	Applications	References
Extracellular synthesis	<i>Stoechospermum marginatum</i>	Au	Sphere, triangle, and hexagonal 18.7 to 93.7 nm	10 min, reduction has been carried out by hydroxyl groups present in the diterpenoids of the brown seaweed	WD-XRF, PL, SEM, TEM, XRD	Antibacterial activities against pathogenic bacteria	[147]
Extracellular synthesis	<i>Sargassum polycystum</i>	Ag	Spherical, 7 nm	-	TEM, XRD, SEM, UV-Vis, FTIR	Broad spectrum antibacterial activities against Gram positive and Gram-negative bacteria	[167]
Extracellular synthesis	<i>Fucus vesiculosus</i>	Au	Spherical, 20–50 nm	pH range of 2–9, incubation time of 1–8 h	TEM, SEM, EDS, FTIR, XRD	Alternative and environmentally friendly process that can be used for recovering Au from dilute hydrometallurgical solutions and leachates of electronic scraps	[105]
Extracellular synthesis	<i>Ecklonia cava</i>	Au	Sphere, triangle, 20–50 nm fcc	-	FESEM-EDX, TEM, FTIR, TEM	Biomedical applications in different area such as drug delivery, tissue engineering, and biosensor	[191]
Extracellular synthesis	<i>Turbinaria ornata</i>	Ag	Spherical and polydispersed, 22 nm	Incubation for 24 h	FE-SEM, UV-Vis, EDS, XRD, FTIR	Applications in different domains	[167]
Intracellular synthesis	<i>Bifurcaria bifurcate</i>	CuO	5–45 nm Spherical and elongated	Incubation at 60°C for 24 h	UV-Vis, XRD, FTIR	Antibacterial activity against two different strains of bacteria <i>Enterobacter aerogenes</i> (Gram negative) and <i>Staphylococcus aureus</i> (Gram positive)	[238]
Intracellular synthesis	1. <i>Padina pavonica</i> 2. <i>Colpomenia sinuosa</i> 3. <i>Petalonia fascia</i>	Fe	1.Spherical (26.60–34.01 nm) 2. Cubic (10.56–19.91 nm) 3.Spherical (6.54–13.46 nm)	–	TEM, SEM, EDS, FTIR, XRD	Bioremediation by reducing nitrogen, phosphorus and reduce the blooming of harmful algae	[239]

(Continued)

Table 3 (Continued).

Location of Synthesis	Algae Involved in Synthesis	NPs	Size, Shape Width and Length	Conditions of Synthesis	Characterization	Applications	References
Intracellular synthesis	<i>Cystoseira crinite</i>	Zn	Rectangular, 23–200 nm	pH 6.5 at 45°C	TEM, EDS, FTIR, XRD	Antimicrobial and antioxidant activities	[240]
Intracellular synthesis	<i>Polycladia myrica</i>	Se	Spherical (9.31–68.65 nm)	Incubation at room temperature	TEM, EDS, FTIR, XRD	Cytotoxicity against PC-3 cells and antiviral activity against HAV HM175 (Hepatitis A), HSV-2 (Herpes simplex II) and Adenovirus strain 2	[241]

Abbreviations: NPs, nanoparticles; Se, selenium; Ag, silver; Au, gold; CuO, copper oxide; Fe, iron; Zn, zinc; fcc, face-centered cubic; SEM, scanning electron microscopy; FTIR, Fourier transform infrared spectroscopy; TEM, transmission electron microscopy; XRD, X-ray diffraction; EDS, energy-dispersive x-ray spectroscopy; FE-SEM, field emission scanning electron microscope; AFM, atomic force microscope; UV-Vis, ultraviolet-visible spectroscopy; FAAS, flame atomic absorption spectrometry; WVD-XRF, wavelength dispersive X-ray fluorescence; PL, photoluminescence; EDX, energy dispersive X-ray.

Several species of brown algae, including *Turbinaria conoides*, *Gelidiella acerosa*, *Sargassum polycystum*, *Desmarestia menziesii*, *Padina pavonica*, and *Cystophora moniliformis*, have been reported to biosynthesize AgNPs.^{193,195,232–234} Extracellularly produced spherical AgNPs (96-nm) from *T. conoides* have high antibacterial effect against *E. coli*, *P. aeruginosa*, *Staphylococcus epidermidis* and *Staphylococcus aureus*, and antifungal effect against *Candida albicans* and *Aspergillus niger*.²³³ *Turbinaria ornata* and *T. conoides* are also reducing precursor agents of Ag salts used in AgNPs production.^{242,243} This could be attributed to their amines, polyamines, free hydroxyl, carbonyl groups and organic moieties.²⁴³

The widely produced AuNPs from different brown algal strains possess many medicinally relevant bioactivities, including anticoagulant, antifouling and antibacterial properties.^{167,232,244} For instance, the brown algal strain, *Laminaria japonica*, is characterized for its production of various NPs.²⁴⁴ *T. conoides* is one of the most common brown algal species that is also employed in AuNPs production.²⁴⁵ *T. conoides* can produce polydispersed, rectangular, spherical and triangular AuNPs. AuNPs are synthesized from chloroauric acid as a precursor of Au ions as well as *T. conoides*.

Brown algae can also biosynthesize metal oxides NPs, such as ZnONPs and TiO₂NPs.²⁴⁶ The hexagonal ZnONPs, having a size of 35–57 nm and containing the bioactive functional groups (carbonyl, sulfate, amine and hydroxyl) can be biosynthesized from the dried seaweed powder of *Sargassum muticum*.²⁴⁷

Red Algal-Driven NPs Biosynthesis

Red algae (Rhodophyta) are largely used up as food source in many countries.²⁴⁸ Due to their reduction in stability, slow crystallization and self-aggregation by the red algae, research on biosynthesis of NPs from this group of seaweeds is still developing.¹⁰³ Due to its role as reducing agent, *Porphyra vietnamensis* is a prominent red algal strain that has been involved in the fabrication of several NPs.^{249,250}

Many species of red algae have been mentioned in the literature for their biosynthesis of AgNPs (Table 4), including *Gracilaria dura*, *Gracilaria acerosa*, *Kappaphycus alvarezii*, *Kappaphycus* sp. and *Palmaria decipiens*.²⁵¹ Red algae-mediated AgNPs are cost-effective, environmentally friendly and efficient approach. Due to their spherical shape and tiny size (20–60 nm), AgNPs produced from red algal strains can be used in biomedical fields. For example, the extracellularly synthesized AgNPs from *Gelidium amansii* or *Hypnea musciformis* that possess anti-microfouling activities are of great interest in medical research.^{251,252}

In addition to AgNPs, species of red algae, including *Chondrus crispus*, *Lemanea fluviatilis*, *Corallina officinalis*, *K. alvarezii*, and *Galaxaura elongata*, are also linked to the biosynthesis of AuNPs.¹⁰⁷ By using chloroauric acid, polydispersed crystalline AuNPs with a size of 5.9 nm have been produced from the marine red alga, *L. fluviatilis*.^{255,256} *C. officinalis* can also

Table 4 Red Algal-Biosynthesized Metal NPs

Location of Synthesis	Algae Involved in Synthesis	NPs	Size, Shape, Width, and Length	Condition of Synthesis	Characterization	Applications	References
Extracellular synthesis	<i>Gracilaria edulis</i>	Ag	Spherical, and about 12.5–100 nm	Incubation at 40°C with an orbital shaker set at 150 rpm	SEM, UV-Vis, TEM, FTIR, XRD	Potential anti micro-fouling coatings for various biomedical and environmental applications	[251]
Extracellular synthesis	<i>Lemanea fluviatilis</i>	Ag	About 5–15 nm, spherical polydispersed	Incubation for 12 h at room temperature	XRD, TEM, FTIR, UV-Vis, DLS	Antioxidant activity	[188]
Extracellular synthesis	<i>Gelidium amansii</i>	Ag	Spherical	Incubation for 48 h at room temperature, followed by a 13,000 rpm centrifugation step	UV-Vis	Antioxidant activity	[253]
Extracellular synthesis	<i>Galaxaura elongate</i>	Au	3.85–77.13 nm rod, triangular and truncate	Stirring at 120 rpm for 10–12 h during incubation	GC-MS, HPLC, TEM, Zeta-potential	Antibacterial activity	[186]
Extracellular synthesis	<i>Chondrus crispus</i>	Au	Spherical and polyhedral, about 30–50 nm	Stirring at room temperature, pH 2,4, and 10	UV-Vis, SEM, EDS, TEM, FAAS, FTIR	Antibacterial activity	[104]
Extracellular synthesis	<i>Kappaphycus alvarezii</i>	Au	Polydispersed, 10–40 nm	Incubation at room temperature and neutral pH	XRD, UV-Vis, TEM, FTIR, FAAS	Antibacterial activity against <i>Pseudomonas fluorescens</i> , and <i>Staphylococcus aureus</i>	[104]
Intracellular synthesis	<i>Hypnea musciformis</i>	Au-Ag	Spherical 14.6 nm	–	UV-Vis, TEM, FTIR	Antimicrobial and antioxidant properties responsible for nanoencapsulation, nanocomposites, and biosensors in the food industry	[254]
Intracellular synthesis	<i>Jania rubens</i>	Ag	Spherical, irregular, and ellipsoidal	–	UV-Vis, TEM, FTIR	Antimicrobial and antioxidant properties	[254]
Intracellular synthesis	<i>Gelidium corneum</i>	Ag	Spherical, 20–50 nm	–	XRD, UV-Vis, TEM, FTIR	Antimicrobial and antioxidant properties	[254]

Abbreviations: NPs, nanoparticles; Ag, silver; Au, gold SEM, scanning electron microscopy; FTIR, Fourier transform infrared spectroscopy; TEM, transmission electron microscopy; XRD, X-ray diffraction; EDS, energy-dispersive x-ray spectroscopy; DLS, dynamic light scattering; UV-Vis, ultraviolet-visible spectroscopy; FAAS, flame atomic absorption spectrometry; HPLC, high-performance liquid chromatography; GC-MS, gas chromatography–mass spectrometry.

be used in the extracellular biosynthesis of spheroid AuNPs using phenol, carbonyl and hydroxyl functional groups as reducing agents.¹ Furthermore, the red alga *Gracilaria edulis* has been successfully reported to synthesize the bimetallic AgNPs-AuNPs.²⁵⁷ These bimetallic NPs have been shown to have notable anticancer characteristics in human breast cancer cell lines.

Blue-Green Algal-Driven NPs Biosynthesis

Blue-green algae (Cyanophyta) contain three orders: Chroococcales, Chamaesiphonales, and Hormogoneales; of which Chroococcales separates into two families– Chroococcaceae and Entophysalidaceae.^{258,259} These two families can be distinguished from their ability to form colonies in their natural habitat, and are considered photoautotrophic, unicellular bacteria.^{258,259} Blue-green algae have been widely used to generate a wide range of NPs, as shown in Table 5.

Table 5 Blue-Green Algal-Biosynthesized Metal NPs

Location of Synthesis	Algae Involved in the Synthesis	NPs	Size, Shape, Width and Length	Condition of Synthesis	Characterization	Applications	References
Extracellular synthesis	<i>Nostoc ellipsosporum</i>	Au	Icosahedral and decahedral about 20–40 nm	Incubation for 3 h, pH 5	SEM, FTIR, UV-Vis	Novel and environmentally benign procedure or green technology for the biosynthesis of exclusively Au nanorods with an approximately uniform distribution of aspect ratio	[198]
Extracellular synthesis	<i>Spirulina platensis</i>	Au	2–8 nm cylindrical, monodispersed	-	FTIR, EDAX, HR-TEM, UV-Vis	Reducing and inhibitory agents for the HSV-I replication	[38]
Extracellular synthesis	<i>Lyngbya majuscula</i>	Au	>20 nm, spherical	Au salts. Exposure can lead to the initiation of synthesis	TEM	Alternative to the hazardous reclamation of precious metal Au from industrial wastes	[178]
Extracellular synthesis	<i>Spirulina platensis</i>	Au	Cubic and octahedral	Incubation for 48 h at room temperature, centrifugation at 10.000 rpm	UV-Vis, SEM	Antibacterial activities against Gram-positive organisms <i>Bacillus subtilis</i> and <i>Staphylococcus aureus</i>	[260]
Extracellular synthesis	<i>Plectonema boryanum</i>	Au	20–25 nm	Incubation for 24 h at 200°C	XPS, TEM, SEM, TOF-SIMS	Metabolic processes from the utilization of nitrate at 25°C and also organic compounds released from the dead cyanobacteria at 25–100°C	[62]
Extracellular synthesis	<i>Synechocystis</i> sp.	Au	Cylindrical, 3–13 nm	Incubation for 16 h at 20°C in darkness and 4°C in darkness respectively in light (50 mmol m ⁻² s ⁻¹)	SERS, TEM, Zeta-potential	The interaction between NPs and model microorganisms to assess the risks associated with the specific use of nanomaterials and to reduce adverse health effects	[199]

(Continued)

Table 5 (Continued).

Location of Synthesis	Algae Involved in the Synthesis	NPs	Size, Shape, Width and Length	Condition of Synthesis	Characterization	Applications	References
Extracellular synthesis	<i>Phormidium tenue</i>	Au	Cylindrical and misshapen, 14.84 nm	Incubation for 72 h, pH 7, and 0 exposure	TEM, XRD, UV-Vis	Advantages in biomedical, health, and environmental applications	[261]
Extracellular synthesis	<i>Phormidium valderianum</i>	Au	Spherical, hexagonal, fcc (24 nm)	Incubation for 72 h at 20°C	UV-Vis, TEM, XRD	Advantages in biomedical, health, and environmental applications	[261]
Extracellular synthesis	<i>Anabaena cylindrica</i>	Au	Spherical, about 10 nm	Incubation for 4–40 h	TEM, XRD, LIBS	Variation between NPs in vegetative cells and in the heterocysts	[262]
Extracellular synthesis	<i>Phormidium ambiguum</i>	Ag	Spherical crystals with face-centered cubic, 6.24–11.4 nm and 6.46–12.2 nm	-	UV-Vis, XRD, TEM, SEM, EDX	Inhibiting the growth of medically important resistance-pathogenic Gram-positive and Gram-negative bacteria	[263]
Extracellular synthesis	<i>Desertifilum tharense</i>	Ag	Spherical crystals with face-centered cubic, 6.24–11.4 nm and 6.46–12.2 nm	-	UV-Vis, XRD, TEM, SEM, EDX	Inhibiting the growth of <i>Micrococcus luteus</i> and methicillin-resistant <i>Staphylococcus aureus</i>	[263]
Extracellular synthesis	<i>Aphanotheca</i> sp. and <i>Oscillatoria</i> sp.	Ag	Spherical, about 40–80 nm	-	UV-Vis, SEM, EDX	Antibacterial activity against pathogenic bacteria	[264]
Extracellular synthesis	<i>Microchaete</i>	Ag	Spherical and polydispersed, 80 nm	60 min at 60°C, pH 5.6, 60 min	UV-VIS, TEM, DLS	Dye decolorization	[265]
Extracellular synthesis	<i>Cylindrospermum stagnale</i>	Ag	38–88 nm, pentagonal	Incubation at 40°C for 45 h	SEM, UV-Vis	Anticancer, antioxidant and antibacterial activities	[266]
Extracellular synthesis	<i>Spirulina platensis</i>	Si	Crystalline, 11.6 nm	Incubation for 24 h at 25°C, pH 7	UV-Vis, XRD	Environmentally friendly method using <i>Spirulina platensis</i> to synthesize SiNPs	[267]
Extracellular synthesis	<i>Spirulina platensis</i>	Au-Ag	Core-shell, 7–16 (Ag), 6–10 (Au) and 17–25 nm (bimetallic 50:50 ratio)	Incubation for 120 h at 37°C, pH 5.6	XRD, SEM, UV-Vis	The use of blue green alga offers a means of developing “nano factories” for production of metal NPs	[102]

(Continued)

Table 5 (Continued).

Location of Synthesis	Algae Involved in the Synthesis	NPs	Size, Shape, Width and Length	Condition of Synthesis	Characterization	Applications	References
Extracellular synthesis	<i>Arthrospira platensis</i>	Fe	Spindle to rod-shaped, 23 nm	Incubation for 96 h at 25°C with pH 5.2	UV-Vis, TEM, SEM, FTIR, EDX, XRD	Biogenic superparamagnetic nano iron synthesis as a new approach in nanobiotechnology.	[268]
Intracellular synthesis	<i>Nostoc ellipsosporum</i>	Au	Hexagonal Sphere 2–25 nm	Incubation for 48 h at 20°C	DLS, UV-Vis, TEM, FTIR	Microalgal nanobiotechnology	[212]
Intracellular synthesis	<i>Lyngbya majuscula</i>	Au	Spherical, about 20 nm	Incubation for 72 h, pH 6, 7 and 8	TEM	Hazardous reclamation of precious metal Au from industrial wastes	[178]
Intracellular synthesis	<i>Spirulina subsalsa</i>	Au	Spherical, about 20 nm	Incubation for 72 h, pH 6, 7 and 8	TEM	Hazardous reclamation of precious metal Au from industrial wastes	[178]
Intracellular synthesis	<i>Phormidium tenue</i>	Au	Spherical, about 5 nm	Room temperature	TEM, FTIR, FT-UV, HR-SEM, EDX	Commercial scale production of stable CdS NPs	[269]
Intracellular synthesis	<i>Plectonema boryanum</i>	Ag	Octahedral, 200 nm	Incubation from 25–100°C for 28 days	XPS, EDS, TEM	Organics released from the dead cyanobacteria	[270]
Intracellular synthesis	<i>Oscillatoria princeps</i>	Ag	Quasi-spherical 3.30–17.97 nm	Room temperature	TEM, FTIR, UV, SEM, EDX	Antibacterials	[271]
Intracellular synthesis	<i>Arthrospira sp</i>	Cu	Spherical	Room temperature	TEM, SEM	The damage of CuONPs to photosynthesis	[272]

Abbreviations: NPs, nanoparticles; Ag, silver; Au, gold; Si, silicon; Fe, iron; Cu, calcium; fcc, face-centered cubic; SEM, scanning electron microscopy; FTIR, Fourier transform infrared spectroscopy; TEM, transmission electron microscopy; LIBS, laser-induced breakdown spectroscopy; XRD, X-ray diffraction; EDS, energy-dispersive x-ray spectroscopy; UV-Vis, ultraviolet-visible spectroscopy; HR-SEM; high resolution scanning electron microscopy; XPS, X-ray photoelectron spectroscopy; EDX, energy dispersive X-Ray analysis; ToF-SIMS, time-of-flight secondary ion mass spectrometry.

Spirulina platensis is the major contributor of AgNPs in blue-green algae. It contains rich nutritional substances, such as protein (60–70%), vitamins, β -carotene and essential fatty acids, to help reduce and cap NPs.²⁰² The contribution of the production of spherical AgNPs (2–8 nm), *S. platensis* is widely used in the pharmaceutical industry, human health and food production. Other blue-green algal species producing different shapes and sizes of AgNPs have also been reported.²⁶⁶

S. platensis also plays an important role in the biosynthesis of AuNPs. *S. platensis*-mediated extracellular production of cubic, spherical and octahedral AuNPs has been reported to be linked with several groups, including peptides and proteins, to act as reducing agents.²⁷³ In *Phormidium valderianum*, an intracellular monodispersive triangle AuNPs was detected at 530 nm wavelengths and 1897 UV-Vis spectrometry absorbance.^{200,274} In addition, *P. valderianum* uses cytoplasmic metabolites as reducing agents in the extracellular biosynthesis of hexagonal, spherical and face-centered cubic (fcc; 24 nm) AuNPs.²⁰² *S. platensis* is also known the biosynthesis of bimetallic NPs (core-shell AgNPs-AuNPs) and crystalline SiO₂NPs.^{102,267}

Micro Green Algal-Mediated Biosynthesis of NPs

The order Cladophorales that belongs to the micro green algae has been widely used in many industrial, pharmaceutical and biotechnological applications. Active compounds, such as phenols, alkaloids, flavonoids, sugars and functional groups, have been described as reducing and stabilizing agents in the biosynthesis of NPs.²⁷⁵ AgNPs are the most commonly in vitro-synthesized monometallic NPs from over 20 species of green microalgae producing them. Spherical (16 nm) from *Chlorococcum humicola*, cubical and hexagonal (24–55 nm) from *Pithophora oedogonia*, triangular (28 nm) from *Chlamydomonas reinhardtii*, and rectangular and rounded (1–15 nm) from both *C. vulgaris* and *Enteromorpha flexuosa* are examples of the ranges of AgNPs produced by green micro algae (Table 6).^{101,207,275,276}

Recently, many studies have been published on green micro algae-driven production of AuNPs (Table 6). The micro algae, *Pithophora crista*, has been extensively used for manufacturing AuNPs.²⁰⁶ Cyclic substances, carboxylic acids, peptides, and proteins make up most of the identified primary metabolites responsible for synthesizing metallic NPs from green micro algae.^{107,214,277}

Table 6 Micro Green Algal-Biosynthesized Metal NPs

Location of Synthesis	Algae Involved in Synthesis	NPs	Size, Shape, Width and Length	Condition of Synthesis	Characterization	Applications	References
Extracellular synthesis	<i>Chlorella vulgaris</i>	Au	9–20 nm	Incubation for 3 h at 45–90°C	FTIR, XRD, UV-Vis, SEM	Applications in catalysis, antimicrobial and surface-enhanced Raman scattering	[203]
Extracellular synthesis	<i>Botryococcus braunii</i>	Cu	Cubical and spherical with an elongated shape (10–70 nm)	-	FTIR, XRD, UV-Vis, SEM	Antimicrobial activity	[278]
Extracellular synthesis	<i>Chlorella pyrenoidosa</i>	Au	Icosahedral and spherical, 25–30 nm	Incubation at 100°C at 100 rpm at pH 8	UV-Vis, XRD, HR-TEM	Controllable tuning of the synthesis of thermodynamically stable AuNP	[217]
Extracellular synthesis	<i>Chlorella vulgaris</i>	Pd	Spherical, truncated triangular (~ 70 nm)	-	FTIR, SEM, XRD	The green approach of Pd catalyst to facilitate the reaction and its environmental impact is the main characteristic of the process	[279]
Extracellular synthesis	<i>Chlamydomonas reinhardtii</i>	Cd	-	Centrifugation, incubation at 65°C	UV-Vis, SEM	Economical, environmentally friendly approach for the large-scale synthesis of NPs that can be used in photocatalysis	[280]

(Continued)

Table 6 (Continued).

Location of Synthesis	Algae Involved in Synthesis	NPs	Size, Shape, Width and Length	Condition of Synthesis	Characterization	Applications	References
Extracellular synthesis	<i>Pithophora oedogonia</i>	Ag	Hexagonal and cubic, 34.03 nm	Centrifugation at 15,000 rpm and incubation for 15 min at room temperature	UV-Vis, DLS, EDS, SEM	Inhibitory activity against pathogenic bacteria	[204]
Intracellular synthesis	<i>Spirogyra submaxima</i>	Au	Triangular and spherical	-	UV-Vis, Zeta-potential, TEM, XR	Green for nanogold production	[281]
Intracellular synthesis	<i>Plectonema boryanum</i> , <i>Chlorella</i> sp., <i>Scenedesmus</i> sp.	Ag	Less than 10 nm	Incubation at 25°C	XPS, TEM, TEM-ED	Pharmaceuticals, agriculture, cosmetics and medicine	[167]
Intracellular synthesis	<i>Chlorococum humicola</i>	Ag	Cylindrical, 16 nm	Incubation at 28°C for 72 h	UV-Vis, TEM, SEM, FTIR, EDX, XRD	Biomedical applications	[276]
Intracellular synthesis	<i>Chlamydomonas reinhardtii</i>	Ag	Spherical, 60–120 nm	2000 lx at 25°C	FTIR, ZETA potential, DSL	Bioremediation and adaptation capabilities of algal cells to Ag-NPs	[282]
Intracellular synthesis	<i>Chlorella vulgaris</i>	Zn	Spherical, 380–950 nm	Incubation at room temperature	UV-Vis, TEM, XRD, FTIR	Antibacterial effect against multidrug-resistant pathogens	[174]
Intracellular synthesis	<i>Scenedesmus dimorphus</i>	Zn	Crystalline, 27.37 nm	Incubation at room temperature	UV-Vis, SEM, FTIR, XRD, XPS	Remediation of dye-containing wastewaters under natural sunlight	[283]

Abbreviations: NPs, nanoparticles; Ag, silver; Au, gold; Cu, copper; Zn, zinc, Cd, cadmium; Pd, Palladium; SEM, scanning electron microscopy; FTIR, Fourier transform infrared spectroscopy; TEM, transmission electron microscopy; XRD, X-ray diffraction; EDS, energy-dispersive x-ray spectroscopy; UV-Vis, ultraviolet-visible spectroscopy; DLS, dynamic light scattering; XPS, X-ray photoelectron spectroscopy; EDX, Energy Dispersive X-ray.

SiO₂NPs, coming from *C. vulgaris* extract, are semiconductors employed as bio-indicators in numerous industrial wastes to detect harmful chemicals.²⁰³ In addition to SiO₂NPs, biosynthesis of other semiconductor as well as metallic, bimetallic and metal oxide NPs is underway, with emphasis on early stages of production. The freshwater green alga, *Chlamydomonas reinhardtii*, has been implicated in the mediation of cadmium sulfide (CdS) bimetallic NPs that are highly used in photocatalysis, LEDs and biosensors.²⁸⁰ Table 6 shows that the commonly biosynthesized NPs coming from different species of micro green algae.

The Role of Algal-Mediated NPs in Cancer Treatment

Due to the severe adverse effects of cancer on normal surrounding cells, many chemotherapeutic drugs diminish clinical efficacy. Alternatively, nanomedicine is the application of nanomaterials to achieve therapeutic benefits for screening, diagnosing, preventing and curing diseases.^{284–286} Because the chemically generated NPs cause high-tissue accumulation and lead to toxicity, scientists have started to pay more attention to the significant role of nanomedicine in drug delivery, especially algal-based nano drug delivery systems. Several treatment strategies to improve diagnostic accuracy, drug specificity, drug design, and drug delivery systems have been suggested.^{286,287} Due to their low toxicity and enhanced drug delivery as excellent nanocarriers, recent research has focused on NPs synthesized from microbial sources against various types of cancer, of which they are considered as excellent nanocarriers due to their low toxicity and enhanced

drug delivery.^{3,10,27,34} Biosynthetic algal NPs are potential methods for chemotherapeutic drug target delivery. Biological NP-based drug delivery systems have shown many advantages in cancer therapy due to drug administration, precise tumor cell selectivity and reduction of side effects.^{3,36}

Due to their low toxicity, biodegradability and large surface area, algal-based NPs are used in various fields of clinical biotechnology and targeted drug delivery for cancer.^{288–290} For instance, the nanodrug delivery systems based on different algal-polysaccharides (alginates, carrageenans, fucoidan, ulvan, and others) have been described.²⁸⁵ Algal polysaccharides are also associated with the production of pharmaceutical substances and drug delivery agents. Drug delivery to cancer cells is made easier and more effective by peptide-drug conjugates.²⁹¹ For example, the anti-A20 leukemic-like cell line efficacy of phage Peptide P4 coupled with 2-chlorotrityl resin has been proven. Recently, AuNPs have been used as a potential candidate for delivering a variety of medications to their intended locations.^{292,293} These payloads include everything from tiny medicinal molecules to large macromolecules, including proteins, RNA, and DNA. Effective release of these payloads must be considered to provide effective therapy.²⁹⁴

Quantum dots are crystalline NPs used to determine the location of cancer cells in the body. AuNPs allow heat from infrared lasers to detect cancerous tumors. FeO₂NPs are used to better diagnose tumors by MRI, immunoassays, tissue healing, and as efficient chemotherapeutic agents.^{295–297} When NPs are attached to the tumour, their magnetic properties improve computed tomography (CT) imaging.^{298,299}

During NPs biosynthesis, no harmful chemicals are used to grow algae because it naturally contains secondary metabolites and biomolecules, making algal-mediated NPs potential candidates in many biomedical applications, including cancer treatment.^{27,300} Due to their cytotoxic and anticancer properties, AgNPs from different algal species are used as drug carriers to deliver anticancer drugs to malignant sites as well as anticancer agents on their own. The anticancer action of AgNPs is mediated by triggering PCD via double-strand DNA breaks, oxidative stress, and chromosomal instability.¹⁴⁶ Cortese et al³⁰¹ have tested hybrid clustered NPs (HCNPs) loaded with a colloidal suspension of AgNPs against leukemia KU812 cells. The binding of HCNPs with cancerous leukemic cells and the release of Ag⁺ ions have resulted in ROS production, allowing the cancerous leukemic cells to be killed. It has been stated in the literature that biogenically produced NPs outperform chemically synthesized NPs in destroying malignant cells.³⁰¹ According to Al-Dulimi et al,³⁰² biogenically produced NPs successfully destroy T-cell leukemia. Similarly, AgNPs produced from an aqueous extract of the macroalga, *Gracilaria edulis*, have shown anticancer effect against human PC3 cell lines and MCF-7 breast cancer cells.²¹⁰ Table 7 summarizes the types of NPs synthesized from algal species against different cancer cells.

Table 7 Algal-Mediated Biosynthesis of NPs and Their Role in Cancer Treatment

Algae	Name of Algae	NPs	Algal-Biosynthesized NPs	Type (Cell Line) of Cancer	References
Brown macroalgae	<i>Sargassum polycystum</i>	Cu	<i>S. polycystum</i> extract was added into a flask with 100 mL of 1 Mm aqueous Cu solution, and the flasks were incubated at room temperature for 24 h. Flasks were centrifuged at 12,000 rpm for 15 min	Breast cancer (MCF-7)	[303]
	<i>Cystoseira Baccata</i>	Au	At room temperature, 1 mL of extract was added to 5 liters of HAuCl 40.01 M for 24 h	Colon cancer	[304]
	<i>Sargassum wightii</i>	MgO	Aqueous extraction was performed for 30 min at 80°C. The two solutions of MgO and aqueous seaweed extract were combined in a 9:1 ratio and stirred continuously at 90°C for 6 h. Then it was carried out for 3 h in a muffle furnace at 500°C	Lung cancer	[185]
	<i>Padina boryana</i>	Crystalline palladium	Green extract was added to 10 mM disodium tetrachloropalladate for 2 h, then using stirring at 200 rpm min ⁻¹ at 60C	Breast cancer (MCF-7)	[305]

(Continued)

Table 7 (Continued).

Algae	Name of Algae	NPs	Algal-Biosynthesized NPs	Type (Cell Line) of Cancer	References
Green macroalgae	<i>Caulerpa taxifolia</i>	Ag	<i>C. taxifolia</i> extract (10 mL) was combined with 100 mL AgNO ₃ for 1 h, then kept in a 90°C water bath and 1 N NaOH and 1 N H ₃ PO ₄ were utilized, until the color changed from yellow to reddish brown	Lung cancer (A549)	[14]
	<i>Chaetomorpha linum</i>	Ag	<i>C. Linum</i> (10 mL) aqueous extract was mixed with 90 mL of 1 mM AgNO ₃ solution. Then incubation for 20 min at room temperature	Colon cancer (HCT-116)	[7]
	<i>Ulva lactuca</i>	Ag and Zn	At 25°C, AgNPs were made. The extract (1 mg mL ⁻¹) was added to the 5 mM aqueous AgNPs solution	Colon cancer (HCT-116)	[7]
Red macroalgae	<i>Corallina officinalis</i>	Au	<i>C. officinalis</i> extract was utilized to synthesize AuNPs. TEM, FTIR, EDX, and UV-Vis were used to characterize NPs, then tested for cytotoxicity against MCF-7 human breast cancer cells grown in Dulbecco's modified Eagle medium supplemented with 10% fetal bovine serum	Breast cancer (MCF-7)	[1]
	<i>Acanthophora spicifera</i>	Au	Aqueous extract (250 mL) was added to 65 mL of a 1 M HAuCl ₄ solution while stirring at 60°C for 4 h. The color change confirmed the production of AuNPs at 10,000 x g centrifugation for 30 min at 4°C after complete reduction	Colon adenocarcinoma (HT-29)	[306]
	<i>Halymenia dilatata</i>	Pt	Aqueous 1 mM solution (H ₂ PtCl ₆) (90 mL) were heated on a hotplate to 60°C and stirred with 10 mL of <i>H. dilatata</i> extract for 1 h. After being created, NPS were centrifuged at 5000 rpm for 30 min to eliminate any impurities before being cleaned with distilled water	Breast cancer (MDA-MB-231)	[307]
	<i>Amphiroa rigida</i>	Ag	For the biomimetic synthesis of AgNPs (90 mL of 1 mM aqueous AgNO ₃) was combined with 10 mL of RS supernatant at 37°C, until the color changed, then incubated at 4°C. <i>A. rigida</i> AgNPs were centrifuged at 9000 rpm for 15 min	Breast cancer (MCF-7)	[308]
	<i>Gracilaria edulis</i>	Ag and Zn	Aqueous 1 mM AgNO ₃ or zinc nitrate solution (90 mL) was combined with 10 mL algal extracts and kept for over a week at room temperature	Prostate cancer (PC3)	[210]
Brown microalgae	<i>Trichodesmium erythraeum</i>	Ag	AgNO ₃ solution was added to the <i>T. erythraeum</i> supernatant; the color changed from white to brown, confirmed AgNPs were biosynthesized	Breast cancer (MCF-7)	[309]
Red micro-algae	<i>Noctiluca scintillans</i>	Ag	Using 2.0%, m/v algae extract and 0.1 M AgNO ₃ . Then algae-capped AgNPs were created	Breast cancer (MDA-MB-231)	[310]

(Continued)

Table 7 (Continued).

Algae	Name of Algae	NPs	Algal-Biosynthesized NPs	Type (Cell Line) of Cancer	References
Green microalgae	<i>Dunaliella salina</i>	Au	A 2.0 mL, 1 mM aqueous solution of HAuCl ₄ was combined with <i>D. salina</i> extract before being centrifuged and exposed to sunshine	Breast cancer	[311]
	<i>Dictyosphaerium</i> sp.	Au	Before stirring, diosgenin was combined with 5 mL distilled water (1 mg mL ⁻¹) and mixed with the solution containing Au salt and algal extract for 24 h, then centrifuged	Breast cancer (HCC1954) and colorectal cancer (HCT116)	[312]
	<i>Chlorella vulgaris</i>	Ag	The culture was centrifuged after 20 days of incubation. The culture supernatant was warmed to 50°C. By combining 30 mL of AgNO ₃ solution with 15 mL of culture supernatant, the final AgNO ₃ concentration was brought down to 5 mM. The reaction mixture was incubated in a water bath at 50°C for 24 h without being agitated or shaken	Liver cancer (Hep-G2)	[313]
Blue green microalgae	<i>Oscillatoria</i> sp.	Ag ₂ O and Au	The biomass of microalgae was washed. They were inoculated five times with sterile distilled water in 100 mL of 10 mM AgNO ₃ . By stirring at room temp for 1 h. The resulting AgNPs and AuNPs were cleaned and dried a 50°C then kept at 4°C	Colon cancer (CaCo-2) and cervical carcinoma (HeLa cells)	[34]

Abbreviations: NPs, nanoparticles; Cu, copper; Au, gold; MgO, magnesium oxide; Ag, silver; Zn, zinc; Pt, platinum; Ag₂O, silver oxide; AgNO₃, silver nitrate; FTIR, Fourier transform infrared spectroscopy; TEM, transmission electron microscopy; UV-Vis, ultraviolet-visible spectroscopy; EDX, energy dispersive X-ray.

Green NPs induce apoptosis by upregulating the expression of caspase-9, caspase 3 and Bax, caspase-8, and downregulating the expression of Bcl-2 and Bid to trigger death of cancer cells.³¹⁴ Chitosan-coated Ag nanotriangles may act as a photothermal agent for a panel of human non-small-cell lung cancer cells (NCIH460).³¹⁵ In addition, the brown alga (*Sargassum vulgare*) is used to make biological AgNPs with a size of 10 nm that can suppress the proliferation of malignant human myeloblastic leukemia cells HL60 and cervical cancer cells HeLa. It has been demonstrated that the green biosynthesized AuNPs have anticancer activity against A549 cell.^{316,317} Biological AuNPs have pivotal role in drug delivery and management of cancer cell.³¹⁸

Different algae (eg, *T. conoides*, *S. platensis*, *Galaxaura elongate*) are used as bio-nanofactories to synthesize AuNPs.^{319,320} AuNPs synthesized from these “green” algal sources have anticancer effects against cancer cell lines HEK-293 and MCF-7.³²¹ In general, AuNPs can be manipulated to absorb light efficiently at the near-infrared region, convert it into heat energy, and transmit it to the surrounding environment. This process is called photo-hyperthermia that is widely used to attenuate cancer cells, where Au nanorods are administered near the tumor region to destroy cancer cells without causing much damage to healthy neighboring cells.³²¹ AuNPs, individually or combined with other treatment modalities, such as radio/chemotherapy, can induce hyperthermia or deliver the drug in the targeted region or cell to produce a synergetic effect, to facilitate cancer treatment. Rezaeian and co-workers³²² have used a green approach to synthesize curcumin-coated AuNPs and performed in vitro studies to compare NP-mediated photothermal therapy and radiofrequency electric field hyperthermia on mouse colorectal cancer (CT26) cell lines. They concluded that NPs could considerably induce apoptosis using photothermal therapy and radiofrequency electric field hyperthermia.

Micro- and macroalgae are responsible for the production of antibodies, vaccines, growth factors, and some hormones used in medical biotechnology.³²³ The marine green alga (*Ulva rigida*), brown alga (*C. myrica*) and red alga (*Gracilaria foliifer*) can produce spherical AgNPs with a diameter of 12, 17 and 24 nm, respectively.³²⁴ AgNPs produced from these

marine algae can be used as reducing and capping agents, and exhibit great selectivity and strong anticancer potential against malignant MCF-7 cells without generating cytotoxicity against *Artemia salina*.³²⁴

The aqueous extract of the red seaweed, *Champia parvula*, contains antioxidant, antibacterial and anticancer phytochemical components that help protect humans from diseases.³²⁵ This could be attributed to the characteristics of AgNPs found in *C. parvula*. It has been reported that AgNPs may have an effect on the induction necrosis and apoptosis through SubG1 cell cycle arrest.^{326–330} The induction of apoptosis can be attributed to the upregulation of caspase-8 and –3 to trigger the induction of Bid and tBid proteins, and the up-regulation of the apoptotic proteins Bax and Bak.³²⁹

The biosynthesized Cu₂ONPs from the brown alga *C. myrica* (CM-Cu₂ONPs) were evaluated for their cytotoxicity against breast cancer cell lines MDA-MB-231 and T47D.¹²⁶ They concluded that Cu₂ONPs could decrease angiogenesis and induce apoptosis, suggesting that CM-Cu₂ONPs have the potential to be employed as a supplement in cancer therapy.

Microalgal colloidal suspensions of NPs have antiproliferative and apoptotic effects on various cancers.²⁹⁹ For example, sulfated polysaccharide such as fucoidan extracted from *F. vesiculosus*, *Sargassum henslowianam*, *Cladosiphon fucoidan* and *Coccolophora longsdorfi* inhibits angiogenesis and metastasis through the down-regulation of kinase activity and activation of caspase-3/7 in the human lymphoma cell line, melanoma, human colon cancer, breast cancer, lung carcinoma, and human promyelocytic leukemia.³³¹ Another microalgal metabolite, mono-acyl glycerides extracted from *Skeletonema marinoi*, can induce selective apoptosis through caspase-3/7 activation in colon cancer cell lines (HCT-116) and hematological cancer cell lines (U-937), without induction of apoptosis in normal cells.³³⁰ Some microalgal lipids (eg, polyunsaturated fatty acids) also have anticancer properties against cervical and breast cancer. Phycocyanin, which is a phycobiliprotein found in the microalgal species *Arthronema africanum*, *Porphyra haitanensis* and *S. platensis*, inhibits the growth of human hepatocellular carcinoma, lung/colon cancer and leukemia cells.³³⁰

Therefore, algal-mediated AgNPs may serve as an important baseline for the development of new nanodrugs for cancer therapy and microbial infections. The role of different green synthesized NPs against different types of cancer along with the mechanisms associated to control/inhibit cancer cells are illustrated in Figure 5.

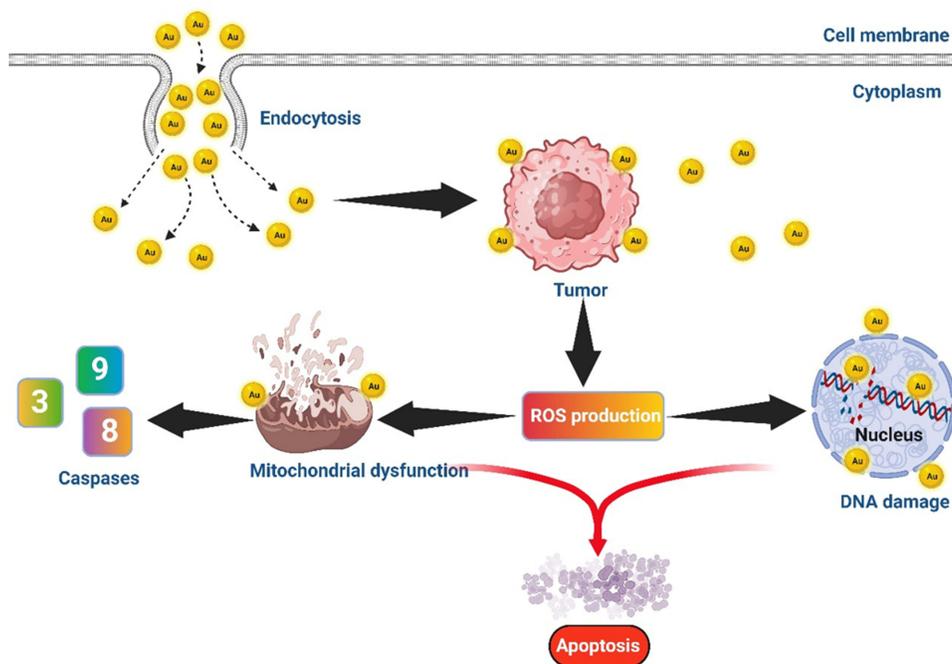


Figure 5 The mechanism of green synthesized nanoparticles in inhibiting cancer in human.

Abbreviations: ROS, reactive oxygen species; Au, gold.

The Future Prospective

Green chemistry is a concept that aims to reduce waste and byproducts, as well as the use of dangerous chemicals and energy needs, by combining renewable and natural resources.^{167,286,321} The combination of green chemistry with nanotechnology is a great trending strategy used in different fields of research.^{179,332} There are many challenges in green synthesis of NPs; among those is to obtain homogeneously dispersed NPs. Due to their distinctive morphological and physiochemical features, NPs have been utilized in many fields, including communication, space, medicine and agriculture.^{95,170,273} Green nanotechnology using algae is biocompatible, bioavailable and biosafe.^{7,34,67,132} There are several applications of green NPs in biomedical fields, including disease detection, cancer therapies, imaging, drug delivery, tissue engineering and treatment.^{172,244,256} Application of NPs in biological entities or biomedical applications, mainly cancer research, is crucial and should come from green precursors.^{14,48,292}

Due to their secondary metabolites, algae have a great ability to synthesize green NPs.^{27,41,127,299} Algal nanotechnology has grown into a distinct field known as phyco-nanotechnology that can successfully provide a variety of applications.^{241,252,259} Many investigations have been undertaken on the production of NPs utilizing macroalgae (seaweed) extracts, where others have demonstrated that microalgae can produce metal NPs.^{1,276}

Due to their appealing properties, algae have been proposed as model organisms for the processing of bio-nanomaterials.^{1,44,103} Because it is difficult to obtain NPs of desired shape and size through mechanical crushing, algal-synthesized NPs could be a feasible and more sustainable alternative for the future.^{9,35,142} This could be attributed to the fact that numerous factors, including temperature, pH, the type of capping agent, and the quantity of active chemicals, may be important in determining the size and morphology. Algal-mediated route to biogenic NPs offers a promising source of potential anticancer agents. For instance, algal-mediated AgNPs have been of great interest in cancer treatment due to their unique physiochemical properties.^{19,40,210}

On the other hand, the selection of algal strains, the slow process of synthesizing NPs, poor morphological characteristics of NPs, low yield of NPs and high level of aggregation of NPs hinder the commercialization of green algal-synthesized NPs.^{38,173} The lack of understanding of the mechanism of biosynthesis can also be added as a limiting factor in the use of algae in green biosynthesis of NPs. Although there are some examples of types and quantities of NPs that have been previously produced from algae, future research may focus on algal-mediated NPs made of carbon (C), SiO₂NPs, ZnO and other metals/metal oxides. With emerging characterization methods/technologies, controlled and comparative algal-based NP biosynthesis is now possible to improve the properties of algal-mediated NPs for commercial applications.

Future research should be considered on the factors affecting the uptake kinetics in order to increase the yield of algal-based NPs for commercial use as well. Further studies to establish new types of green synthesis of C-NPs, ZnONPs, palladium (Pd) NPs, and SiNPs using algal extracts are also required. It is also important to develop new technologies to help produce large quantities of algal-synthesized NPs with high efficacy to satisfy the biomedical applications for targeted effects against cancer cells without affecting normal cells. In addition, there is a big gap in the knowledge within the scientific community regarding the physiochemical characteristics of NPs produced using traditional technologies and those of algal origin. The role of biomolecules as reducing and capping agents during algae-mediated biosynthesis of NPs must also be elucidated.

Extensive research on identifying the proteins and enzymes involved in the formation of algal-mediated NPs should be on top of our priorities. Rapid, simple, cost-effective and environmentally safer procedures for alga-mediated synthesized NPs should be taken into account. Future research on the size, distribution and chemical composition of algal-derived NPs should be assessed. In general, the application of nanobiotechnology using algae is still in its infancy and needs further investigation.³³³ In addition to in vitro studies, in vivo testing of algal-synthesized NPs is a vital part of safety assessment and is a regulatory requirement before a drug can progress into clinical trials.³³⁴

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Disclosure

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