



# **Marine-Bioinspired Nanoparticles as Potential Drugs for Multiple Biological Roles**

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Abstract: The increased interest in nanomedicine and its applicability for a wide range of biological functions demands the search for raw materials to create nanomaterials. Recent trends have focused on the use of green chemistry to synthesize metal and metal-oxide nanoparticles. Bioactive chemicals have been found in a variety of marine organisms, including invertebrates, marine mammals, fish, algae, plankton, fungi, and bacteria. These marine-derived active chemicals have been widely used for various biological properties. Marine-derived materials, either whole extracts or pure components, are employed in the synthesis of nanoparticles due to their ease of availability, low cost of production, biocompatibility, and low cytotoxicity toward eukaryotic cells. These marine-derived nanomaterials have been employed to treat infectious diseases caused by bacteria, fungi, and viruses as well as treat non-infectious diseases, such as tumors, cancer, inflammatory responses, and diabetes, and support wound healing. Furthermore, several polymeric materials derived from the marine, such as chitosan and alginate, are exploited as nanocarriers in drug delivery. Moreover, a variety of pure bioactive compounds have been loaded onto polymeric nanocarriers and employed to treat infectious and non-infectious diseases. The current review is focused on a thorough overview of nanoparticle synthesis and its biological applications made from their entire extracts or pure chemicals derived from marine sources.

**Keywords:** marine; nanoparticles; infectious disease; antimicrobial; anticancer; antioxidant; antiinflammatory; antidiabetic

# 1. Introduction

Infectious diseases have the potential to contribute to an increase in the global death rate [1]. Infectious diseases can be caused by viruses, fungi, and bacteria [2]. These microorganisms cause a variety of diseases, including cholera, candidiasis, and COVID-19 [3,4]. COVID-19 is a recent example that has triggered a pandemic [5]. Multiple drug resistance in viruses, fungi, and bacteria has reached alarming levels that must be addressed promptly. Various health organizations throughout the world have stated that various drug-resistant pathogenic microorganisms must be eradicated quickly [6]. Furthermore, current drugs for treating infectious diseases to patients suffering from non-infectious illnesses, such as cancer, inflammation, obesity, and diabetes, might possibly harm the human body [7–9]. To meet this demand, novel molecules that can function as antimicrobials against pathogenic microbes must be investigated [10]. The terrestrial ecosystem has yet to investigate the



Citation: Jeong, G.-J.; Khan, S.; Tabassum, N.; Khan, F.; Kim, Y.-M. Marine-Bioinspired Nanoparticles as Potential Drugs for Multiple Biological Roles. *Mar. Drugs* **2022**, *20*, 527. https://doi.org/10.3390/ md20080527

Academic Editor: Cédric Delattre

Received: 27 July 2022 Accepted: 16 August 2022 Published: 18 August 2022

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**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). marine environment [11]. Many applications for marine compounds have been documented [12]. Secondary metabolites produced by marine microorganisms have a wide range of applications [13]. The potential biological activity of marine organisms stems from communication and defensive systems in their natural habitat [13]. Many possible antimicrobial applications from marine sources have been investigated [14].

Furthermore, due to their biodiversity and production of various molecules with varying chemical structures, marine organisms can be exploited as valuable biologics to treat cancer, inflammation, and immune system diseases [15]. As a result of their diverse biological activities, natural compounds derived from marine resources have significantly contributed to disease treatment in place of conventional pharmaceuticals [16]. Nanotechnology is a developing technology with several applications in various sectors [17]. Recent research trends have demonstrated that nanoparticles have a wide range of therapeutic potential [18]. The biosynthesis of nanoparticles is a simple and inexpensive method [19]. Furthermore, the approach of synthesizing nanoparticles from diverse natural products is extensively employed as an eco-friendly method, since it does not produce toxic byproducts [20]. Various techniques have been developed to synthesize different types of inorganic nanoparticles, such as gold, zinc, titanium, magnesium, and silver [21]. The biosynthesis of nanoparticles provides antibacterial, drug delivery, sensing, and anticancer treatment. Nanoparticles produced from pure compounds, in particular, outperform traditional drugs in terms of biological activity [22]. This review paper advances our understanding of marine-derived compound nanoparticles as possible therapeutics for a variety of biological roles.

## 2. Green Synthesis of Nanoparticles (NPs) for Its Application in the Field of Medicine

Nanotechnology is a new discipline of research that works with chemical, biological, and physical sciences to produce nanosized particles with various applications. The size range of nanoparticles has been investigated between 1–100 nm [23–25]. Because of their high surface area to volume ratio, nanoparticles have a substantially larger proportion of surface, which leads to enhanced reactivity [26]. Because of their small size, nanoparticles can have a variety of sizes and forms [27]. Nanoparticles have a wide range of applications, including the medicinal, diagnostic, drug discovery, biological sensor, and reagent industries [28]. These biologically active nanoparticles are produced by employing various biological fluids as reducing agents for metal and non-metal ions, such as gold, silver, copper, zinc oxide, platinum, and titanium oxide [29]. The diverse therapeutic applications of nanoparticles, as well as the outbreak of several infectious diseases, motivate this research [30]. The general approaches for nanoparticle production include bioassisted, chemical, and physical methods [31]. Researchers are currently more interested in biological entities than chemical approaches. Fungi, bacteria, plants, and algae from the marine have been found to produce nanoparticles [12]. Green synthetic nanoparticles can be easily decomposed using enzymes included in the nanoparticles, making them more environmentally benign than conventional agents [29]. The reduction of metal ions by reducing agents found in the organism is essential for the synthesis of metal nanoparticles [32]. These reactions are driven by phenolics, terpenoids, alkaloids, amines, carbonyl groups, flavanones, proteins, pigments, and amides found in the organism [33]. Because marine organisms dwell on the unexplored seabed, it is critical to understand the metabolic mechanisms leading to metal ion reduction by diverse types of marine organisms [33]. Figure 1 depicts the different marine organisms, such as algae, bacteria, fungi, and animals, employed in the synthesis of metal nanoparticles.



**Figure 1.** Different types of metal and metal-oxide nanoparticles are synthesized using natural products from various marine organisms.

#### 3. Marine Organisms and Compounds for the Green Synthesis of NPs

Current research and innovation in marine science are contributing to the exponential growth of numerous sectors, including pharmaceuticals, environmental trends, nanomedicine, and food [14]. The ocean covers around 70–71% of the earth's surface [34]. Previous research studied the oceans, accounting for around 2.2 million distinct species [35]. The ocean contains an unimaginable number of marine-derived compounds with varied applications that are beneficial to humans, such as antimicrobial compounds [36]. The marine ecosystem contains around 25,000 physiologically active chemicals with various applications [37]. Currently, the marine environment paves the way for numerous antibacterial, antifungal, and antiviral compounds. Seaweeds, bacteria, and fungus are possible sources for combating infectious diseases [14,38]. According to prior research, the market for marine-derived compounds has surpassed 10 billion USD [39]. The production of marine-based nanoparticles from a variety of sources, including bacteria, fungus, seaweeds, and marine plants, has received considerable attention [33]. Algae with high cell growth rates, high stress tolerance, and an abundance of physiologically active substances, such as Ulva lactuca, Spirulina platensis, and Sargassum muticum, are regarded as promising biocatalysts for the synthesis of various types of nanomaterials [40-42]. Among pure algal compounds, phloroglucinol, eckol, phlorofucofuroeckol A, fucodiphlorethol G, 7phloroeckol, 6,6'-bieckol, and dieckol act as effective reducing agents in the nanoparticle synthesis process [43]. Diverse marine microorganisms adapt to harsh marine environments as well as a broad variety of temperatures, salinity, and pH, making them suitable biological factories for green nanoparticle synthesis [44]. Bacteria and fungi produce intracellular or extracellular inorganic compounds that react with metal ions to form nanoparticles [45,46]. Furthermore, nanoparticles made from marine-derived animals show good biocompatibility [47]. Seafood waste, in particular, may be used to make a variety of biological products by utilizing its high value-added qualities during the purification process [48]. Figure 2 shows numerous pure compounds obtained from marine organisms that act as reducing agents in the nanoparticle synthesis process.



**Figure 2.** Chemical structures of various pure compounds derived from marine organisms used as reducing agents in nanoparticle synthesis.

## 4. Marine Bioinspired NPs Used for Bacterial Infection

Table 1 summarizes a detailed review of marine-based nanoparticles utilized in treating various infectious diseases. Bacterial infection has a negative impact on public health [49]. Nanoparticles are attractive options since they have excellent bactericidal activity when treating pathogenic bacteria [50]. Several studies have been carried out to investigate the mechanisms of marine-inspired nanoparticles as antibacterial agents [51]. In general, marine antimicrobial macromolecules exhibit antibacterial mechanisms, such as (1) inhibition of DNA replication, (2) inhibition of expression of enzymes and other cellular proteins required for ATP production, (3) structural changes and damage to bacterial cell membranes, and (4) ROS production by inhibiting respiratory enzymes [52]. Several marine bacteria, including Vibrio spp., Pseudoalteromonas spp., and Ruegeria spp., generate antimicrobial compounds, a feature seen globally [53]. The marine bacterium Pseudomonas rhizosphaerae, in particular, has been shown to produce benzene-type secondary metabolites with potent antibacterial properties [54]. Secondary metabolites produced by marine algae, on the other hand, include polyphenols, terpenes, acetogenin, and aromatic compounds, which have a variety of biological functions, including antibacterial effects [55]. Silver nanoparticles derived from the marine cyanobacterium Chroococcus minutus showed antibacterial action against pathogenic strains of *Escherichia coli* and *Streptococcus pyogenes*, which have been discovered to be novel antibacterial for upper respiratory tract infection [56]. The synthesis of silver nanoparticles from cyanobacterium sources had improved control over pathogenic bacteria. Silver nanoparticles derived from the marine endophytic fungus Penicillium polonicum showed antibacterial activity against Acinetobacter baumanii, with MIC value of  $15.62 \ \mu g/mL$  and MBC value of  $31.24 \ \mu g/mL$  [44]. These findings were attributed to the activation of apoptosis by altering the osmotic pressure regulation of cells during the interaction of silver nanoparticles and bacteria. Silver nanoparticles using *S. muticum* extracts as a capping agent significantly suppressed the growth of Bacillus subtilis, E. coli, Klebsiella pneumoniae, and Salmonella Typhimurium [57]. These silver nanoparticles interacted with the bacterial membrane and penetrated the bacterium. Moreover, silver nanoparticles synthesized using S. swartzii showed antibacterial action by producing considerable deterioration in *E. coli* [58]. When combined with silver nanoparticles, *S. wightii* and *Valonopsis* pachynema demonstrated increased antibacterial activity against *Micrococcus* luteus and *S. marcescens* [59]. Silver nanoparticles produced from these seaweeds had a strong antibacterial activity because silver ions caused bacteria to release K<sup>+</sup> ions. Silver nanoparticles produced from an aqueous extract of *Gelidiella acerosa* inhibited the growth of *P. aeruginosa* and *B. subtilis* [60]. These bacteria were discovered to absorb silver nanoparticles from the cell surface. Silver nanoparticles produced using a culture-free extract of marine *Streptomyces* sp. Al-Dhabi-87 had excellent antibacterial activity against wound-infecting microorganism strains such as *Staphylococcus aureus*, *S. epidermidis*, and *Enterococcus faecalis* [61]. These nanoparticles displayed antibacterial action by releasing intracellular components and altering the cellular structure. Secondary metabolites found in *S. longifolium* extract reduced CuSO<sub>4</sub> to Cu<sup>2+</sup>, resulting in copper oxide nanoparticles [62]. These CuSO<sub>4</sub> nanoparticles showed remarkable antibacterial activity against *V. parahemolyticus*, *V. harvey*, *Aeromonas hydrophila*, and *Serratia marcescens*.

Carrageenan is a water-soluble, high-molecular-weight, sulfated polysaccharide isolated from many species of red algae. Carrageenan has been widely used in the pharmaceutical, medical, and food industries due to its high viscosity, gelling capacity, and biocompatibility [63,64]. Vijayakumar et al. [65] synthesized Kappa-carrageenan wrapped zinc-oxide nanoparticles (KC-ZnONPs) with antibacterial and antibiofilm activity against Methicillin-resistant *S. aureus* (MRSA) (Figure 3). Based on hemocompatibility studies on human RBCs and eco-safety studies using *Artemia salina*, the synthesized KC-ZnONPs showed high biocompatibility and were non-toxic to the environment.

Fucoidan, a pure chemical derived from *Fucus vesiculosus*, was used to synthesize gold nanoparticles, which demonstrated antibacterial action against P. aeruginosa (MIC value of 512  $\mu$ g/mL) [66]. In addition, the fucoidan-gold nanoparticles reduced the production of virulence factors, such as rhamnolipid, pyocyanin, and pyoverdine. Due to the presence of mannose, the capsular polymeric material isolated from marine *B. altitudinis* proved efficient as a stabilizer for CuO nanoparticle synthesis [67]. The MIC value of CuO nanoparticles containing mannose against P. aeruginosa was 1.0 µg/mL. Silver nanoparticles synthesized by the marine fungus Aspergillus flavus utilizing amylase showed antibacterial efficacy against Gram-positive and Gram-negative bacteria [68]. In particular, amylasesilver nanoparticles had the strongest antibacterial activity against A. hydrophila (MIC value of 1.6  $\mu$ g/mL). Khan et al. [69] synthesized gold nanoparticles from chitosan oligosaccharide, a natural marine compound, to treat *P. aeruginosa* biofilm infections. Chitosan oligosaccharide-gold nanoparticles exhibited antibiofilm efficacy by lowering bacterial hemolysis and P. aeruginosa virulence factors. P. aeruginosa hemolysis and protease activity were reduced by a nanocomposite of chitosan and polypyrrole [70]. Moreover, the production of various virulence factors, such as rhamnolipid, pyoverdine, and pyocyanin was reduced by this nanocomposite.



**Figure 3.** Synthesis of Kappa-Carrageenan wrapped Zinc-oxide nanoparticles (KC-ZnONPs) as an antibacterial agent against Methicillin-resistant *Staphylococcus aureus*. Reprinted with permission from reference [65]. Copyright, 2019 Elsevier B.V.

## 5. Marine Bioinspired NPs Used for Fungal Infection

Fungal infection is a constant cause of death [71]. The number of fungal infection cases is increasing, and it has been claimed that over 150 million fungal infections occur yearly, with a 1.5 million death rate from fungal infection [72]. Several secondary metabolites with antifungal action are produced by marine microorganisms, mammals, and algae, similar to antibacterial activity [73]. Antifungal chemicals are produced by a variety of marine species, including bacterial chitinases, lipopeptides, and lactones [74]. Brown algae phlorotannins, on the other hand, have antifungal activity by altering the composition of ergosterol in the yeast cell membrane [75]. The marine depsipeptidepapuamide A has been shown to trigger fungus apoptosis by binding to phosphatidylserine in the cell membrane and entering the plasma membrane [76]. Plakortide F acid, a polyketide endoperoxide produced from marine sponges, also had antifungal activity through affecting Ca<sup>2+</sup> homeostasis [77]. As a result, many researchers continue to look for antifungal activity in a variety of marine organisms for application to nanoparticles. Green synthesis of silver nanoparticles from *U. rigida* had antifungal action against the fungus *Trichophyton mantigrophytes* and *T. cutaneum*, which are linked toskin infections [78].

Name of Marine-Derived Compound/Product	Sources/Organism	Name of NPs	Size Range of MNPs	Shape/ Morphology	Antimicrobial Types	Microbial Pathogens	References
Extracts	<ul> <li>Ulva rigida</li> <li>Cystoseira myrica</li> <li>Gracilaria foliifera</li> </ul>	AgNPs	12 nm	Spherical	Antibacterial	<ul> <li>Bacillus cereus</li> <li>Escherichia coli</li> <li>Candida albicans</li> <li>Staphylococcus aureus</li> <li>Cryptococcus neoformans</li> </ul>	[78]
Extracts	U. lactuca	AgNPs	20–50 nm	-	Antibacterial	<ul> <li>E. coli</li> <li>Enterobacter spp.</li> <li>Klebsiella pneumonia</li> <li>Methicillin-resistant S. aureus (MRSA)</li> <li>Pseudomonas aeruginosa</li> <li>S. aureus</li> </ul>	[79]
Extracts	<ul><li>Halimeda opuntia</li><li>Kappaphycus alvarezii</li></ul>	SeNPs	30, 80 nm	Spherical	Antibacterial	<ul><li>Vibrio harveyi</li><li>V. parahaemolyticus</li></ul>	[80]
Extracts	Spirulina platensis	SNPs	200–450 nm	Spherical	Antibacterial	V. parahaemolyticus	[81]
Extracts	Chroococcus minutus	AgNPs	-	-	Antibacterial	<ul><li>E. coli</li><li>Streptococcus pyogenes</li></ul>	[56]
Extracts	U. lactuca	SeNP	85 nm	Spherical	Antibacterial	<ul> <li>Lactobacillus</li> <li>C. albicans</li> <li>S. mutans</li> <li>S. aureus</li> </ul>	[82]

 Table 1. List of marine-bioinspired metallic nanoparticles treating infectious diseases.

Name of Antimicrobial Shape/ **Microbial Pathogens** Marine-Derived Sources/Organism Name of NPs Size Range of MNPs References Morphology Types **Compound/Product** E. coli • B. subtilis Sargassum muticum AgNPs Spherical Antibacterial [57] Extracts 20–54 nm Salmonella Typhimurium K. pneumoniae ٠ Spherical Extracts S. swartzii AgNPs 20-40 nm Antibacterial E. coli [58] Gelidium corneum Spherical E. coli [83] Extracts AgNPs 20–50 nm Antibacterial E. coli • B. cereus P. aeruginosa Extracts Laminaria ochroleuca AgNPs 10–20 nm Antibacterial [84] Spherical S. aureus K. pneumoniae Micrococcus luteus Enterococcus faecalis • E. coli • *Streptomyces* sp. S. aureus AgNPs Spherical Antibacterial [61] Extracts 10–17 nm Al-Dhabi-87 S. epidermidis P. aeruginosa K. pneumoniae • S. wightii M. luteus ٠ AgNPs . Extracts 30–40, 55–70 nm Antibacterial [59] Valonopsis pachynema Serratia marcescens ٠ . *Streptomyces* sp. B. subtilis . . Rhodococcus E. coli Extracts AgNPs Spherical Antibacterial [85] 5.52, 35 nm P. aeruginosa rhodochrous S. aureus ٠

Name of Shape/ Antimicrobial Marine-Derived Name of NPs Size Range of MNPs **Microbial Pathogens** Sources/Organism References Morphology Types **Compound/Product** B. subtilis . AgNPs [60] Extracts Gelidiella acerosa Antibacterial P. aeruginosa \_ -. S. aureus • V. harveyi ٠ Acanthophora spicifera AuNPs <20 nm Spherical Antibacterial [86] Extracts S. aureus • Aeromonas hydrophila • V. parahaemolyticus P. aeruginosa Spherical [87] Extracts G. amansii AgNPs 27–54 nm Antibacterial E. coli S. aureus . B. pumilus • S. pneumonia • MRSA . S. wighitii MgONPs 68.06 nm Flower Antibacterial [88] Extracts E. coli . P. aeruginosa • A. baumannii • S. aureus ٠ Oscillatoria princeps AgNPs Spherical [89] Extracts 3.30-17.97 nm Antibacterial S. pyogenes . E. coli •

Name of Antimicrobial Shape/ Name of NPs Size Range of MNPs Marine-Derived **Microbial Pathogens** Sources/Organism References Morphology Types **Compound/Product** Enterococcus sp. . *Klebsiella* sp. B. subtilis Nocardiopsis Streptococcus sp. [90] Extracts AgNPs 30–80 nm Circular Antibacterial dassonvillei-DS013 Proteus sp. Pseudomonas sp. *Shigella* sp. E. coli • B. subtilis • S. aureus S. epidermidis *Streptomyces* sp. 11–21 nm Extracts AgNPs Cubic Antibacterial **[91]** P. aeruginosa Al-Dhabi-87 E. coli • E. faecalis K. pneumoniae • Penicillium polonicum AgNPs Spherical Extracts 10 nm Antibacterial A. baumanii [44] E. coli ٠ AgNPs Spherical [92] Chitosan Marine Seafood 5-20 nm Antibacterial P. aeruginosa ٠  $4.5\pm20.0\text{--}$ • Aspergillus sp. Chitosan-AgNPs  $50.2\pm74.0~\text{nm}$ . ٠ Chitosan Spherical Antibacterial S. aureus [93] Alternaria sp.  $3.47 \pm 2.00 -$ Chitosan-AuNPs ٠ ٠ ٠  $35.50\pm2.00~\text{nm}$ 

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Name of Marine-Derived Compound/Product	Sources/Organism	Name of NPs	Size Range of MNPs	Shape/ Morphology	Antimicrobial Types	Microbial Pathogens	References
Extracts	<ul> <li>Chlorococcum humicola</li> <li>Chlorella vulgaris</li> </ul>	AgNPs	10.69, 12.83 nm	Spherical	Antibacterial	<ul> <li><i>E. coli</i></li> <li><i>S.</i> Typhimurium</li> <li><i>K. pneumoniae</i></li> </ul>	[94]
Extracts	Cymodocea serrulata	AgNPs	40.49–66.44 nm	-	Antibacterial	V. parahaemolyticus	[95]
Extracts	S. longifolium	CuONPs	40–60 nm	-	Antibacterial	<ul> <li>V. parahemolyticus</li> <li>A. hydrophila</li> <li>Serratia marcescens</li> <li>V. harveyi</li> </ul>	[62]
Extracts	C. crinita	ZnONPs	23–200 nm	Rectangular	Antibacterial	<ul> <li>E. coli</li> <li>B. cereus</li> <li>S. Typhimurium</li> <li>S. aureus</li> <li>C. albicans</li> <li>A. niger</li> </ul>	[96]
Extracts	Synechocystis sp.	AgNPs	10–35 nm	Spherical	Antibacterial	MRSA	[97]
Extracts	O. limnetica	AgNPs	3.30–17.97 nm	Quasi-spherical	Antibacterial	<ul><li>E. coli</li><li>B. cereus</li></ul>	[98]
Extracts	Red algae	Co <sub>3</sub> O <sub>4</sub> NPs	$29.8\pm8.6~\text{nm}$	Spherical	Antibacterial	<ul><li>P. aeruginosa</li><li>E. coli</li></ul>	[99]
Extracts	U. lactuca	AgNPs	20–50 nm	-	Antiviral	<ul><li>Aedes aegypti</li><li>Culex pipiens</li></ul>	[79]

Name of Shape/ Antimicrobial **Microbial Pathogens** Marine-Derived Sources/Organism Name of NPs Size Range of MNPs References Morphology Types **Compound/Product** Spherical • Ag<sub>2</sub>O/AgONPs 14.42-48.97 nm *Oscillatoria* sp. ٠ Octahedral, Extracts Antiviral HSV-1 [100]S. platensis AuNPs 15.60-77.13 nm ٠ pentagonal and triangular Streptomyces sp. . AgNPs Spherical [85] Extracts 5.52-35.00 nm Antiviral Poliovirus R. rhodochrous Pectinodesmus sp. . strain HM3 50-65, 15-30, and Dictyosphaerium sp. Newcastle disease virus Extracts AgNPs Spherical Antiviral [101] 40–50 nm strain HM1 Dictyosphaerium sp. ٠ strain HM2 Trichophyton mentagrophytes . Extracts U. rigida AgNPs 12 nm Spherical Antifungal [78] T. cutaneum S. griseus 14.54 nm Spherical C. albicans Extracts AgNPs Antifungal [102] Spherical AgNPs 20–50 nm C. albicans Extracts G. corneum Antifungal [83] Fusarium udum ٠ P. fluorescens [103] Extracts AgNPs Antifungal \_ A. niger • Pyriporia oryzea Helminthosporium oryzae C. serrulate Extracts AgNPs Antifungal Alternaria sp. [104]Padina australis Rhizoctonia solani Xanthomoanas oryzae F. solani C. umhumicola . 10.69,12.83 nm [94] AgNPs Spherical Antifungal Extracts F. moniliforme C. vulgaris • Penicillium sp. •

These silver nanoparticles produced an insoluble chemical that inactivated the fungal cell wall's sulfhydryl group and disrupted the membrane, resulting in an antifungal effect. Silver nanoparticles synthesized from aqueous extracts of *Cymodocea serrulata* and *Padina australis* had antifungal action against plant fungi, including *Pyriporia oryzea*, *Alternaria* sp., *Helminthisporium oryzea*, *Rhizoctonia solani*, and *Xanthomanas oryzae* [104]. These antifungals were discovered as a consequence of cell wall disruption, DNA damage, and an increase in ROS. Silver nanoparticles (AgNPs) synthesized from *Gelidium corneum* extract, which served as a reducing agent had excellent antifungal and antibiofilm properties against *Candida albicans* [83]. Biosynthetic silver nanoparticles, in particular, demonstrated antifungal effectiveness by generating cell membrane and cell wall destruction, as well as cytoplasmic damage (Figure 4).



**Figure 4.** Synthesis and characterization of AgNPs using extract of marine red algae *Gelidium corneum* with antimicrobial and antibiofilm inhibition characteristics towards *Escherichia coli* and *Candida albicans*. (A) UV-vis absorption spectra of AgNPs synthesized using extract in the presence of different silver salt concentrations and (B) Change in color of the reaction mixture indicates the formation of AgNPs. Reprinted with permission from reference [83]. Copyright, 2019 Elsevier Ltd.

## 6. Marine Bioinspired NPs for Treating Viral Infection

A viral particle is smaller than a live cell. Several viral infections have been documented to be caused by a pathogenic virus. Viruses cause a variety of diseases, leading to increased death rate. Viral infections include smallpox, polio, HIV, and hepatitis C [105]. Antiviral compounds produced by marine organisms include polyphenols, alkaloids, lipids, carbohydrates, steroids, terpenoids, exopolysaccharides, polyketides, zoanthoxanthins, and peptides [106]. Virus adsorption, penetration, capsid decoration, biosynthesis, virus assembly, and virus release are all inhibited or inactivated by marine polysaccharides [107]. One of the metabolites produced by marine organisms, phlorotannins, has been shown to interfere with viral attachment, penetration, and replication [15]. Silver nanoparticles derived from the seaweed *U. lactuca* showed cytotoxic efficacy against the vector-borne pathogens *Aedes aegypti* and *Culex pipiens* [79]. Because of their small particle size, silver nanoparticles synthesized from *U. lactuca* demonstrated more effective action than conventional insecticides. Additionally, these silver nanoparticles bonded to the insect cuticle and entered within the cell, disrupting additional cell functions. Silver nanoparticles mediated by *Oscillatoria* sp. and gold nanoparticles mediated by *S. platensis* displayed antiviral efficacy against herpesvirus [100]. These nanoparticles induced glycoprotein aggregation and surface changes, both of which might inhibit viral binding and penetration. Silver nanoparticles derived from extracellular extracts of the marine actinomycetes *Rhodococcus rhodochrous* and *Streptomyces* sp. inhibited poliovirus in RD cells [85]. The interaction of viral proteins with silver nanoparticles caused poliovirus inhibition. Silver nanoparticles derived from *Dictyosphaerium* sp., a freshwater microalgae, had substantial antiviral activity against the Newcastle disease virus [101]. These silver nanoparticles were bound to the viral glycoprotein envelope, limiting virus penetration.

## 7. Marine Bioinspired NPs for Treating Non-Infectious Diseases

Table 2 shows studies that have used marine bioinspired nanoparticles to treat a wide range of non-infectious diseases. Inflammation is the body's natural response to tissue injury, infection, and genetic alterations [108]. The immune system is activated within the body under inflammatory circumstances, resulting in the release of various inflammatory mediators, such as bradykinins and prostaglandins [109]. Thus, reducing prostaglandin levels can aid in the prevention of chronic disease by controlling inflammation [110]. To reduce inflammation and inflammatory mediators, steroids and nonsteroidal antiinflammatory medications constitute one of the treatment paths for inflammatory diseases [111]. These synthetic antiinflammatory drugs, on the other hand, can have substantial negative effects [112]. As a result, it is required to use marine-based organisms with high biological activity to generate nanoparticles with similar therapeutic benefits and no negative effects. Silver nanoparticles produced from macroalgae such as *Galaxaura elongate*, *Turbinaria ornate*, and Enteromorpha flexuosa have shown considerable antiinflammatory action via membrane stabilization [113]. Silver nanoparticles, in particular, reduced prostaglandin production by inhibiting protein denaturation, cyclooxygenase, and 5-lipoxygenase. At 500 µg/mL, ZnO nanoparticles wrapped in Kappa-carrageenan demonstrated 82% antiinflammatory efficacy (Figure 3) [65]. Because of their high surface area to volume ratio, these nanoparticles were more effective than bulk materials in inhibiting cytokines and inflammatory coenzymes. Cancer is caused by the uncontrollable growth of cells and tissues [114]. Cancer treatment options include surgery, radiation, and potentially toxic medication therapy [115]. As a result, several investigations are being done to discover anticancer drugs that kill cancer cells without hurting humans [116]. Nanoparticles loaded with various physiologically active chemicals are one of the most effective drug delivery techniques for cancer therapy [117]. Marine-derived natural products, in particular, are potential molecules for the development of anticancer drugs because they may influence multiple pathways, such as immunity, cancer cell death, and tumor growth [118]. Silver nanoparticles derived from Caulerpa taxifolia showed antitumor efficacy against A549 lung cancer cells [119]. Necrosis and condensation of A549 cells were shown to be mediated by silver nanoparticles derived from marine algae, suggesting that nanomaterials are relevant for cancer cell research. Furthermore, gold nanoparticles inhibited phosphorylation of AKT and ERK, which are essential for cell growth in HeLa cancer cells [47]. Interestingly, these gold nanoparticles derived from jellyfish extract exhibited a significant lethal effect on HeLa cancer cells. Cu<sub>2</sub>O nanoparticles derived from Rhodotorula mucilaginosa showed anticancer activity against SKOV-3, MCF-7, HepG2, A549, SW620, and HT-29 [117]. In particular, reactive oxygen species production and oxidative stress enhanced the anticancer mechanism of Cu<sub>2</sub>O nanoparticles. Similarly, Shunmugam et al. [120] synthesized gold nanoparticles from the marine bacterium V. alginolyticus, which had antioxidant and anticancer activity (Figure 5). The anticancer activity was attributed to the treated cells' nuclear condensation.

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Organisms/Sources	Name of NPs	Size Range of MNPs	Shape/ Morphology	Types of Non-Infectious Disease Treatment	Effects/Activities	References
<ul><li>Ulva rigida</li><li>Cystoseira myrica</li><li>Gracilaria foliifera</li></ul>	AgNPs	12 nm	Spherical	Anticancer	Human breast adenocarcinoma cell line	[78]
<ul><li>Streptomyces sp.</li><li>Rhodococcus rhodochrous</li></ul>	AgNPs	5.52, 35 nm	Spherical	<ul><li>Anticancer</li><li>Anti-leishmanial</li></ul>	<ul><li>HepG2 cell line</li><li><i>Leishmania tropica</i></li></ul>	[85]
Acanthophora spicifera	AuNPs	<20 nm	Spherical	Anticancer	Human colon adenocarcinoma (HT-29) cells	[86]
Sargassum wighitii	MgONPs	68.06 nm	Flower	Anticancer	A549	[88]
Rhodotorula mucilaginosa	Cu <sub>2</sub> ONPs	51.6–111.4 nm	Spherical	Anticancer	<ul> <li>SW620</li> <li>SKOV-3</li> <li>MCF-7</li> <li>HT-29</li> <li>HepG2</li> <li>A549</li> </ul>	[117]
Pterocladia capillacea	CuONPs	62 nm	Spherical	Anticancer	Breast cancer, ovarian cancer, and hepatocellular carcinoma cell lines	[121]
Laminaria digitata	ZnONPs	100–350 nm	Spindle	Anticancer	Fibroblasts cells and human colon cancer cells	[122]
Hamigera pallidass	AgNPs	$5.85 \pm 0.84$ , 3.69–16.11 nm	Spherical	<ul><li>Anticancer</li><li>Antioxidant</li></ul>	<ul> <li>Human breast cancer</li> <li>DPPH (2, 2-diphenyl1-picrylhydrazyl)</li> </ul>	[123]
	<ul> <li>Ullva rigida</li> <li>Cystoseira myrica</li> <li>Gracilaria foliifera</li> <li>Streptomyces sp.</li> <li>Rhodococcus rhodochrous</li> <li>Acanthophora spicifera</li> <li>Sargassum wighitii</li> <li>Rhodotorula mucilaginosa</li> <li>Pterocladia capillacea</li> <li>Laminaria digitata</li> </ul>	<ul> <li>Ullva rigida</li> <li>Cystoseira myrica</li> <li>Gracilaria foliifera</li> <li>Streptomyces sp.</li> <li>Rhodococcus rhodochrous</li> <li>AgNPs</li> <li>Acanthophora spicifera</li> <li>AuNPs</li> <li>Sargassum wighitii</li> <li>MgONPs</li> <li>Rhodotorula mucilaginosa</li> <li>Cu2ONPs</li> <li>Pterocladia capillacea</li> <li>Laminaria digitata</li> <li>ZnONPs</li> </ul>	Organisms/SourcesName of NPsMNPs•Ulva rigida •AgNPs12 nm•Gracilaria foliiferaAgNPs5.52, 35 nm•Streptomyces sp. •AgNPs5.52, 35 nm•Rhodococcus rhodochrousAuNPs<20 nm	Organisms/SourcesName of NFSMNPsMorphology•Ullva rigida • Cystoseira myrica • Gracilaria foliiferaAgNPs12 nmSpherical•Streptomyces sp. • Rhodococcus rhodochrousAgNPs5.52, 35 nmSpherical•Acanthophora spicifera • Sargassum wighitiiAuNPs<20 nm	Organisms/SourcesName of NPsSize Kange of MNPsShape MorphologyNon-Infectious Disease Treatment•Ultva rigida •AgNPs12 nmSphericalAnticancer•Gracilaria foliiferaAgNPs5.52, 35 nmSpherical•Anticancer•Streptomyces sp. •AgNPs5.52, 35 nmSpherical•Anticancer•Streptomyces sp. 	Organisms/SourcesName of NPsSize Kange of MNPsSinaper MorphologyNon-Infectious Disease TreatmentEffects/Activities•Ultra rigida •AgNPs12 nmSphericalAnticancerHuman breast adenocarcinoma cell line•Streptomyces sp. •AgNPs5.52, 35 nmSpherical• Anticancer• HepG2 cell line • Leishmanial tropica•Streptomyces sp. •AgNPs5.52, 35 nmSpherical• Anticancer• HepG2 cell line • Leishmanial tropicaAcanthophora spiciferaAuNPs<20 nm

Table 2. List of marine-bioinspired metallic nanoparticles for treating non-infectious diseases.

Name of Types of Size Range of Shape/ Marine-Derived **Organisms/Sources** Name of NPs **Non-Infectious Disease Effects/Activities** References Morphology **MNPs Compound/Product** Treatment HepG2 • Anticancer DPPH, ABTS scavenger Galaxaura elongate . Antioxidant 30-90, 20-60,  $\alpha$ -Amylase inhibition Turbinaria ornata • Extracts AgNPs Spherical [113] Antidiabetic 30–90 nm . Proteinase inhibition and Enteromorpha flexuosa • Antiinflammatory • albumin denaturation inhibition Extracts U. lactuca AgNPs 8–14 nm Spherical Anticancer Human colon cancer [124] Anticancer A549 cell lines . ٠ Alternaria chlamydospora AuNPs Spherical [125] Extracts \_ Antioxidant DPPH • •  $16.9 \pm 2.5$ , Chondrus crispus • Monocytic cell line Antitumoral • . Extracts AuNPs  $15.0 \pm 3.0$ , Spherical [126] Gelidium corneum Antioxidant Human promyelocytic cells •  $44.2\pm6.1\,\text{nm}$ Porphyra linearis . DPPH Extracts C. crinita ZnONPs 23-200 nm Rectangular Antioxidant [96] Wound-healing Extracts *Synechocystis* sp. AgNPs 10-35 nm Spherical Diabetic wounded animals [97] Carrageenan &Carrageenan Marine red algae AuNPs  $141 \pm 6 \,\mathrm{nm}$ Spherical Anticancer HCT-116 and HepG2 cells [127] oligosaccharide A549 Anticancer • . AuNPs Spherical Extracts Paracoccus haeundaensis  $20.93\pm3.46\,\text{nm}$ [128] AGS cancer cells Antioxidant . DPPH ٠ Caulerpa taxifolia A549 lung cancer cells [119] Extracts AgNPs \_ \_ Anticancer Nemopilema nomurai AuNPs  $35.2\pm8.7\,nm$ Spherical HeLa cancer cells [47]Extracts Anticancer

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Name of Marine-Derived Compound/Product	Organisms/Sources	Name of NPs	Size Range of MNPs	Shape/ Morphology	Types of Non-Infectious Disease Treatment	Effects/Activities	References
Extracts	Oscillatoria limnetica	AgNPs	3.30–17.97 nm	Quasi-spherical	Anticancer	<ul><li>Human colon cancer cell line</li><li>Human breast cell line</li></ul>	[98]
Extracts	Red algae	Co <sub>3</sub> O <sub>4</sub> NPs	$29.8\pm8.6~\text{nm}$	Spherical	Anticancer	HepG2 cancer cells	[99]
Extracts	Vibrio alginolyticus	AuNPs	50–100 nm	Monodispersed, irregular shape	Anticancer	HCA-7 cells	[120]





Silver nanoparticles derived from shrimp shell chitin acted as a reducing agent and had anticancer action against human hepatocarcinoma [129]. In HepG2 cells, chitin-silver nanoparticles increased the expression of apoptosis-related proteins Bax, PARP, cytochromec, caspase-3, and caspase-9, while decreasing the expression of antiapoptosis proteins Bcl-2 and Bcl-xl. Phloroglucinol-encapsulated starch biopolymer exhibited dose-dependent anticancer activities against the HepG2 liver cancer cell line [130]. These findings were ascribed to the biopolymer's hydrophobicity, which increased adhesion and adsorption capability to the cancer cell surface.

Cells produce potentially harmful ROS as a result of oxygen metabolism, which involves enzymatic and non-enzymatic reactions [131]. High levels of ROS caused by oxidative stress induce a variety of diseases in the body, including diabetes, hypertension, and Alzheimer's [132]. Antioxidants, on the other hand, have a role in delaying, regulating, and avoiding the oxidative process that leads to the beginning and progression of the disease [133]. Through SOD enzymes, which catalyze the recombination of oxygen radicals, these antioxidants counteract the consequences of oxidative stress [134]. Currently, research is being performed to investigate natural substances capable of controlling oxidative stress, which leads to the investigation of nanoparticles with antioxidant activities. Many species with antioxidant activity in marine organisms, in particular, have been found and have piqued the interest of researchers due to their potential biological activity [135]. The antioxidant activity of gold nanoparticles produced by the marine fungus A. chlamydospora (inhibition of DPPH radicals) was dose-dependent [125]. Furthermore, in a concentrationdependent way, gold nanoparticles mediated by the marine bacteria Paracoccus haeundaensis cell-free supernatant demonstrated strong reducing power via DPPH scavenging activity [128]. Selenium nanoparticles produced from Spirulina phycocyanin protected INS-1E rat insulinoma cells against palmitic acid-induced cell death [136]. Phycocyanin and selenium shielded cells from oxidative damage and signaling pathways downstream. These findings indicate that marine-derived nanoparticles can be employed as effective natural antioxidants.

Figure 6 depicts the biological activity of nanoparticles synthesized using phloroglucinol. Silver nanoparticles synthesized using phloroglucinol showed anticancer efficacy against the MCF-7 breast cancer cell line [137]. Silver ions from phloroglucinol silver nanoparticles entered cancer cells and interacted with intracellular macromolecules, such as organelles, proteins, and DNA, to trigger apoptosis. Another study found that phloroglucinolgold nanoparticles triggered death in HeLa cancer cells via enhancing mitochondrial membrane permeability [138]. Phloroglucinol-encapsulated chitosan nanoparticles showed antibiofilm action against single-species biofilms, such as *K. pneumoniae, S. aureus, S. mutans*, and *C. albicans*, and mixed-species biofilms, such as *C. albicans-S. aureus/K. pneumoniae/S. mutans* [139]. Gold and zinc oxide nanoparticles produced with phloroglucinol showed significant antibacterial action against *P. aeruginosa* [140]. Moreover, these nanoparticles inhibited *P. aeruginosa* twitching, swimming, and swarming motility, all of which have virulence features. Similarly, several marine-derived pure compounds are employed in synthesizing nanoparticles and encapsulating drugs for application in the field of medicine (Table 3).



**Figure 6.** Application of phloroglucinol in the form of nanoparticles for treating infectious and noninfectious diseases. (**A**) The cytotoxicity action of phloroglucinol-engineered AgNPs towards MCF-7 breast cancer cell lines. (**a**) SEM image of AgNPs and (**b**) TEM image of AgNPs. Reproduced with permission from reference [137]. (**B**) Synthesis of the phloroglucinol-conjugated gold nanoparticles, which exhibit therapeutic potential towards cancer cells. The action mechanism involved apoptosis of cancer cells by promoting mitochondrial transmembrane permeation, as evident by fluorescence staining and gene expression studies. Reprinted with permission from reference [138], (**C**) Encapsulation of phloroglucinol into the chitosan nanoparticles. The PG-CSNPs exhibit antibiofilm properties towards single- and mixed-species biofilms of *C. albicans-S. aureus/S. mutans/K. penumoniae*. Reprinted with permission from reference [139], and (**D**) Synthesis of metal (AuNPs) and metal oxide (ZnONPs) nanoparticles using phloroglucinol. The synthesized PG-AuNPs and PG-ZnONPs showed antibiofilm and antivirulence properties towards *P. aeruginosa*. Reproduced with permission from reference [140]. Copyright 2021 by the authors and licensee MDPI, Basel, Switzerland.

Classification of Sources	Natural Pure Compounds	Types of Nanomaterial	Size	Morphology	Biological Activity	Action Mechanism	References
Algae	Fucoidan	AuNPs	~53 nm	Spherical	Antibacterial activity against Pseudomonas aeruginosa	<ul> <li>Reduced the generation of numerous important virulence factors</li> <li>Impaired bacterial motility, including twitching, swimming, and swarming</li> </ul>	[66]
Algae	Phloroglucinol	AuNPs and ZnONPs	$41.6 \pm 3.9,$ $52.7 \pm 3.8$ nm	Spherical and hexagonal	Antibacterial activity against P. aeruginosa	<ul> <li><i>P. aeruginosa</i> virulence factors, such as rhamnolipid, pyocyanin, pyoverdine, protease, and hemolytic capabilities, were reduced.</li> <li>Impaired bacterial motility, including twitching, swimming, and swarming</li> </ul>	[140]
Algae	Phycocyanin	SeNPs	165, 235, 371, 815 nm	Spherical	Antioxidant	Protected INS-1E cells against palmitic acid-induced cell death by reducing oxidative stress and signaling pathways downstream	[136]
Algae	Fucoxanthin	AgNPs	20–25 nm	Spherical	Antibacterial activity against Escherichia coli, Bacillus stearothermophilus, and Streptococcus mutans	-	[141]
Algae	Phloroglucinol	Starch biopolymer	1–100 nm	Spherical	Anticancer	Adhesion and adsorption on the surfaces of cancer cells are enhanced	[130]

Table 3. Application of marine-derived compounds in the synthesis of nanoparticles and encapsulation of drugs for application in the field of medicine.

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Classification of Sources	Natural Pure Compounds	Types of Nanomaterial	Size	Morphology	<b>Biological Activity</b>	Action Mechanism	References
Algae	Phloroglucinol	CSNPs	$414.0 \pm 48.5\mathrm{nm}$	Spherical	Antibiofilm activity against <i>Klebsiella pneumoniae,</i> <i>Staphylococcus aureus, Candida</i> <i>albicans, S. mutans,</i> and mixed-species such as C. <i>albicans-S. aureus/K.</i> <i>pneumoniae/S. mutans</i>	The positive charge of CSNPs allows for easy biofilm penetration and binding	[139]
Algae	Usnic acid	Nanofibrous poly(ε- caprolactone)/ decellularized extracellular matrix scaffolds	$\begin{array}{l} 3.89 \pm 2.52, \\ 4.95 \pm 2.19, \\ 5.00 \pm 2.05 \ \mu\text{m} \end{array}$	Fusion of the fiber junctions	<ul> <li>Antibacterial activity against <i>Cutibactrium acnes</i>, <i>S. mutans</i>, <i>S. aureus</i>, <i>S.</i> <i>epidermidis</i>, and <i>C. albicans</i></li> <li>Antibiofilm activity against <i>K. pneumoniae</i> and <i>P.</i> <i>aeruginosa</i></li> <li>Wound healing capability</li> </ul>	<ul> <li>Increased swelling, surface erosion, and degradation due to high release qualities</li> <li>Improved cellular activities, such as cell adhesion, proliferation, differentiation, and migration</li> </ul>	[142]
Algae	Carrageenan	ZnONPs	$97.03 \pm 9.05$ nm	Hexagonal wurtzite phase	<ul> <li>Antibacterial activity against MRSA</li> <li>Antiinflammatory activity</li> </ul>	<ul> <li>Penetrated quickly through the bacterial cell membrane and had a greater bactericidal impact</li> <li>Inflammation enhancers such as cytokines and inflammation-assist enzymes are blocked</li> </ul>	[65]
Bacteria	Mannose	CuONPs	108 nm	Spherical	Antibacterial activity against P. aeruginosa	Entered the cell membrane, causing lysis and cell rupture	[67]
Fungi	<ul><li>Asperpyrone B</li><li>Asperpyrone C</li></ul>	AgNPs	8–30 nm	Spherical	Acetylcholine esterase inhibitory activity	Enzyme structural alterations	[143]
Fungi	α-amylase	AgNPs	22.88–26.35 nm	Spherical	Antibacterial activity against Aeromonas hydrophila, P. aeruginosa, Vibrio anguillarum, S. faecium, S. agalactiae, and Listeria spp.	Damage to cell membranes, oxidative stress, and protein and DNA damage	[68]

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Classification of Sources	Natural Pure Compounds	Types of Nanomaterial	Size	Morphology	Biological Activity	Action Mechanism	References
Animal	Chitin	AgNPs	17–49 nm	Spherical	Anticancer activity in human hepatocellular carcinoma HepG2 cells	<ul> <li>Increased levels of apoptosis-related proteins, such as PARP, cytochrome-c, Bax, caspase-3, and caspase-9</li> <li>Reduced expression of the antiapoptotic proteins Bcl-xL and Bcl-2 in HepG2 cells</li> </ul>	[129]
Animal	Astaxanthin	AuNPs	$58.2\pm4.6~\mathrm{nm}$	Polygonal and spherical	Antioxidant	Reduced ROS and increased antioxidant enzyme activity in rice plants treated to Cd to alleviate oxidative stress	[144]
Animal	Chitosan oligosaccharide	AuNPs	$56.01 \pm 3.48$ nm	Spherical	Antibacterial activity against <i>P. aeruginosa</i>	<ul> <li>Inhibited bacterial hemolysis</li> <li>Reduced <i>P. aeruginosa</i> virulence factor synthesis</li> <li>Reduced bacterial swimming and twitching motilities</li> </ul>	[69]
Animal	Thiol chitosan	AuNSs	$185\pm19~\text{nm}$	Spherical	Antibacterial activity against <i>E. coli, P. aeruginosa,</i> and <i>S. aureus</i>	-	[145]
Animal	Chitosan	Polypyrrole nanocomposites	$55.77 \pm 3.48$ nm	Spherical	Antibiofilm activity against P. aeruginosa	<ul> <li><i>P. aeruginosa</i> hemolytic and protease activities were inhibited</li> <li>Reduced the production of many virulence factors, including pyocyanin, pyoverdine, and rhamnolipid</li> </ul>	[70]

#### 8. Conclusions and Future Perspectives

In conclusion, because of their potential biological activity, marine-derived products have been widely used in the pharmaceutical industry. With an increased understanding of their biological functions, various marine-derived compounds have been used in the synthesis of nanoparticles. These products comprised polymers, organic compounds, and extract, which act as a powerful reducing agent in synthesizing metal and metal-oxide nanoparticles. Furthermore, certain polymeric material is used to effectively deliver the drug in the treatment of infectious and non-infectious diseases. The review detailed the list of the marine organism from which the extract was extracted and which was used to synthesize several forms of nanoparticles. Furthermore, these nanoparticles have been shown to have antimicrobial properties against bacterial, fungal, and viral pathogens. Antimicrobial mechanisms include the breakdown of cell membranes, as well as damage to cell walls and DNA. These marine-inspired nanoparticles have also shown promise in the treatment of non-infectious diseases, such as diabetes, cancer, wounds, inflammatory reactions, and leishmanial infections. Though significant progress has been made in the production of nanoparticles utilizing extracts from marine sources, relatively little information is known on the synthesis of nanoparticles using pure active compounds. This is because of the fact that there are several variations in extract preparation due to a number of environmental factors. As a result, future research should prioritize the use of pure active compounds for nanoparticle synthesis. Most antimicrobial research involving these nanoparticles has been conducted at the phenotypic level; however, investigations at the gene level are highly needed to explain the molecular mechanism.

Author Contributions: G.-J.J.: Literature Search, Writing—original draft and Editing, S.K.; Literature Search, Writing—original draft, and Editing, N.T.: Literature Search, Writing—original draft and Editing, F.K.: Conceptualization, Literature Search, Writing—original draft, and Writing—review and Editing, Y.-M.K.: Supervision, Funding, Writing—review and Editing. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) grant funded by the Ministry of Education (2021R1A6A1A03039211 and 2022R1A2B5B01001998).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

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