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Potential of Marine Algae (Seaweeds) in the Biosynthesis of Nanoparticles and their Biomedical Applications

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Abstract

Since 3000 BC, seaweeds have played an important role in human life due to their nutritional and therapeutic properties. In recent years the ability of seaweeds to biosynthesize nanoparticles has increased their potential in a variety of industrial, agricultural, and medical applications. In this review, we attempted to shed some light on the various traditional applications of seaweeds and the potential of biosynthesized nanoparticles, with a focus on the wide medical applications of biosynthesized nanoparticles in modern life.

1. Introduction

Marine species approximately constitute one-half of the global biodiversity. The marine environment is an enormous resource of novel compounds possessing nutritional and health benefits [1]. Macroalgae (seaweeds) are a diverse group of predominantly marine, photosynthetic, multicellular, chlorophyll "a" containing eukaryotic organisms, which lack true roots, leaves, stems, and possess simple reproductive structures. These algae are found from the intertidal zone to 300-m depth. The evaluation of macroalgae is diverse and belongs to three main phyla, such as Rhodophyta (red algae), Phaeophyta (brown algae), and Chlorophyta (green algae). Approximately 10,000 known marine macroalgal species have been segregated based on pigment content, flagellum, carbohydrate food reserve, cell wall components, and structure of cell wall [2].

Seaweeds are a good source of fibers, minerals, proteins, vitamins, and carbohydrates [3]. Seaweeds are rich in minerals like phosphorus, sodium, magnesium, calcium, potassium, sulfur, chlorine, and micronutrients such as cobalt, iodine, zinc, iron, copper, molybdenum, selenium, fluoride, boron, manganese, and nickel. The highest iodine content is also found in brown seaweed. Seaweed has relatively low-fat content and consists mainly of lipids or fatty acids. The calcium and protein contents of seaweed vary among species. Generally, the higher protein content is found in green and red seaweeds that can reach up to 30%, whereas the lower protein content can range up to 15% [4].

Modern scientific techniques have uncovered several bioactive seaweed substances. These seaweed active compounds have been separated and purified into high-value bio-products, which are widely applied in health-related industries. Cultivated and natural seaweeds are a unique source to produce seaweed-based bio-products. These bio-products are renewable, environment friendly, and green. Seaweed biomass and its derived natural products are biocompatible, hydrophilic, biodegradable, and contain highly bioactive compounds, which are a major supplement to land-based resources [1].

The prefix 'nano' is referred to Greek prefix meaning 'dwarf' or something very small. Nanotechnology can be defined as the science and engineering of material design, synthesis, characterization, and application with at least one dimension on the nanometer scale (one billionth of a meter). The biological, chemical, and physical properties

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of nanoparticles are fundamentally different from bulk material. The control and understanding of matter at the nano level could emerge new techniques of product development [5]. Nanoparticles are of interest because at this scale unique biological, chemical, electrical, magnetic, optical, and physical properties emerge. These unique properties could potentially have exciting implications in biomedical, chemical, electronic, and optical applications [6].

2. History of Nanoparticles

Nanoparticles and nanostructured materials have been present in nature for a long time and their human use may be traced back to ancient times. Naturally occurring NPs include organic (e.g., proteins, polysaccharides, viruses) as well as inorganic materials (e.g., iron oxyhydroxides, alumino-silicates, metals) produced by microbial processes, weathering, volcanic eruptions, and wildfires [7]. There are many examples of ancient artifacts using nanocomposites. The most renowned example is the Lycurgus Cup, which was made by the Romans in the 4th century AD. This extraordinary cup is made of dichroic glass, a very special type of glass that changes color when exposed to light. It is ruby red in transmitted light and green in reflected light, due to the presence of gold colloids [8].

In 1618, Francisci Antonii a doctor and philosopher published the first book “Panacea Aurea” on colloidal gold. This book contains information about the formation of colloidal gold sols and their successful medical applications. According to the book, soluble gold was known in the Middle Ages for its curative property for various diseases including epilepsy, heart disease, venereal problems, tumors, dysentery, and diagnosis of syphilis [9]. In 1676, Johann Kunckel, a German chemist, published a book about the use of colloidal particles in the manufacturing of stained glass. In this book, he described “drinkable gold that contains metallic gold in a neutral, slightly pink solution that exerts curative properties for several diseases”. He concludes that “gold must be present in such a degree of communition that it is not visible to the human eye” [10]. The "Purple of Cassius," a colorant in glasses, was a colloid formed by the heterocoagulation of gold particles and tin dioxide that was popular in the 17th century [11]. In 1718, Hans Helcher published a complete treatise on colloidal gold and stated that the use of boiled starch during the preparation of drinkable gold significantly enhanced its stability [12]. In a book published in 1794, Mrs. Fuhlame described dyeing silk with colloidal gold [13]. In 1818, Jeremias Benjamin Richters suggests an explanation for the color differences observed in different preparations of drinkable gold. Pink or purple-colored solutions contain gold in the finest degree of subdivision, whereas yellow-colored solutions form when fine particles are aggregated [8]. In 1857, Faraday reported the formation of a deep red solution of colloidal gold through the reduction of chloroaurate aqueous solution by phosphorus in a two-phase system (CS_2). He investigated the optical properties of thin films made from dried colloidal solutions and observed reversible color changes from bluish-purple to green of the films when mechanically compressed [14].

3. Synthesis of Nanoparticles

Nanoparticles are generally synthesized by top-down and bottom-up approaches using chemical, physical, and biological methods (Fig. 1). In a top-down approach, NPs are synthesized using physical and chemical treatments, whereas the bottom-up approach is based on chemical and biological methods. In a top-down approach, nanosized structures or particles are produced by size reduction from suitable bulk material. Top-down methods introduce imperfections in the surface structure of the generated product. This is a major limitation of these methods because imperfections in the surface structure would have a significant impact on the physical and chemical properties of nanoparticles. The bottom-up approach involves the building of nanoparticles from smaller entities, such as atoms, molecules, and smaller particles along with the precipitation or condensation of the product from solvents and subsequent separation of unwanted solvents. Bottom-up synthesis methods are often termed “wet” methods since they involve solvents and other chemicals. This approach results in a more homogeneous size, shape (physical parameters), and chemical composition of the final product [15,16,17].

3.1 Methods for nanoparticle synthesis

Nanoparticles can be synthesized using a variety of methods, including physical, chemical, and biological techniques (Fig. 2).

3.1.1 Physical and chemical methods for nanoparticle synthesis

Evaporation-condensation, electrolysis, diffusion, laser ablation, sputter deposition, pyrolysis, plasma arcing, and high-energy ball milling are some of the physical methods commonly used for the synthesis of NPs. However, low production rates, higher costs, and high energy consumption are the major limitations of physical methods. In contrast, chemical synthesis methods such as chemical reduction, micro-emulsion/colloidal, electrochemical, and thermal decomposition are the most common and widely used methods for the synthesis of NPs. Metallic precursors, stabilizing agents (dodecyl benzyl sulfate, polyvinyl pyrrolidone), and reducing agents (sodium borohydride, potassium bitartrate, formaldehyde, methoxypolyethylene glycol, hydrazine) are the main components in the chemical synthesis of NPs. The chemical methods are economical for large-scale production. However, the use of toxic chemicals and the production of harmful by-products are lethal to humans and the environment, limiting their biomedical applications [18,19,20,21].

3.1.2 Biological Synthesis of Nanoparticles

Green nanotechnology is an emerging field that involves a green chemistry approach to generate novel nanoparticles (Fig. 3). Biological methods for NPs synthesis offer new possibilities by using natural reducing and stabilizing agents. It is an economical and eco-friendly alternative to chemical and physical methods that do not require the use of energy and toxic chemicals [19]. The biological synthesis of NPs can be performed using a wide range of biological entities such as plants and plant products, algae, fungi, yeast, bacteria, and viruses. The presence of biomaterials, such as proteins, alkaloids, flavonoids, polyphenols, reducing sugars, etc., acts as reducing and capping agents for the synthesis of NPs from their metal salt precursors. The change in color of the colloidal solution may initially confirm the reduction of metal salt precursor to its subsequent NPs. In recent years, several studies have reported the synthesis of Ag, Au, Cu, Pt, Cd, Pt, Pd, Ru, Rh, and other metals using various biological agents [18].

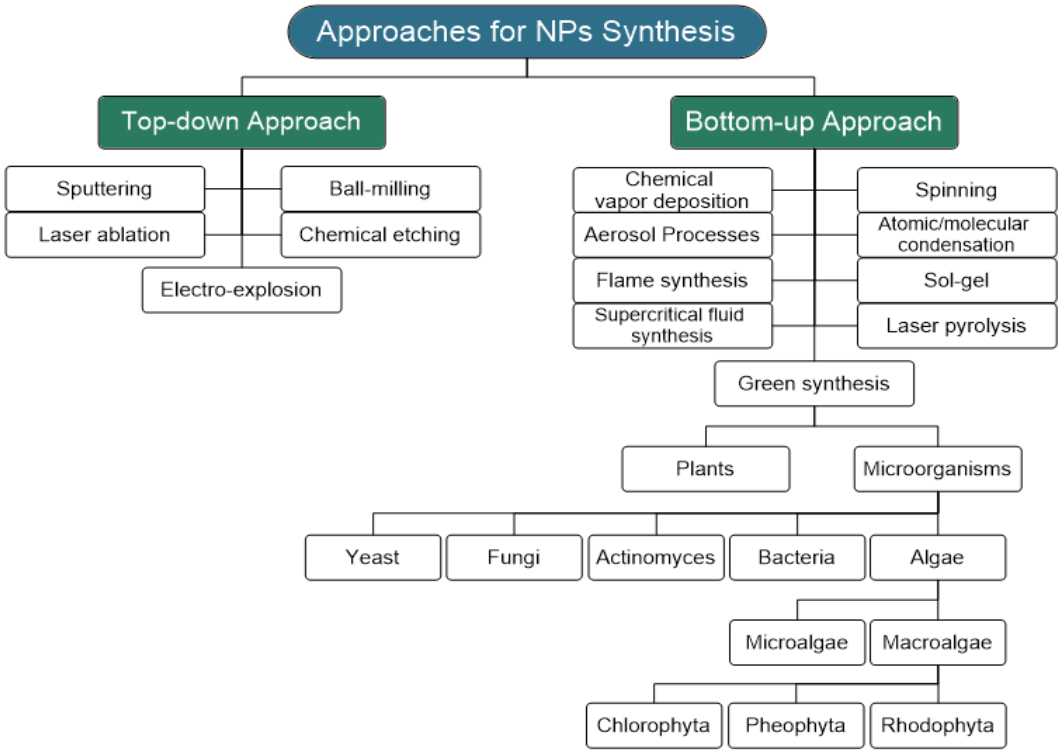

Fig. 1: Top-down and Bottom-up approaches used to synthesize nanoparticles.

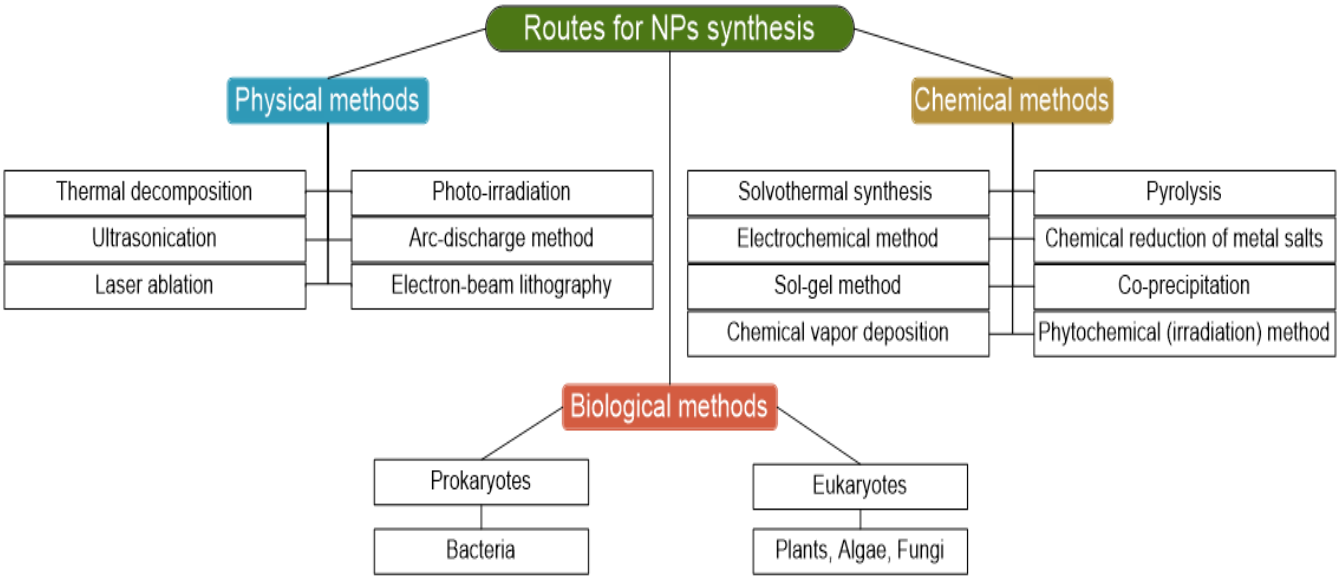

Fig. 2: Routes for nanoparticle synthesis.

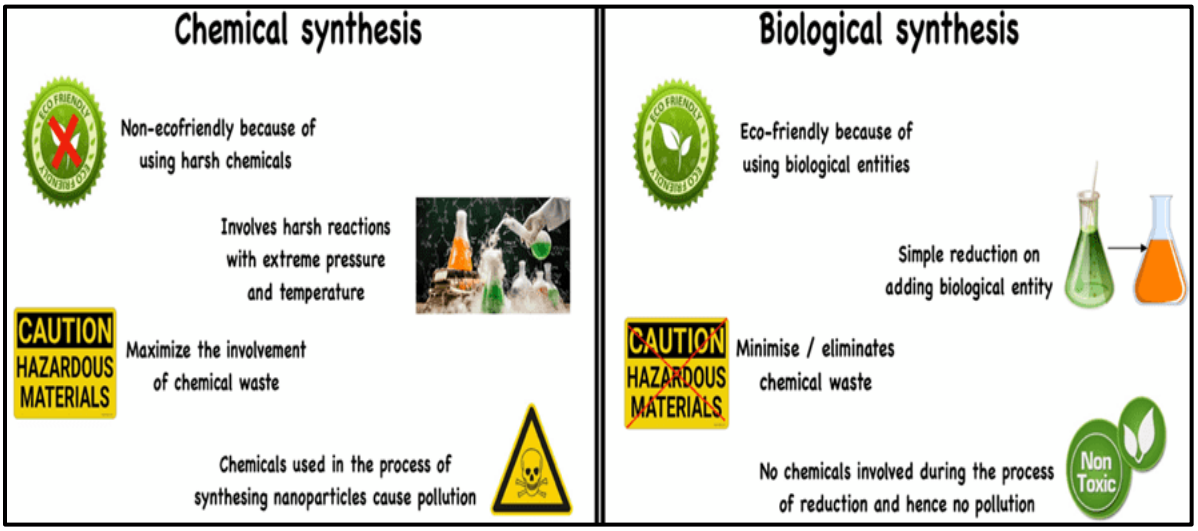

Fig. 3: Comparison of chemical and biological synthesis of nanoparticles.

4. Traditional and commercial uses of seaweeds

Initially, seaweeds were most often used as food, feed, and medicine in many maritime countries especially among the Asiatic communities and some European regions, whereas later, industrial uses such as gels and fertilizer emerged [22].

4.1 Seaweed as food

The use of seaweed dates back to the period of Shen Nung (3000 B.C.), known as the father of medicine and husbandry [23]. The "Chinese Book of Poetry" (800-600 B.C.) praised housewives for cooking seaweed as food, and a book entitled Sze tsen (600 B.C.), refers to algae as "Some algae are a delicacy fit for the most honorable guest, even for the King himself" [24,25].

Seaweeds are used as the food source in the preparation of meat dishes, fish, soups, and as a vegetable with rice [26]. Some seaweeds have excellent dietary contents mainly including protein, vitamins A, B, B_2, and C, carbohydrates, minerals, and a lot of trace elements. Seaweeds are low in calories and suitable for all types of vegetarians [27,28].

4.2 Therapeutic use of Seaweeds

Seaweed applications for medicinal purposes are historically well known. In general, the traditional pharmaceutical uses of seaweeds may include their use for the treatment of lowering blood pressure (e.g., *Laminaria* spp.), obesity defects, goiter, sore knees, healing wounds, and laxative effects (e.g., *Fucus vesiculosus*), diarrhoea, dysentery, and gastric ulcers (e.g., *Chondrus crispus*), colds and scrofula (e.g., *Gelidium cartilagineum*), gout and as an astringent (e.g., *Ulva lactuca*), as a laxative (e.g., *Gracilaria* spp.), and as a vermifuge drug (e.g., *Caloglossa* spp., *Codium* spp., *Dermonema* spp., *Hypnea* spp.) [29]. A phycological extract of commercial red algae (e.g., *Gracilaria*) known as "agar" has been used as a laxative since the 17th century. Agar has been used for wound dressing during wars because of its anti-blood-clotting property that helps in the proper disinfection of wounds [30].

Seaweeds possess excellent antioxidant properties, which facilitate to fight against cancer, atherosclerosis, chronic inflammation, aging, and cardiovascular disorder [31]. Antioxidant features also prevent the rate of cancer cell formation [32]. Seaweed consumption can help to control heart diseases by reducing plasma cholesterol [33].

4.3 Agricultural Applications of Seaweed

Nutrients (e.g., nitrogen, phosphorus, potassium), growth-promoting hormones (e.g., cytokinins, auxins, gibberellins, abscisic acid), and essential amino acids present in seaweeds make them excellent fertilizers. Seaweeds increase soil fertility and have good moisture-holding capacity. Different species of macroalgae such as *Fucus, Laminaria, Ascophyllum, Sargassum*, etc. are used as organic manure. These are non-polluting, non-toxic, biodegradable, and non-hazardous to humans, farm animals, and birds [34].

4.4 Seaweed as Animal feed

Incorporation of seaweeds in livestock diets was shown to enhance immune function, health, weight gain, and meat grade quality depending on the alga species, dietary level, and growth stage of the animal. Seaweeds may improve the average daily gain due to prebiotic activity in the intestine, marbling score, color uniformity, redness, and reduce saturated fatty acids in ruminant meats [35]. The presence of vitamin E in seaweeds increased animal fertility and birth rate. The use of seaweed as animal feed has been found to increase milk production, fat level, and iodine content. The supplementation of *Gracilaria* and/or *Spirulina* to white leghorn feed increased egg number, size, and yolk color. In cattle, a diet rich in *Laminaria* sp. increases natural resistance to diseases such as foot and mouth [36].

Several seaweeds, including *Asparagopsis taxiformis*, *Alaria esculenta*, *Ascophyllum nodosum*, and *Chondrus crispus*, have been identified as having the potential to reduce CH_4 emissions from ruminants [37]. Incorporating seaweed into fish diets improves their growth, lipid metabolism, physiological activity, stress response, and disease resistance [38].

4.5 Industrial Applications of Seaweed

Initially, seaweed was mostly used for domestic purposes such as food and feed, however, industrial applications of seaweed emerged later. The most important industrial application of seaweeds is as a raw material for the extraction of polysaccharide hydrocolloids such as agar, alginate, and carrageenan. Hydrocolloids are used by various industries due to their physical-chemical characteristics. Agars and carrageenans are extracted from red seaweeds whereas alginates are only extracted from brown seaweeds [39]. Seaweed polysaccharides are commonly used in laboratories, processed foods, pharmaceutical products, and medicine as gelling and stabilizing agents [40]. More recently, several other industries have increased their interest in algal-derived products, e.g. cosmetics, cardboard, paper, textile, paint, bioethanol production, and as a source of feedstock for biorefinery applications [41].

4.6 Biogas Production by Seaweeds

Seaweed has emerged as an alternative feedstock for biogas production. The most direct route to producing biofuel from seaweeds is via its anaerobic digestion (AD) to biogas. Biogas produced by seaweeds can be used for heat and electricity or compressed for use as a transport fuel [42]. Brown seaweed species such as *Laminaria digitata* and *Saccharina latissima* have been extensively evaluated as potential AD feedstocks due to their abundance and high specific methane yield [43].

4.7 Role of Seaweeds in Wastewater Treatment

Environmental pollution is a growing worldwide problem that is directly related to anthropogenic activities. Untreated wastewater from industrial and domestic sources changes the aquatic ecosystem significantly, resulting in a loss of biological diversity as well as the magnification and bioaccumulation of toxic agents in the food chain [44].

Seaweeds can be used to balance the ecosystem in mitigating eutrophication for nutrients (e.g., minerals, nitrogen, phosphorus) or as bioremediation. Biosorption with seaweeds has shown promising results in removing pollutants (e.g., dyes, nitrogen, phosphorous, phenolic compounds), as well as heavy metals (e.g., copper, nickel, lead, zinc, cadmium) from various sources. Therefore, macroalgae are considered valuable bioindicators of heavy metals contamination. Wastewater containing nitrogen and phosphorus can be treated using red seaweed (*Gracilaria*) and green seaweed (*Ulva*). Various species of brown seaweeds such as *Ecklonia*, *Laminaria*, and *Sargassum*, and green seaweeds *Enteromorpha* and *Ulva* efficiently accumulate toxic metals. The high capacity of macroalgae to bind pollutants, such as trace metals, is due to the presence of sulfated polysaccharides in the cell wall, primarily its fibril matrix and intercellular spaces [45].

5. Algae-mediated Biosynthesis of Nanoparticles

Nanoparticles (NPs) can be synthesized using a variety of methods. There is a growing interest in developing high-yield, low-cost, non-toxic, and eco-friendly procedures. Cost-effectiveness, reduced use of toxic chemicals, and abundant availability of resources are all major advantages of greener synthesis. Biological entities such as plants, algae, fungi, bacteria, and viruses have been used to elevate novel, greener, and cost-effective methods for the synthesis of NPs [46]. The selection of the NPs generation method is not only based on the physical and chemical properties (such as size, dispersion, shape, chemical miscibility, optical properties) of the final product but environmental aspects should also be considered [21]. The use of biogenic synthesis of NPs reduces the hazardous effect on the environment as well as produces large numbers of NPs which are non-toxic, have well-defined dimensions, have diverse nature, and have greater stability [47].

In recent years, algae have received more attention for the biosynthesis of nanomaterials. Bioactive organic compounds present in algae include pigments, carbohydrates, vitamins, polysaccharides, proteins, enzymes, and secondary metabolites, making them an excellent choice for the biosynthesis of NPs by acting as reducing and stabilizing agents to form size- and shape-controlled NPs. The role of different algae (Phaeophyta, Chlorophyta, Rhodophyta) in the biosynthesis of NPs has been verified [48,49,50,51]. Biomolecules in algae extracts such as sulfated polysaccharides, proteins, and amino acids can serve as stabilizers or capping agents during the biosynthesis of NPs with variable properties [52]. Algae extracts based biosynthesis of NPs is a sustainable, facile, and eco-friendly approach. Several algal species can be considered promising candidates for the biosynthesis of NPs because of their distinct properties of rapid growth, abundant organic content, and high metal accumulation. Algae provide a robust coating on the metal nanoparticles in a single step [53].

5.1 Chlorophyta (Green seaweeds) Mediated Biosynthesis of Nanoparticles

The members of the phylum Chlorophyta or chlorophytes are closely related to terrestrial plants and are categorized under the kingdom Plantae. This phylum is comprised of 7000 species, most of which grow in freshwater (90%) as compared to sea (10%) [54].

It has been reported that AgNPs biosynthesized at room temperature using *Ulva lactuca* were effective in photocatalytic degradation of methyl orange [55]. Rajesh *et al.*, (2012) biosynthesized metallic AgNPs by using crude ethyl acetate extract of *Ulva fasciata* (Delile) at ambient temperature. These AgNPs efficiently inhibited the growth of *Xanthomonas campestris* pv. *malvacearum*, a Gram-negative bacterium of cotton plants, at a concentration of 40.00 ± 5.77 µg/ml [56]. Suriya *et al*., (2012) studied the bioreduction of silver nitrate by *Urospora* spp. extract and evaluate its antibacterial potential against *E. coli*, *S. aureus*, and *P. aeruginosa* [57]. *Codium capitatum* fresh and dried extracts were employed in the biosynthesis of AgNPs in prospective biological and agricultural applications [58]. The antimicrobial activity of AgNPs synthesized from the *Enteromorpha flexuosa* has also been evaluated [59].

5.2 Rhodophyta (Red seaweeds) Mediated Biosynthesis of Nanoparticles

Rhodophyta (red algae) are a distinct eukaryotic lineage, which lacks chlorophyll b and c but contains allophycocyanin, phycocyanin, and phycoerythrin in the form of phycobilisomes on unstacked thylakoids. Rhodophyta consists of about 6,000 species of mostly multicellular, marine algae [60].

The biosynthesis of spherical AgNPs was carried out using an aqueous *Acanthophora spicifera* seaweed extract that inhibited the production of the exopolysaccharides by biofilm-forming pathogens such as *Shigella flexneri*, *E. coli*, *Vibrio cholerae*, *Salmonella typhi*, and *S. aureus* [61]. Kumar *et al.*, (2013) biosynthesized AgNPs from *Gracilaria corticata* and reported its effective antifungal activity against *Candida glabrata* and *Candida albicans* [62]. Similarly, Vivek *et al.*, (2011) carried out the biogenic synthesis of AgNPs utilizing *Gelidiella acerosa* extract and reported significant antifungal activity against *Mucor indicus*, *Fusarium dimerum*, *Trichoderma reesei*, and *Humicola insolens* [63]. Green synthesized *Hypnea musciformis* mediated AgNPs effectively degraded methyl orange under visible light illumination [64]. *Hypnea musciformis* fabricated nanoparticles showed significant larvicidal and pupicidal activity against *Aedes aegypti* and *Plutella xylostella* [65]. AuNPs synthesized using *G. elongata* powder served as potent antibacterial agents against *P. aeruginosa*, *K. pneumoniae*, and *E. coli*, whereas ethanolic extract is effective against MRSA [66]. Biosynthesis of AgNPs using an aqueous extract of *Pterocladiella capillacea* showed effective cytotoxic activity against $HepG_2$ cell line and promising bactericidal effect, especially against *B. subtilis* [67]. The cytotoxic property of AuNPs produced from *Corallina officinalis* on MCF-7 human breast cancer cell line has also been reported [68]. $Cu@Cu_2O$ core-shell NPs were synthesized in an aqueous solution in the presence of *Kappaphycus alvarezii* as a capping agent and hydrazinium hydroxide as a reducing agent [69].

5.3 Phaeophyta (Brown seaweeds) Mediated Biosynthesis of Nanoparticles

Brown algae belong to the phylum Phaeophyta (Heterokontophyta), a group of multicellular algae that comprises approximately 2000 known species, 95% of which are found in cold to temperate waters [70].

Singaravelu *et al.*, (2007) described the use of *Sargassum wightii* in the extracellular production of monodispersed AuNPs [71]. Govindaraju *et al.*, (2009) described the extracellular synthesis of AgNPs with *S. wightii* and potent antibacterial activity was reported against Gram-positive bacteria (*B. rhizoids*, and *S. aureus*), Gram-negative bacteria (*E. coli*, and *P. aeruginosa*) [72]. In another study, *S. wightii* was used to synthesize AgNPs, and effective antibacterial activity was found against human pathogens such as *S. typhi*, *K. pneumoniae*, and *S. aureus* [73]. *Sargassum longifolium* was used to synthesize AgNPs and different concentrations were tested against Human laryngeal Hep-2 cancer cell lines, revealing a direct dose-response relationship [74]. Aqueous extract of *Padina tetrastromatica* was used under direct sunlight conditions to synthesize AgNPs within 72 h of incubation [75]. Kumar *et al.*, (2012) reported the biosynthesis of AgNPs using *Sargassum ilicifolium* aqueous extract, which showed high antibacterial activity and inhibited the growth of *V. cholera*, *E. coli*, *S. typhi*, *K. pneumoniae*, and *S. aureus* [76]. AgNPs synthesized from the extract of *Sargassum tenerrimum* exhibited good antibacterial activity against nine pathogens, including both Gram-positive and Gram-negative bacteria [77]. *Sargassum myriocystum* was used to synthesize biofunctionalized AuNPs with 1-cyclopentyl-4-(3-cyclopentylpropyl)dodecane as a potential capping agent [78]. AgNPs synthesized using *Sargassum polycystum* crude methanolic extract showed effective antibacterial and anticancer activity [79]. *Sargassum myriocystum* was used to synthesize ZnO NPs having antibacterial activity, with fucoidan as a potential reducing and stabilizing agent [80]. A single-step process has been reported to synthesize AuNPs mediated by *Turbinaria conoides* [81]. AgNPs and AuNPs obtained from *Turbinaria conoides* aqueous extract exhibited antibiofilm activity against biofilm-forming marine bacteria [82]. An effective antibacterial activity has been reported in AuNPs synthesized from *Stoechospermum marginatum* biomass [83]. Prasad *et al.*, (2013) reported the biosynthesis of AgNPs using *Cystophora moniliformis*, an Australian marine brown alga [84]. Shiny *et al.*, (2013) recently explained that spherical 25-40 nm AgNPs synthesized by *Padina gymnospora* have antimicrobial activity and their potential application in wound dressing or sterile hospital clothing [85]. Platinum-based nanoparticles generated using *P. gymnospora* through a green approach were capable of oxidizing NADH to NAD^+ and had hemolytic assay [86]. A facile green method for the biosynthesis of AuNPs using *P. gymnospora* has also been reported [87]. Another study found that AuNPs produced using *P.*

gymnospora had cytotoxic effects with cellular stress in liver ($HepG_2$) and lung (A549) cancerous cell line [88]. Magnetic iron-oxide nanoparticles (MIONPs) synthesized using *Sargassum muticum* have been reported to be cytotoxic and induced cell cycle arrest against liver ($HepG_2$ cells), leukemia (Jurkat cells), cervical (HeLa cells), and breast (MCF-7 cells) cancer cell lines [89]. The same seaweed species was also used to synthesize ZnO NPs, which are expected to have high biomedical and UV absorption capabilities [90]. Madhiyazhagan *et al.*, (2015) observed effective mosquitocidal activity of AgNPs fabricated using *S. muticum* [91]. Promising antimicrobial activity of *Sargassum cinereum* derived AgNPs was observed against multidrug-resistant organisms such as *E. aerogenes*, *S. aureus*, *S. typhi*, and *P. vulgaris* [92]. AuNPs synthesized from *Sargassum swartzii* were found to be cytotoxic to cervical carcinoma (HeLa) cells [93]. Marine alga *Sargassum plagiophyllum* was used to create antibacterial AgCl NPs [94].

6. Applications of Biosynthesized Nanoparticles

Nanotechnology has been widely applied in almost every field of science and technology including biomedical sciences. Nanoparticles are the most investigated as they all possess unique physicochemical properties. Due to the biocompatibility and safety of biosynthesized NPs, the algal NPs have also been studied for their different biomedical applications, such as targeted therapy, drug and gene delivery, bioimaging, biosensing activities, etc. (Fig. 4).

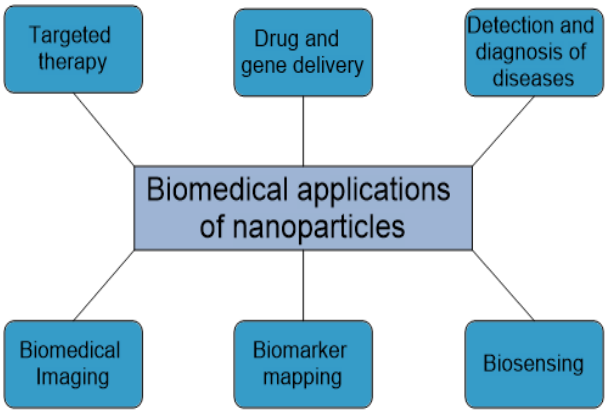

Fig. 4: Biomedical applications of algal-based nanoparticles.

6.1 Algae-mediated Nanoparticles as Anticancer

Cancers or tumors are generally treated with surgery followed by radiotherapy and chemotherapy. However, limitations and adverse effects restrict the rate of success. For example, chemotherapy can have serious adverse effects, including local reactions, such as tissue necrosis and thrombophlebitis, and systemic reactions, including dysfunction of the liver and kidney, myelosuppression, and immunosuppression [95]. Chemotherapy failure is caused by intrinsic or acquired multidrug resistance (MDR), which leads to the recurrence of malignant tumors [96]. Therefore, the development of advanced cancer treatment methods and novel drugs to minimize the adverse effects is essential for improving therapeutic effects [95].

Nanoparticles have gained increased interest in cancer therapeutics in recent years, due to their unique physical and chemical properties [97]. Drug delivery based on NPs has specific advantages compared to conventional anticancer agents, including enhanced permeability and retention effect, improved stability and biocompatibility, and precision targeting [98]. In the search for anticancer or antitumor therapeutic agents, AgNPs are an excellent choice among metal NPs [95]. AgNPs possess excellent antitumor activity and induce cytotoxic effects in tumor cells [99]. Anticancer activity of AgNPs has previously been reported against various types of cancer, including breast [100], cervical [101], colon [102], ovarian [103], pancreatic ductal adenocarcinoma [104], lung [105], and osteosarcoma [106] cancers. AgNPs of different sizes, shapes, and dosage/concentrations have varying anti-cancer activities in different cancer cells. The anticancer activity of AgNPs is also influenced by cell lines, exposure time, tumor microenvironment, and pH of lesions [95]. Small-sized AgNPs can enhance endocytosis and induce more significant cytotoxicity and genotoxicity [107]. Cytotoxicity and genotoxicity of NPs are influenced by several physicochemical characteristics, including dispersion rate, concentration, surface charge, size, morphology, and surface functionalization [108]. Compared with other shapes, spherical AgNPs may exhibit stronger endocytosis and more effective anticancer activity due to the higher surface-to-volume ratio [95,107]. AgNPs induced cytotoxicity with apoptosis and DNA damage in a dose-dependent manner through the production of ROS and the release of silver ions [109].

Nanoparticles exhibit broad-spectrum anticancer activity through a variety of pathways [107,110,111]. Numerous *in vitro* and *in vivo* studies have shown that NPs can significantly reduce cell viability and proliferation of cancer cells. NPs cause apoptosis and necrosis by destroying the ultrastructure of cancer cells, inducing ROS generation and DNA damage by regulating multiple signaling pathways [110,112]. NPs can induce cell apoptosis by up-regulation or down-regulation of p53 gene expression and regulating essential HIF (Hypoxia Inducible Factor) signaling pathway. NPs have been shown to induce cell cycle arrest in different cell lines [113]. The effects on the cell cycle appear to be cell type-dependent, some studies have suggested S-phase arrest, whereas others have reported G2-phase arrest [114]. Autophagy is induced by NPs in both cancer cells and CAFs, resulting in decreased angiogenesis and metastasis [115]. Anticancer mechanisms of nanoparticles are shown in Fig. 5.

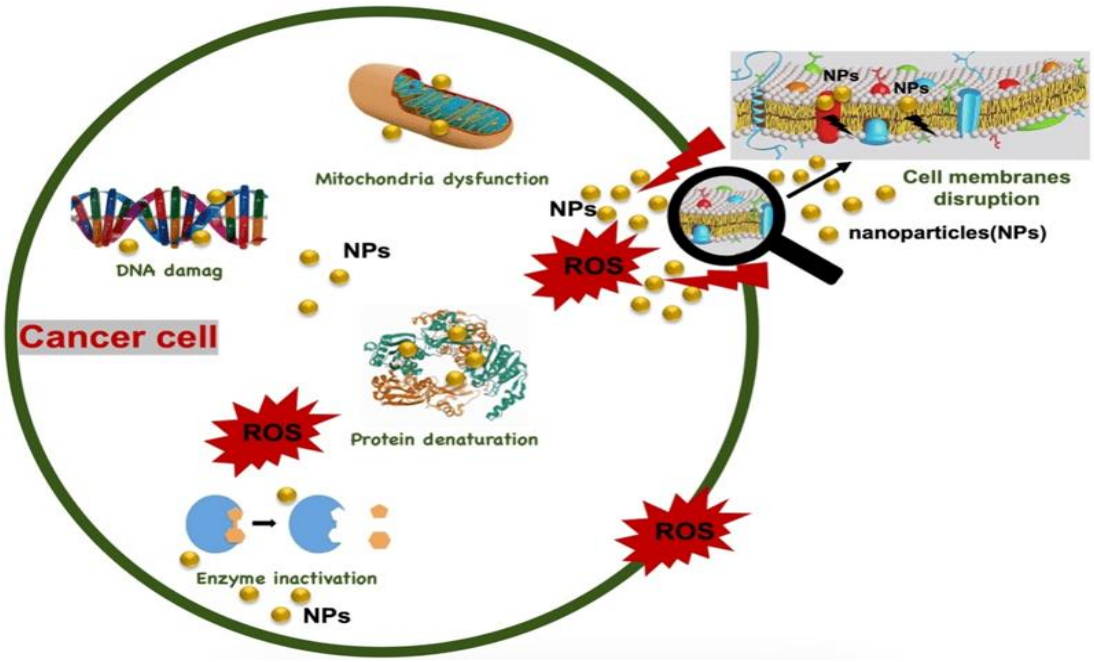

Fig. 5: Schematic diagram of anticancer mechanisms of nanoparticles (destroys the ultrastructure of cancer cells, induces ROS generation, and DNA damage).

6.2 Algae-mediated Nanoparticles as Antimicrobial

The overuse or inappropriate use of antibiotics to treat bacterial infections has led to the emergence of multi-drug-resistant bacterial strains [116]. The applicability of NPs is increasing in the field of medicine as an antibacterial agent. As an alternative antibacterial agent, NPs can deliver an optimum dosage range of drugs, which improves therapeutic efficiency, patient compliance and reduces side effects [117].

The biosynthesis of AgNPs and AuNPs has been a focus of research because of their antimicrobial properties [118]. Several studies reported that AgNPs have significant antimicrobial properties, especially against bacterial infections [119]. The antimicrobial activity of AgNPs can change with physicochemical properties, such as their shape, size, and capping agents, as well as pH, concentration, surface charge, and organic macromolecules. The physicochemical properties are mostly dependent on the method used for nanoparticle synthesis [120]. The antimicrobial properties of AgNPs depend on the size of the nanoparticles [121]. Smaller AgNPs with greater binding surface exhibited higher antimicrobial activity than larger AgNPs [122]. Shameli *et al.*, (2012) reported significant inhibition of Gram-positive (*S. aureus*) and Gram-negative (*Salmonella typhimurium*) bacterial growth and concluded that the antibacterial activities of AgNPs in PEG can be modified by controlling the nanoparticle size because the activity of AgNPs decreases as particle size increases [123]. According to previous research, reduced NPs size showed the best antibacterial activity such as disrupting the cell membrane functions (permeability or respiration), generation of ROS, penetrating cell membrane; and induction of intracellular antibacterial effects, including interactions with DNA and proteins [124].

The difference in the sensitivities of AgNPs between gram-positive and gram-negative bacteria is due to the variation in the thickness and molecular composition of their membrane structures [125]. Bactericidal activity of AgNPs is presumably due to changes in the structure of the bacterial cell wall caused by interactions with embedded AgNPs, leading to increased permeability of bacterial cell membrane and which may ultimately result in cell death [126]. Due to the presence of negatively charged lipopolysaccharide, peptidoglycan, and multiple groups, including carboxyl, amino, and phosphate groups on the bacterial surface, the positive charge of AgNPs can facilitate adherence on bacterial membranes through electrostatic attraction. Following adhesion, AgNPs can penetrate the membrane and enter the bacteria. Interaction of AgNPs with cellular structures and biomolecules such as proteins, lipids, and DNA inside the bacterial cell, cause bacterial dysfunction and, finally death [113]. AgNPs also interact with sulfur- and phosphorus-rich biomaterials in the bacterial cell, which include intracellular components, such as DNA or proteins, and extracellular components such as membrane proteins. These biomaterials influence the cell division, respiratory chain, and ultimately survival of cells [127,128]. Radhakrishnan *et al.*, (2018) revealed that AgNPs affected multiple cellular targets crucial for pathogenicity and drug resistance in *C. albicans*, as well as new cellular targets, including fatty acids like oleic acid, which are required for hyphal morphogenesis [129].

AuNPs have natural biocidal properties, and their use as antibacterial agents is not as prominent as that of

AgNPs [130]. AuNPs primarily react with sulfur or phosphorus-holding bases. These NPs bind to thiol groups of enzymes (nicotinamide adenine dinucleotide (NADH) dehydrogenases) and disrupt the respiratory chains by producing a large number of free radicals. Another proposed hypothesis is that AuNPs change membrane potential, inhibiting ATPase activities and preventing tRNA binding to ribosomal subunit [131]. AuNPs inhibited *Leishmania* growth by generating a large number of electrons, which resulted in the production of ROS [132]. Another possible mechanism is that AuNPs inhibits the transmembrane H^+ efflux of the *Candida* species [133].

The significant antiviral activity of AgNPs against hepatitis B virus [134], vaccinia virus [135], respiratory syncytial virus [136], herpes simplex virus, human parainfluenza virus 3 [137], human immunodeficiency virus 1 [138], tacaribe virus [139], monkeypox virus [140] and influenza A virus [141] has also been reported in various studies. AgNPs can prevent viral infection by blocking entry steps by preventing viral cell attachment or directly inactivating the virus [142]. AgNPs with a size of less than 10 nm exhibit good antiviral activity, which might be due to the large reaction area and strong virus attachment [143]. Seaweeds provide a wide range of bioactive compounds with antimicrobial activity, such as polysaccharides. Seaweed-derived polysaccharides, especially sulfated polysaccharides possess antiviral activity against a wide range of enveloped and non-enveloped viruses [144]. The cell wall of seaweed consists of about 40% sulfated polysaccharides. Some of the major sulfated polysaccharides are derived from green macroalgae (e.g., ulvans), red macroalgae (e.g., carrageenans, agar), and brown macroalgae (e.g., fucoidans, laminarians) [145]. These compounds inhibit the virus cycle at different stages, such as virus-cell contact, virus interaction with the host cell surface, virus internalization, uncoating of the virus, virus transcription and replication process, or even directly killing the virus [146]. Moreover, sulfated polysaccharides are potential agents in treating COVID-19 as entry inhibitors and vaccine adjuvants [144].

Furthermore, AgNPs were reported to have efficient antimicrobial activity against a wide range of fungi. However, the underlying mechanism for the inhibition of fungal growth by AgNPs is not clear. Some studies have reported that treatment with AgNPs altered surface morphology, cellular ultrastructure, membrane microenvironment, membrane fluidity, ergosterol content, and fatty acid composition, especially oleic acid [129]. Some other mechanisms for the antifungal activity of AgNPs have also been reported. In pathogenic fungi, silver ions can form cross-links with DNA bases and then replace hydrogen bonds adjacent to nitrogen in purines and pyrimidines. It will change the DNA structure of the fungal and cause it to lose its ability to replicate. In addition, the interaction of AgNPs and protein molecules on the surface of fungi causes denaturation, cleavage the proton pump, and increased permeability of the membrane protein or phospholipid bilayer. The leakage of H^+ causes lysis of the fungal cell membrane, resulting in fungal cell damage [147]. Previous research has shown that AgNPs exhibit excellent antifungal activities in a size- and dose-dependent manner, the type of culture media may also affect the inhibition activity [148]. The antibacterial mechanisms of NPs are illustrated in Fig. 6.

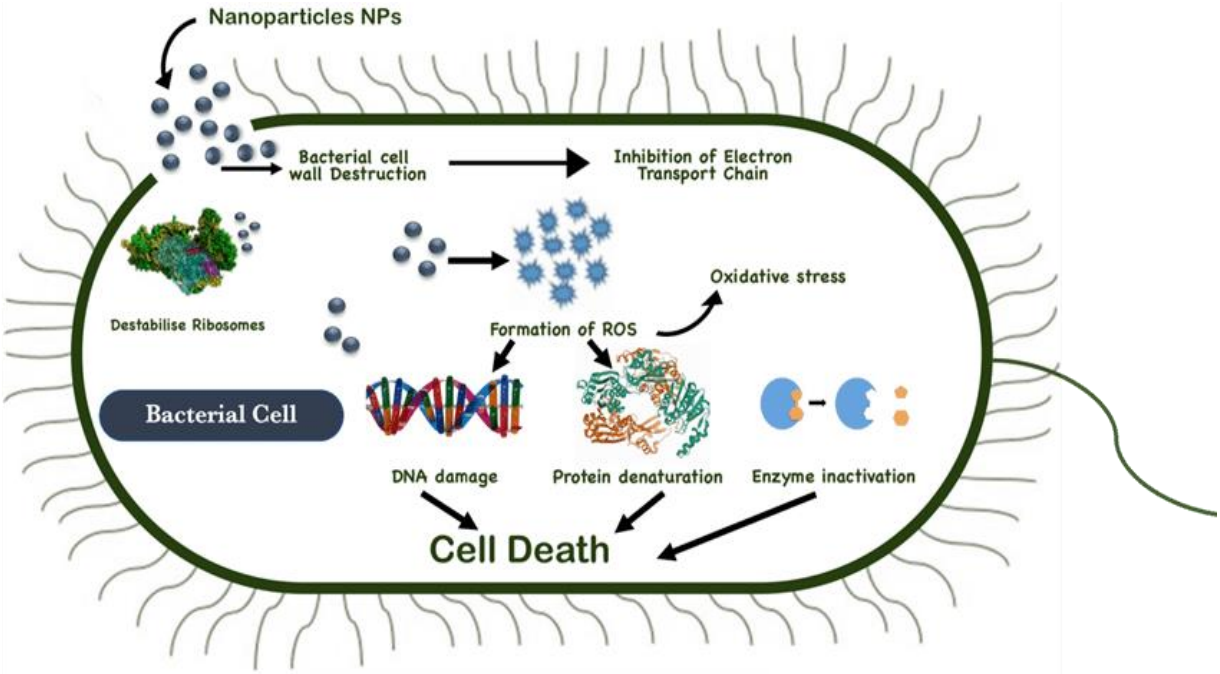

Fig. 6: Schematic representation of the mechanisms of nanoparticles antibacterial activity (formation of ROS, DNA damage, protein denaturation, and enzyme inactivation).

6.3 Algae-mediated Nanoparticles as Antifouling Agents

Biofouling is the undesired growth of micro-(bacteria and protists) and macro-fouling (invertebrates and algae) organisms on submerged surfaces [149]. To prevent biofouling, antifouling coatings applied to exposed surfaces contain toxic inorganic (copper) and organic biocides (isothiazolone) that kill organisms and accumulate in the environment [150]. Eco-friendly solutions and nanotechnology-based applications can be highly beneficial in the development of non-toxic or low-toxic antifouling agents [151]. Nanotechnology allows the development of antimicrobial compounds as well as the use of "nano-functionalization" surface techniques. “Nano-functionalized biomaterials” may inhibit bacterial colonization and biofilm formation by coating, impregnation, or embedding nanomaterials [152]. NPs can effectively inhibit bacterial adhesion through NP-ligand interaction. After approaching the biofilm surface from the bulk phase, AuNPs and AgNPs interact with it to exert antimicrobial action. Depending on the surface chemistry, charge, and hydrophobicity of the biofilm, NPs interact with lipids, LPS or proteins of the bacterial cell membrane and gain access to the biofilm. Penetration efficacy of NPs is dependent on several factors, including biofilm maturity, biofilm surface composition, and chemistry as well as nanoparticle size, surface charge, surface chemistry, and concentration. The NPs then migrate internally as a whole or as ions (Au^+ and Ag^+) to interact with biofilm and cellular components. Therefore, the antimicrobial activity of AuNPs and AgNPs is based on the disruption of several biofilms and bacterial components [153,154].

Seaweed extracts are used to synthesize different biogenically nanoparticles, which are found to be used as potent antibiofilm agents. Sulfated polysaccharides, which have antibacterial and antibiofilm properties, are the most important component in the seaweed extract. Sulfated polysaccharides such as fucoidan from *Fucus vesiculosus* completely inhibited dental plaque biofilm formation and planktonic cell growths of *S. mutans* and *S. sobrinus* [155]. Genome editing by CRISPR/Cas9 may make precise modifications in the algal DNA, resulting in improved algal strains and the production of more effective anti-biofouling agents [156]. Seaweed-based NPs are well-known to provide bactericidal, fungicidal, and algicidal properties to surfaces [151].

6.4 Algae-mediated Nanoparticles as Antidiabetic Agents

Nanotechnology transformed antidiabetic treatment significantly in many ways, including in the delivery of therapeutic molecules, fabrication of glucose biosensors to monitor dynamic changes in blood glucose levels, and development of smart molecular imaging strategies to visualize and quantify β-cells [157]. Furthermore, green nanotechnology-based approaches reveal antidiabetic potential and assisted in the understanding of different treatment processes, and significantly manipulated regulatory mechanisms related to diabetes management through pancreatic α-amylase, intestinal α-glucosidase, insulin secretion or its action, glucose uptake, receptor affinity, and other biochemical/histological parameters in different *in vivo* and *in vitro* systems [158].

Inhibiting α–amylase and α-glucosidase enzymes that catalyze starch hydrolysis in the intestine is one of the effective therapeutic strategies for controlling hyperglycemia associated with diabetes [159]. The inhibitory activities of the α–amylase and α-glucosidase enzymes have frequently been used to evaluate the anti-diabetic potential of green synthesized nanoparticles [160]. AgNPs biosynthesized from a marine red alga, *Halymenia Poryphyroides* effectively inhibit both α-amylase and α–glucosidase enzymes *in vitro* in a dose-dependent manner [161]. Dhas *et al.*, (2016) biosynthesize AuNPs using aqueous extracts of *Sargassum swartzii* and indicated that AuNPs could significantly improve insulin resistance and glucose level in alloxan-induced diabetic rats. Fasting blood glucose levels, serum insulin, hemoglobin, and glycosylated hemoglobin levels in diabetic treated rats with AuNPs were significantly decreased compared to the control group [162].

7. Challenges and Toxicity Risks of Nanomaterials

7.1 Instability

The stability of prepared nanomaterials has always been a major concern. The kinetics associated with nanomaterials is rapid which increases their instability and it becomes highly challenging to retain active metal nanoparticles. To retain their size and shape, nanoparticles are encapsulated in another matrix. Nanomaterials lie in the region of high-energy local-minima and are thermodynamically metastable. Hence, they undergo transformations such as phase change, high solubility, and poor corrosion resistance. This causes the properties of nanomaterials to deteriorate and it becomes challenging to retain the structure. Nanomaterials with a high surface area that come into direct contact with oxygen, act as strong explosives and their exothermic combustion can easily result in an explosion [163].

7.2 Impurity

NPs inherently interact with impurities because they are highly reactive. Thereby, the generation of pure NPs becomes highly difficult due to secondary impurities. Due to this reason, encapsulation becomes necessary for NPs synthesized in a solution. The engulfment of reactive nano-entities by a non-reactive species results in NP stabilization. The synthesis of NPs in an impure environment aggravates the formation of nitrides and oxides. Hence, retaining high purity in NPs synthesis can be difficult [163].

7.3 Biologically harmful

Nanomaterials are generally considered harmful because they become transparent to the cell dermis. They can enter the human body through the skin, respiratory and gastrointestinal tract [164]. Their absorption may occur as a consequence of the first interaction with biological components such as cells and proteins. Some NMs have been shown to induce adverse biological effects at cellular, subcellular, protein, membrane, tissue, and organ levels. Interaction at the nano-bio interface could have a variety of consequences, including, enzyme failure, oxidant injury, mutational alteration, signaling effects, membrane permeability changes, conformational changes, biocatalytic changes, ionic exchanges, and new epitope exposure in proteins [165].

8. Future Prospectives and Applications of Green Nanotechnology

In recent years, there has been a significant increase in research and synthesis of nanoparticles because of their innovative applications in various fields. Green nanotechnology is an emerging area of research and a significant approach for the synthesis of novel nanoparticles using biomaterials [166]. Green synthesis of nanoparticles is an eco-friendly and cost-effective method and opens new possibilities for the development of new materials and the assessment of their properties by modulating particle size, morphology, and distribution [167]. Green-synthesized nanoparticles have received a lot of attention because of their wide range of applications in biomedicine. The most important characteristic of nanoparticles is their high surface area to volume ratio, which enhances their interaction with other molecules [168].

Despite the passage of over two decades, no effective antiviral treatment against the CoV family has been approved. Currently, research is being conducted all over the world to find effective vaccines or drugs, which include both traditional therapies and emerging therapies such as nanomedicine. Nanomedicine has the potential to play a significant role in COVID-19 prevention, diagnosis, treatment, vaccination, and research. Nanotechnology has the potential to improve the safety of healthcare workers and patients. COVID-19 can be detected using nanomaterials such as quantum dots as biosensors. Nanotechnology offers multiple benefits from the use of nanosystems, such as polymeric and lipid nanoparticles, metallic nanoparticles, liposomes, and micelles, for drug encapsulation, and helps to improve the pharmacological properties of drugs. Nanoparticles antiviral functions can target the entry, binding, replication, and budding of COVID-19. The most promising approach for combating coronavirus is vaccination. Nanoparticles can play a role in the design, delivery, and administration of COVID-19 vaccines, because of their multivalent antigen presentation and antigen stability. Compared to conventional vaccines based on antigens, vaccines based on nanoparticles can induce a higher protective immune response. The toxicity of inorganic nanoparticles is one of the limiting factors that should be further studied [169].

9. Conclusion

Seaweeds are nutrient-dense dietary materials that can be employed in the biosynthesis of metal nanoparticles. Polysaccharides, proteins, enzymes, polyphenols, and other chelating agents are potential reducing agents that play a significant role in the formation of nanoparticles. However, further research is required to develop methods for achieving NPs desirable size, stability, shape, and controlled crystal growth structure. More research is required to have a better understanding of NPs and their potential future applications in biology and biomedical research. Moreover, the biological nanoparticles derived from seaweeds can be scaled up to meet future drug demand.

Declaration of competing interest

None to declare.

Author contributions

All authors have contributed equally to this review article.

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