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Review

Nanotechnology to the Rescue: Therapeutic Strategies Based on Brown Algae for Neurodegenerative Diseases

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Abstract: In the last decades, marine macroalgae have drawn attention mainly because of their bioactive constituents. Most brown algae are distributed over coastal areas of the Atlantic Ocean, Mediterranean Sea, Aegean Sea and Black Sea, and their composition varies with endogenous and exogenous factors. Phlorotannins, fatty acids, sterols and carbohydrates are some of the compounds responsible for biological activities related to cytotoxic, antiviral, antifungal, antibacterial, antidiabetic, antioxidant and anti-inflammatory potential. In this review we seek to highlight some of the compounds responsible for these last two biological activities, which have enormous importance for the management of neurodegenerative diseases, such as Alzheimer and Parkinson's, with neuroinflammation and oxidative stress as hallmarks. However, one of the major problems associated with treating these diseases is the highly selective blood-brain-barrier, which can be overcome with nanocarriers used as delivery systems. Weighing the risks, benefits and toxicity of the used nanoparticles is nevertheless important. We also discuss zebrafish as an upcoming adequate biological model for in vivo screening of risks and benefits of such treatment strategies. This review aims to enable researchers working in the exploitation of these macroalgae and in the use of nanocarriers to potentiate the controlled delivery of bioactive compounds.

Keywords: brown algae; antioxidant activity; anti-inflammatory activity; neurodegenerative diseases; nanoparticles; zebrafish model

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1. Introduction

In the last decades, marine macroalgae have drawn attention mainly due to their bioactive components, which have a wide range of biological activities [1]. As marine organisms are exposed to extreme environmental conditions, they produce unique secondary metabolites, which have been recognized as important compounds for the development of innovative medicines. Part of the diversity of the oceans comes from algae, which constitute one of the most important groups of organisms, both in number and in diversity of species [2]. Macroalgae, that comprise a varied group of organisms, are eukaryotic, macroscopic and photosynthetic organisms and are among the largest oxygen producers on Earth [2]. Currently, the use of macroalgae is relevant for different areas such as agriculture, aquaculture, food, cosmetics, pharmaceutical industry, and is also widely used as a source of gelling agents, phycocolloids, such as agar, which are usually used as thickeners, and stabilizers for suspensions and emulsions [3].

They can be classified as red (phylum Rhodophyta), green (phylum Chlorophyta) or brown macroalgae (phylum Ochrophyta), depending on their pigment composition, which will be responsible for the different colors that characterize them [4] (Figure 1).

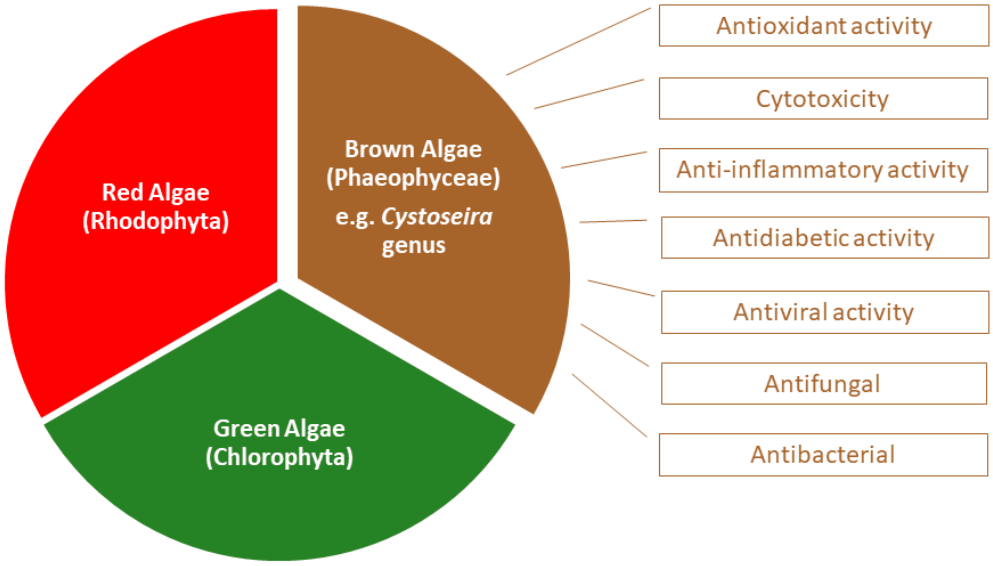


Figure 1. Biological activities associated to *Cystoseira*, an important genus belonging to the group of brown algae.

Brown macroalgae are grouped in the Phaeophyceae class and present fucoxanthin as the main carotenoid which gives them a typical brown color. They include macroalgae with a wide range of sizes and shapes, from a few centimeters to tens of meters. The formation of seaweed forests are common, allowing efficient capture of sunlight and serving as habitat for many marine animals [2]. Of the approximately 2000 known species in this class, less than 1% live in fresh water [5]. From the marine macroalgae, the brown algae of the Sargassaceae family have been intensely studied. Chemically, they are essentially composed of water (80–90%) and polysaccharides, namely cellulose, alginic acid, laminarin and fucoidan, the latter being present only in brown algae. Other compounds include polyunsaturated fatty acids, vitamins, proteins, peptides, terpenoids, pigments, and sterols. Furthermore, and among marine algae, brown algae contain the highest levels of phenolic compounds [6]. One of the known genera of this family is the former *Cystoseira* genus (Figures 1 and 2), which currently comprises 123 species in Algaebase, considering accepted taxonomically species and homotypic or heterotypic synonym (due to the rearrangement of classification systems) [7,8]. *Cystoseira* spp. is distributed over the Atlantic Ocean, Mediterranean Sea, Aegean Sea and Black Sea [9,10] and their composition varies according to several exogenous factors, such as geographical location, season and environmental factors, or endogenous factors, such as age and species [11,12]. Over the years it has also been discovered that the solvents used in the extraction of these metabolites significantly influence the constitution of the extracts and, consequently, their biological activity [1,9,13–16].

This genus represents one of the most important elements of the marine coast ecosystem [17], being essential for the rocky structure of marine forests and ensuring food to numerous species of organisms that live in the rocky reefs. In addition, it has economic value [18]. It has been widely studied from a chemical and biological point of view, with most studies focusing on species from the coastlines of the Atlantic Ocean and Mediterranean Sea, such as *C. tamariscifolia*, *C. nodicaulis*, *C. usneoides*, *C. abies-marina*, *C. crinite* (currently designated as *Ericaria selaginoides*, *Gongolaria nodicaulis*, *Gongolaria usneoides*, *Gongolaria abies-marina*, *Ericaria crinite*, respectively), *C. sedoides* and *C. compressa* [13,19,20].

Although a huge diversity of compounds has been identified in these algae, making it possible to relate them to the biological activities selected for this review (Figure 1, Table 1), lipid and phenolic compounds are the metabolites that have aroused the most interest due to the various biological properties with which they have been associated [2,21–23]. This review focuses on a limited set of biological activities, namely anti-inflammatory and antioxidant potential, and some of the compounds conferring such activities.

Figure 2. Example of specimen *Ericaria selaginoides*, previously designated as *Cystoseira tamariscifolia*, (**left**) collected from the north coast of Portugal (**right**).

Table 1. Compounds identified in species of the genus *Cystoseira* and their respective biological activity.

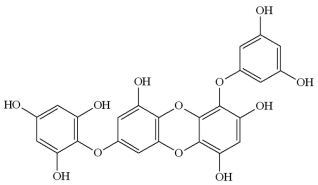
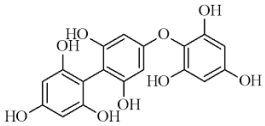
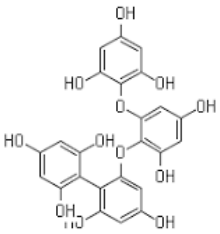
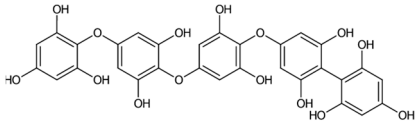
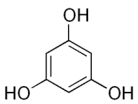
Compound Class and Name	Species	Biological Activity
Phlorotannins and Phenolic Compounds		
7-Phloroethol 	*C. humilis* [24] *C. tamariscifolia* [20]	Antioxidant
Fucophloroethol 	*C. barbata* [25] *C. baccata* [24] *C. usneoides*, *C. nodicaulis* [20]	Antioxidant/cytotoxic Antioxidant Antioxidant
Fucodiphloroethol 	*C. tamariscifolia*, *C. nodicaulis* [20]	Antioxidant
Fucotriphloroethol 	*C. usneoides*, *C. nodicaulis* [20]	Antioxidant
Phloroglucinol 	*C. baccata* [24] *C. compressa* [26] *C. foeniculacea* [26] *C. humilis* [24] *C. nodicaulis* [24] *C. tamariscifolia* [27] *C. usneoides* [24,27]	Antioxidant

Table 1. *Cont.*

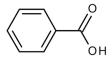
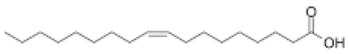
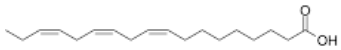
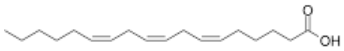
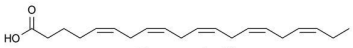
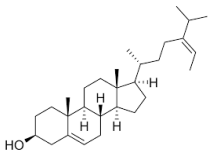
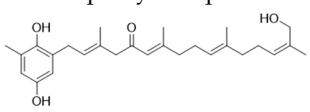
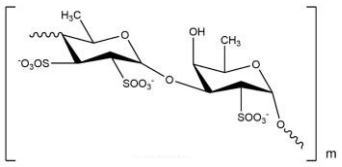
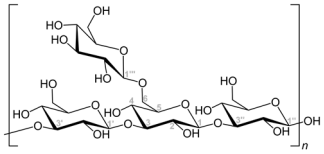
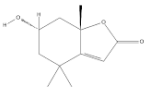
Compound Class and Name	Species	Biological Activity
Benzoic acid 	*C. abies-marina* [28] *C. crinita* [29]	Antioxidant, anti-inflammatory
Undefined/mixed	*C. compressa* [24] *C. tamariscifolia* [28] *C. nodicaulis* [28] *C. usneoides* [28]	Antioxidant, antimicrobial Anti-inflammatory Anti-bacterial, anti-fungal Anti-fungal
Fatty Acids		
Oleic acid (C18:1) 	*C. baccata* [30] *C. barbata* [30] *C. brachycarpa* [31] *C. compressa* [30] *C. crinita* [29] *C. humilis* [27] *C. nodicaulis* [30] *C. tamariscifolia* [30]	Anti-inflammatory, antioxidant
α-Linolenic acid (C18:3, ω-3) 	*C. barbata* [30] *C. crinita* [29]	Anti-inflammatory
γ-Linolenic acid (C18:3, ω-6) 	*C. crinita* [29] *C. compressa* [30] *C. tamariscifolia* [30]	Anti-inflammatory
Eicosapentaenoic acid (C20:5) 	*C. baccata* [32] *C. compressa* [30] *C. humilis* [30] *C. nodicaulis* [30] *C. tamariscifolia* [30] *C. brachycarpa* [31] *C. crinita* [29]	Anti-inflammatory
Quinones and Sterols		
Fucosterol 	*C. crinita* [27,29] *C. nodicaulis* [27] *C. tamariscifolia* [27] *C. usneoides* [27]	Antioxidant, anti-inflammatory
Tetraprenyltoluquinols 	*C. amentacea*, *C. jabukae*, *C. crinita*, *C. elegans*, *C. algeriensis*, *C. elegans*, *C. algeriensis*, *C. barbata* [27]	Antioxidant
Carbohydrates		
Fucoidans 	*C. compressa* [33,34] *C. crinita* [33] *C. sedoides* [33] *C. indica* [35] *C. trinodis* [36] *C. indica* [36] *C. crinita* [36]	Anti-inflammatory, antioxidant, Anti-viral Antidiabetic, Anti-hypertension
Laminaran 	*C. barbata* [36]	Antioxidant, antibacterial, wound healing

Table 1. *Cont.*

Compound Class and Name	Species	Biological Activity
	Others	
Isololiolide 	*C. tamariscifolia* [37]	Anticancer
Meroterpenoids (several variations for chemical structure)	*C. usneoides* [38] *Cystoseira abies-marina* [25] *C. tamariscifolia* [25]	Anti-inflammatory, antioxidant, anticancer Cytotoxic Antifungal, antibacterial
Diterpenes (several variations for chemical structure)	*C. myrica* [39]	Cytotoxic

These two biological activities are of great importance for the prevention and treatment of several diseases, some in the field of neurology. Among the increasingly prevalent neurodegenerative diseases in the world, Alzheimer's and Parkinson's diseases stand out as two of the most debilitating ones [40], presenting neuroinflammation and oxidative stress as hallmarks [41], and for which there is still no treatment, which means that prevention is a key point. Alzheimer's diseases is the most common neurodegenerative disorder, occurring mostly in people over 65 years old, mainly in women [42]. It is estimated that in the United States there are about 13.8 million people who suffer from dementia, with Alzheimer's being the most frequent disease of dementia [42]. These types of illnesses make patients very weak, where caregivers are usually needed both at the hospital level and at home, and such care incurs high costs. This disease is characterized by neuron loss, glia cell proliferation and neurofibrillary tangles (NFT) accumulation. Alzheimer's has as hallmarks the accumulation of the beta-amyloid protein outside the neurons and twisted strands of the tau protein inside the neurons, that consequently provokes a progressive memory loss [42]. Parkinson's disease, on the other hand, is a chronic and progressive neurodegenerative disorder caused by various risk factors and genetic mutations. This disease is normally characterized by the loss of dopaminergic cells in the substantia nigra pars compacta with consequent decreased motor function, which leads to resting tremor, bradykinesia and muscular rigidity, also due to the presence of Lewy bodies (cytoplasmic aggregates) that play a role in the neurodegeneration [43].

Although the use of natural compounds of marine origin can be useful in the treatment and/or prevention of certain neurological diseases, it is often difficult to ensure the adequate amount of the desired compound reaches the target site. In this way, the biological activity of macroalgae can be potentiated by nanocarriers that deliver the algal extracts or derived compounds to the desired cells, tissues or organs. Moreover, the properties of some nanoparticles (NPs) can have synergetic activities with the algal extracts, namely anti-inflammatory, antioxidant, antifungal and antibacterial properties. Nanotechnology has grown to the point where its applications reach several areas such as the food industry and agriculture, to the processing and packaging of food products, cosmetics, textile industry, pharmaceutical industry and medicine [44–47]. In this way, applications of NPs in medicine, diagnosis, imaging and disease therapy will also be addressed. One of the most significant applications of NPs is in drug delivery [48]. These revolutionary carriers come without the aid of conventional drug administration, since it constitutes a major problem in the performance of the drug at target site, especially in the brain.

An important step in the use of NPs is the knowledge of their risks, benefits and toxicity. For that, zebrafish is considered a good biological model for the in vivo tests of neurotoxicity and bioactivity of NPs, since it present a neuronal system similar to that of humans [49], thus allowing to obtain more reliable results. In vivo testing in zebrafish is a very important step before translating any intervention into humans.

This review paper may be a valuable tool for researchers working in the exploitation of brown macroalgae, namely species belonging to the *Cystoseira* genus, with special focus on compounds responsible for anti-inflammatory and anti-oxidant activities. Furthermore, we reviewed the literature concerning the use of nanocarriers to potentiate the controlled delivery of bioactive compounds for the prevention and treatment of neurodegenerative diseases. The search methodology on PubMed search engine focused on the keywords "*Cystoseira*", "bioactivity", "neurodegenerative diseases" and finally "zebrafish".

2. Bioactive Compounds Present in *Cystoseira* Extracts for Neurodegenerative Disease Management

Inflammation is a physiological process in response to invading pathogens or endogenous signals. This process is initiated by the immune cell's migration from blood vessels and the production of mediators. At this stage, inflammatory cells are recruited and the secretion of greater amounts of growth factors, chemokines, cytokines, and secondary metabolites to eliminate invading pathogens occurs [50–52]. Nitric oxide (NO) is as an example of such an inflammatory mediator, being a highly permeable molecule that quickly diffuses through membranes [53,54]. If all these mediators are produced in appropriate amounts, the inflammatory response is helpful. However, deregulation of cytokine expression, especially tumor necrosis factor α (TNF-α), has a role in chronic and autoimmune inflammatory diseases [25,37]. Inflammation is also often associated with oxidative stress, which is accompanied with the production and release of reactive oxygen species (ROS), namely hydrogen peroxide, hydroxyl, superoxide and NO radicals. In this way, ROS overproduction is harmful to body homeostasis, since they can easily react with proteins, lipids, or DNA, causing oxidative damage. In addition, they can be responsible for an inflammatory state and associated to neurodegenerative disorders [55], among others pathogenesis such as coronary heart disease, atherosclerosis, cancer and aging [56].

In this way, compounds that have anti-inflammatory or antioxidant activities can be used in pharmacology, as potential sources in the food and cosmetics industry. Additionally, and bearing in mind that neuroinflammation and oxidative stress are hallmarks of neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases [41], these compounds can also be used as potential sources in medicine, to treat these conditions.

2.1. Phlorotannins

Among marine algae, species of the Phaeophyceae contain the highest levels of phenolic compounds. Of the phenolic compounds present in *Cystoseira*, the group of tannins reveals the strongest bioactivity [57]. They are considered one of the most widely distributed types of natural plant products and are classified into distinct groups, according to their structure. Phlorotannins are restricted to brown algae and can also be divided into different hydrophilic compound groups (fucols, phlorethols, fucophlorethols, fuhalols, isofuhalols and eckols), with very different molecular weights, ranging from 126 to 650 kDa [11,58]. However, it was found that its percentage in algae is quite variable, depending on factors such as the size of the alga, its age, the season, the light intensity and also the salinity and temperature of the water [2,27]. This may be reflected in differences of anti-inflammatory activity since the potential to reduce inflammatory mediators will be proportional to the content of phlorotannins [59,60]. Over the years, several biological properties associated with phlorotannins have been discovered, highlighting their capability to absorb UV radiation and avoiding the consequent photo-oxidative stress, but also the antioxidant, antimicrobial, antiallergic and anti-inflammatory properties [61–63]. The anti-inflammatory activity in vitro of purified extracts of phlorotannins obtained from three different *Cystoseira* species (*C. usneoides*, *C. nodicaulis* and *C. tamariscifolia*—currently designated as *Gongolaria usneoides*, *Gongolaria nodicaulis* and *Ericaria selaginoides*, respectively)—was demonstrated via an inhibitory effect on the production of NO by RAW 264.7 macrophage cells stimulated by lipopolysaccharides (LPS) [60]. LPS is one of the main components of the membrane of Gram-negative bacteria [64] capable of promoting the secretion of pro-inflammatory

cytokines [65] and NO [66]. After the incubation period, the phlorotannins extracts of the three *Cystoseira* species were able to considerably reduce NO levels produced by cells, especially *C. tamariscifolia* extract which presented the greatest anti-inflammatory potential [60]. Furthermore, the antioxidant activity of purified phlorotannins extracts was also confirmed in the same *Cystoseira* species enunciated above [20]. Ferreres and collaborators found that these species could eliminate superoxide radicals, avoiding lipid peroxidation.

Considering these two properties, it would be interesting to use phlorotannins for the treatment of neurodegenerative diseases, and there are already some studies developed for this application. In two different studies, both Ferreres [20] and Barbosa [67] found that these compounds had anti-inflammatory and neuroprotective properties that could slow down the progression of neurodegenerative diseases. Furthermore, it was also proved that *Cystoseira* species contain compounds that allow it to protect neurons from oxidative stress through DPPH (2,2-diphenyl-1-picrylhydrazyl) capture activity and increasing in SH-SY5Y cell viability after exposure to H_2O_2 [68], thus evidencing a correlation between antioxidant activity and phenolic content.

2.2. Fatty Acids

Fatty acids (FA) have been extensively studied, not only for their significant anti-inflammatory effect but, particularly, for their anti-tumor and antimicrobial potential. They are composed of an aliphatic chain and a carboxyl group and can be extracted from *Cystoseira* [27,30,69,70]. FA can be classified as saturated fatty acids (SFA) when they have no double bond between carbons, or as unsaturated in cases where they have at least one carbon-carbon double bond. FA ω-3 and ω-9 have an excellent anti-inflammatory effect. Regarding FA ω-3, their activity is due to precursors of anti-inflammatory molecules, namely resolvins, docosatrienes and protectins, but also to their ability to replace arachidonic acid in cell membranes, which causes a decrease in the production of pro-inflammatory compounds such as prostaglandins E2 (PGE2), thromboxane B2, among other arachidonic acid derivatives [71]. In addition, FA ω-3 inhibits the activity of nuclear factor kappa B (NFκB), which is a transcription factor with a very important role in many inflammatory signaling pathways since it interferes with the production of several cytokines (IL-1, IL-2, IL-6, IL-12, TNF-α). The production of adhesion molecules and chemokines, such as IL-8, monocyte chemoattractant protein 1, among others, is also affected by FA ω-3. Additionally, this fatty acid also inhibits effector enzymes such as iNOS and cyclooxygenase 2 (COX-2) [69,72]. On the other hand, and although less studied for this purpose, extracts with FA ω 9 demonstrated an inhibitory capacity of COX-2 enzyme and NO production, as well as pro-inflammatory cytokines (TNF-α and IL-1β) [73]. Furthermore, they stimulate the production of anti-inflammatory cytokines and inhibit the migration and accumulation of neutrophils and macrophages at the infection site [74]. Fatty acids can also be part of human diet, providing neuroprotection and reducing the risk of incident Alzheimer's disease [75,76]. Andrade [27] proved that fatty acids extracted from different species of *Cystoseira* were able to scavenge DPPH and inhibit enzymes associated with the formation of β-amyloid plaques, the main cause of Alzheimer's disease.

2.3. Sterols

Sterols, which belong to the steroids family, are constituted by a tetracyclic structure and are abundant in species belonging to the genus *Cystoseira* [27]. Several health benefits have been attributed to these compounds as they were able to reduce low density lipoproteins (LDL) and, consequently, were associated with a reduction in the risk of cardiovascular diseases, representing the principal cause of death globally, according to the world health organization [77]. Phytosterols have been studied for their potential to suppress the secretion of inflammatory factors, such as TNF-α, IL-1β, IL-6, IL-8, NO and ROS. In addition, a partial inhibitory effect of the transcription factor NF-κB on macrophages and the ability to inhibit the expression of the enzymes COX-2 and iNOS have been reported [78,79].

Neuroprotective functions of sterols extracted from marine organisms have already been confirmed [27,80], although there are few studies with seaweed extracts.

2.4. Fucoidans

Fucoidans form a group of sulfated polysaccharides present in brown algae and are generally linear, composed mainly of repeated units of sulfated fucoses in C-2 and/or C-4 with α-(1–3) and/or α-(1–4) bonds [81]. The chemical composition varies according to the species of algae and can vary within the same species [33].

The anti-inflammatory and antioxidant activities of fucoidan extracts from three Mediterranean species of the genus *Cystoseira* (*C. sedoides*, *C. compressa* and *C. crinite* (currently designated as *Ericaria crinite*) was demonstrated in vivo [33]. An edema was induced in Wistar rats, and the tested extracts exhibited a significant anti-inflammatory activity with the edema inhibition percentage above 50%. This sulfated polysaccharide has also proved to reduce the inflammatory response in BV2 microglia, and the generation of ROS and inflammatory cytokines in primary microglia [82,83].

3. Macroalgae Compounds Delivery Optimization by Nanoparticles

As discussed above, macroalgal compounds have excellent bioactivity against some neurodegenerative diseases. However, in many situations, it is not possible to deliver the bioactive constituents to the desired location. Considering that, one of the objectives of using NPs in nanomedicine is to transport substances, namely bioactive compounds to the targeted tissues and cells, the combination of macroalgae and NPs may potentiate their therapeutic efficiency and reduce even further eventual toxicity of the transported substances [48]. Drug delivery systems can overcome some of the biggest problems in drug administration such as lack of specificity, low biodistribution, reduced efficiency, lack of selectivity and side effects (Figure 3). With enormous potential as drug carriers, the small size of NPs (1 to 100 nm) confers them unique properties such as their surface/area ratio [84]. Additionally, their different shapes, sizes and compositions, have shown enormous importance in medicine, having applicability in the diagnosis and therapy of diseases [85]. They possess advantages in reducing the concentration of drugs, reducing toxicity, improving solubility, providing protection of drugs during circulation and preventing degradation [86–89].

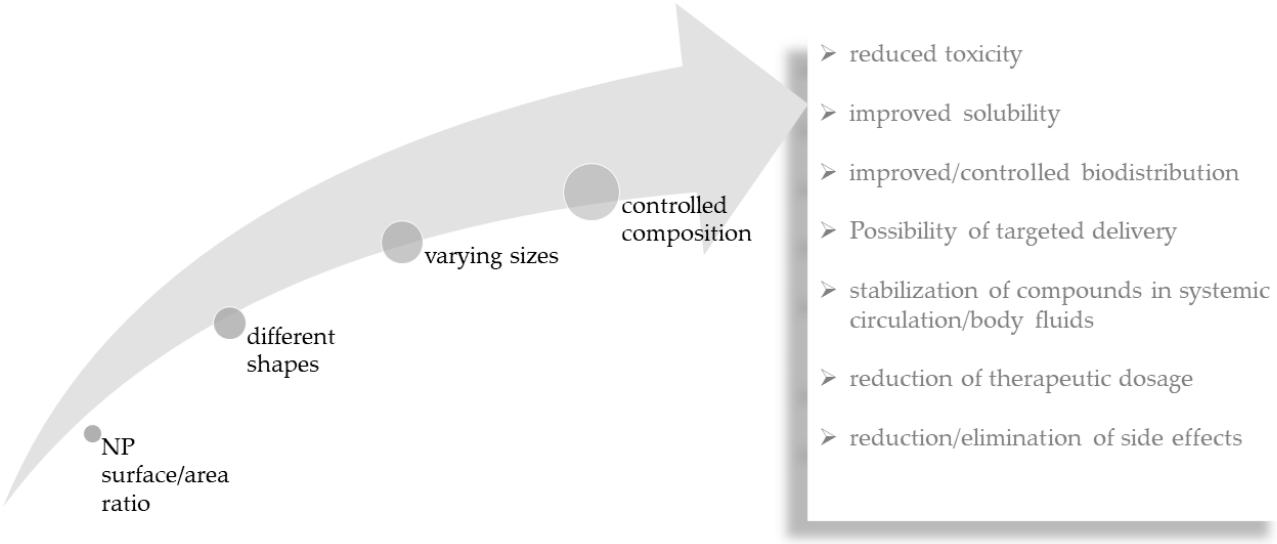


Figure 3. Relationship between important nanoparticle (NP) features and advantages of nanoparticle-mediated delivery of compounds.

NPs are often divided into two groups: organic and inorganic nanocarriers. Inorganic NPs incorporate mostly metallic particles. In this group we can evidence that some of the

most common ones consist in carbon nanotubes, gold, silver and magnetic NPs, among others. Micelles, liposomes, solid lipid NPs and dendrimers fit the organic type of carriers. NPs are very versatile and have numerous applications in the field of biomedicine, which are listed in Table 2 and Figure 4.

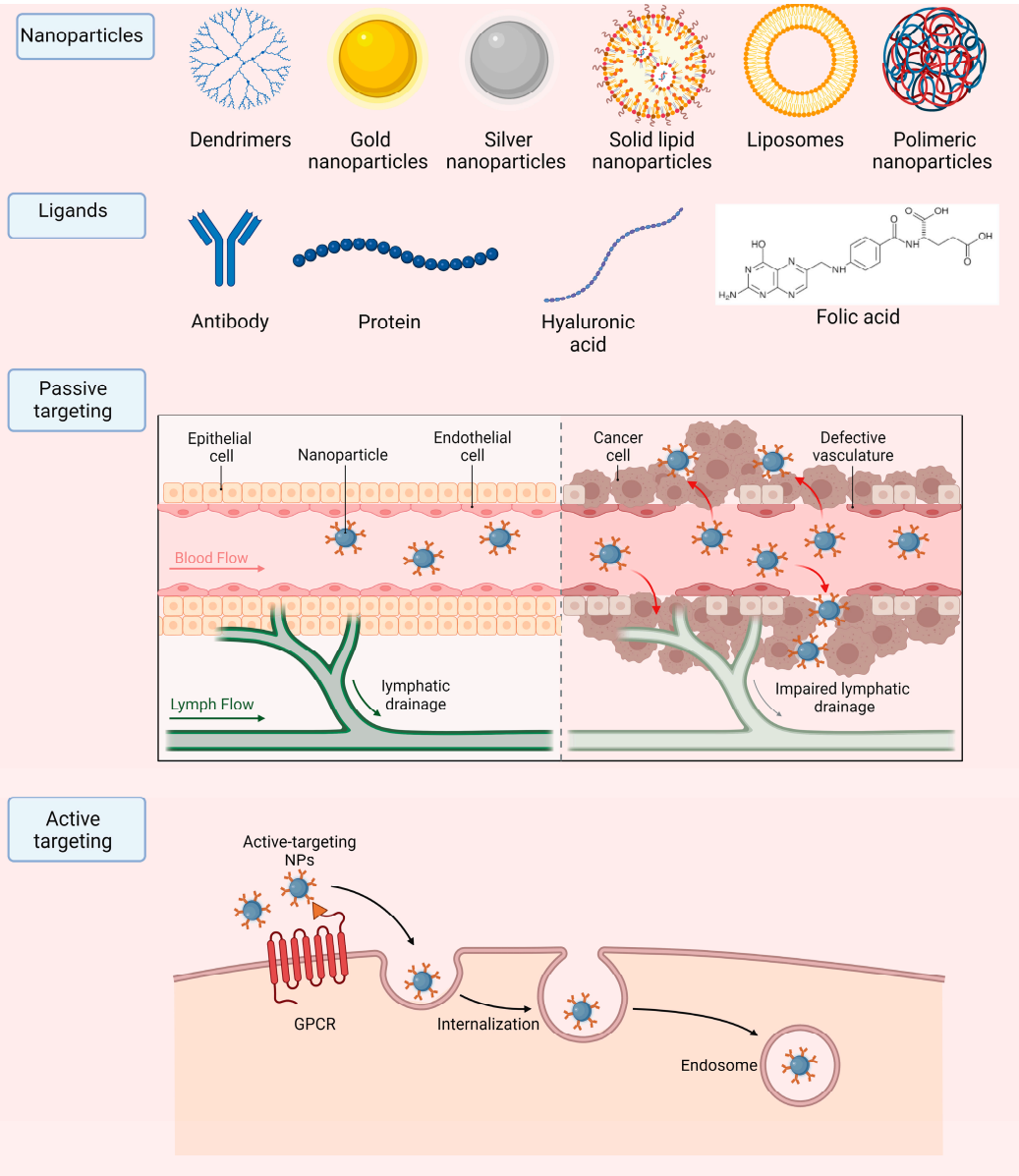


Figure 4. Main nanoparticle types and strategies to achieve accumulation in target tissues, by passive or active (including ligand-mediated) targeting.

NPs can be directed to the desired local of the treatment either by passive or active targeting. Passive targeting is often associated with the treatment of various types of tumors. This is due to the irregularities that the vascularity around tumors present, having various leakages such as leaky vasculature and defective lymphatic drainage due to the rapid and uncontrolled growth needed to supplement cancer cells, for the growth of the tumor. One can use NPs with a small size that can accumulate specifically in these leakage sites around the tumor and reach their desired therapeutic site [90]. Although this method can be simple and efficient, active targeting is normally preferred since there is no efficient passive method to deliver molecules to other diseases in other parts of the human body. Active targeting consists in the functionalization of the surface of nanoparticles with molecules that are

specifically recognized by cells in the local of the treatment. Moreover, this functionalization can improve the nanoparticles pharmacokinetic and pharmacodynamic properties [91]. These can include various types of antibodies, folic acid, proteins, and hyaluronic acid, among others (Figure 4).

Interestingly, algae extracts are often utilized not only as compounds that are encapsulated in NPs for the treatment of various diseases, but also as stabilizers and catalyzers for metallic NPs production [92,93]. In addition, some studies combine the use of chitosan-based NPs with commercially acquired bioactive compounds, such as fucoidan, developing thus chitosan/fucoidan NPs for the delivery of chemicals in breast cancer treatment and nerve regeneration [94,95]. Regarding the last three years, we can find some studies based on fucoidan-based nanoparticles, which allow the enhancement of fucoidan biological activity. In addition, it has already been demonstrated that the synthesis of NPs is promoted by the molecular weight, as well as the structure of fucoidan [96]. Furthermore, the combination of this natural compound with others, or even drugs, may result in the enhancement of the desired effect. As example, Xu Zhang and colleagues have developed fucoidan-coated mesoporous silica NPs to deliver curcumin to the colon tumor site microenvironment [97], which is a polyphenol compound that has also been shown to have neuroprotective effects [98]. The green synthesis of NPs is also a very current topic, which makes it possible to take full advantage of the therapeutic properties, avoiding the use of highly toxic materials and proving to be an ecologically correct and low-cost technique [99,100]. A much smaller number of studies that deliver compounds using NPs are found. Min-Hsuan Tsou and colleagues have developed mesoporous silica NPs to deliver fucoidan to A549 cells [101], and, in line with the main application that we review in this article, PLGA-PEG NPs were developed by Mengxiang Yang and colleagues to facilitate anti-Alzheimer's effects of fucoxanthin [102].

Table 2. Examples of nanosystem types, their characteristics and applications in biomedicine.

Type of Nanosystem	Size (nm)	Characteristics	Applications	Refs.
Carbon nanotubes	0.5–3 nm diameter and 20–1000 nm length	Formed from graphene sheets rolled in cylindrical shape. Classified in single-walled nanotubes (SWNTs) and multiwalled nanotubes (MWNTs).	Cancer photothermal therapy; tissue engineering	[103]
Magnetic nanoparticles	5–50 nm	Normally constituted by iron, cobalt and nickel, with magnetic susceptibility.	Detecting amyloid plaques and biomarkers in Alzheimer's disease; colon cancer cell theragnostic; treatment of gastric cancer	[104–106]
Silver nanoparticles	10–500 nm	Unique optical, electrical and thermal properties.	Antimicrobial properties; anti-proliferative activity; infections of the central nervous system treatment	[39,107,108]
Gold nanoparticles	5–400 nm	Unique optoelectronic properties.	X-ray contrast agent; Alzheimer's disease diagnostic; HIV diagnostic; tuberculosis diagnostic; angiogenesis therapy; antibacterial therapy	[48,109–113]

Table 2. *Cont.*

Type of Nanosystem	Size (nm)	Characteristics	Applications	Refs.
Polymeric nanoparticles	10–1000 nm	Solid and spherical particles formed from natural or synthetic polymers. Can be organized into nanospheres and nanocapsules.	Uveitis treatment; treatment of chronic obstructive pulmonary disease; neuroinflammation in Parkinson's diseases; therapeutic agents for peripheral arterial disease; treatment of periodontal disease	[114–117]
Liposomes	100–200 nm	Spherical vesicles consisting of phospholipids and other components. Composed of successive bilayers that close on themselves, originating vesicles.	Cancer immunotherapy; antimicrobial therapy; respiratory disorders treatment; arthritis therapy; treatment of Parkinson's diseases; ocular delivery drugs	[118–120]
Dendrimers	Up to 10 nm	Polymeric macromolecules in the form of a branched tree. Three fundamental components: the central nucleus, the lower layer where branches linked to the nucleus appear polymerization and the outside region.	Treatment of osteoarthritis; cancer therapy; corneal tissue engineering; antiamyloidogenic agent	[121–123]
Micelles	10–100 nm	Lipid aggregates in a globular form. Amphipathic character of these molecules makes them have a natural tendency to aggregate when exposed to water.	Breast cancer therapy; cervical cancer chemotherapy	[124,125]
Solid lipid nanoparticles	50–1000 nm	Composed by solid lipids and surfactants. The surfactants are composed by hydrophilic head and a lipophilic tail.	Glioblastoma treatment; rheumatoid arthritis therapy; topical treatment of pityriasis versicol	[126–128]

Nevertheless, with the growing use of NPs and their application in the biomedical field, which implies exposure and incorporation into the human body, the need for studies to assess their toxicity effects emerges.

Nanoparticle Toxicity and Bioactivity Screening for Neurodegenerative Diseases

Nanotoxicology is the science that studies the toxicity of nanotechnology products, and their interactions in the body, assessing the risks and benefits [129]. This toxicity depends on nanoparticle physicochemical properties, such as composition, size, surface area and charge, among others [130]. These properties also control what will happen to the nanoparticles in vivo and their degradability after excretion from the organism and once in the environment. So, nanomaterial characterization is essential and usually achieved by chromatography techniques, microscopy techniques, and spectroscopic techniques. Some of the techniques are energy dispersive X-ray spectroscopy (EDS); scanning electron microscopy (SEM); dynamic light scattering (DLS); differential scanning microscopy (DSC);

inverse gas chromatography (IGC); atomic absorption spectroscopy (AAS), inductively coupled plasma spectroscopy (ICPS); transmission electron microscopy (TEM); atomic force microscopy (AFM); zeta potential and UV-visible spectroscopy and Fourier-transformed infrared spectroscopy (FTIR) [131]. These analytical methods are therefore very important to predict their behavior in storage and during their intended application (in vitro, in vivo, ex vivo) [130]. An upcoming area in recent years implies the use of in silico methods, which will certainly become more potent and useful in their predictive power with the assistance of artificial intelligence.

Regarding nanomaterial degradation, the mechanistic studies will greatly depend on whether it is a natural or synthetic material [130]. The degradation pathways that may be analyzed are: (1) hydrolysis of water-sensitive groups, (2) oxidative degradation, (3) photodegradation, and (4) enzymatic degradation. This assessment will provide crucial understanding on nanoparticle stability, safety, efficacy and potential side effects.

One of the major problems associated with the treatment of neurodegenerative diseases is the blood-brain-barrier (BBB), which separates systemic circulation and central nervous system through highly selective permeability, not allowing the drugs to freely reach and act on the brain [132]. One of the very advantageous characteristics of some NPs is the ability to cross the BBB, revealing a non-invasive alternative path due to their favorable characteristics such as reduced size and low hydrophilicity [133]. Additionally, beyond the good ability to cross the BBB, the nanocarriers must comply some other important parameters: good targeting to the target site, reduced toxicity and high circulation time [134].

A toxicity assessment can be performed in vitro, using cell culture, ex vivo, using cells and tissues collected from humans, or in vivo, using animal models [130]. The in vitro models are simpler biological systems that allow a quick assessment of the effects of NPs. They are low cost and easy to manipulate, making it easy to control and interpret the results. An advantage of these models is that they do not present such ethical restrictions as for in vivo studies [129]. For the in vitro study of the neurotoxicity of NPs, specific brain cell types can be used, namely glial cells, BBB and blood-blood barrier cells and neurons with or without myelin sheath [135]. There are several in vitro techniques usually used to study drug uptake in central nervous system, such as in situ brain perfusion, microdialysis, intravenous injection, brain uptake index, determination of the blood/plasma ratio, cerebrospinal fluid sampling and quantitative autoradiography [136]. The most common nanotoxicity parameter assessed in the brain is related to oxidative stress, resulting from the intense production of ROS, induction of apoptosis that leads to neurons death and neuronal inflammation due to the release and circulation of pro-inflammatory cytokines [137]. However, 2D cell cultures have an important limitation: they do not mimic the 3D microenvironment to which tissues are exposed in organisms. In living organisms, the cells are arranged in a 3D environment, which provide an adequate metabolism, cell-cell and matrix-cell interactions and responses to physiological signals or injuries [38,138,139]. In addition, there are some important factors in assessing the toxicity of NPs that can only be correctly evaluated through in vivo studies, such as biodistribution, biodegradability, route of administration, occurrence of developmental damage, long-term disposition, and activation of the immune system. The correlation between the results of in vitro and in vivo studies of nanotoxicity is scarce, as well as in the correlation between studies in cells and animals [140].

For in vivo toxicology studies, one of the most used animal models are rodents, due to their small size, great similarity of their biochemical processes with humans, easy adaptation to life in the laboratory and short time between generations [133]. However, there are some disadvantages, namely that they are more cumbersome, have a higher cost relatively to cell lines and associated ethical issues. Directive 2010/63/EC on the protection of animals for scientific purposes has pushed laboratories in Europe to actively develop alternatives to animal testing or strategies to greatly reduce them. In this way, zebrafish have been singled out by OECD as a good alternative for toxicology [141]. Furthermore, zebrafish have a cardiovascular, nervous and digestive systems very similar to those of mammals, and signaling pathways present a high level of genomic homology comparing

with humans or other mammals [49,142], being possible to evaluate many parameters in preparation for mammal (and human) testing. Most of the toxicity tests are generally carried out in zebrafish embryos until 120 h post-fertilization, which are legally considered as non-animal model, thus not requiring additional ethical permits [143]. This organism has a small size which promotes an easier handling, a very high reproducibility making possible a weekly procedure repetition and a quick development that leaves to faster experiments on zebrafish. At the embryo stage, this organism provides an easier collection of multiple data points by using high-quality imaging. In addition, a low volume of solutions is required, with the possibility of testing various conditions at each experiment. The embryos are transparent which allows to observe the cells since early larval stages and are generally used to assess the development of acute toxicity, while adult fish are used to study chronic toxicity, as well as transport and bioaccumulation of NPs [144,145].

Neurodegenerative diseases such as familial Alzheimer's disease can be originated through mutations, leading to characteristic hallmarks of this pathology in zebrafish [146–148], through addition of various acids to cause oxidative stress [149], which is known to result from a cellular redox state originated inside the cells by complex redox reactions. Oxidative stress causes DNA damage, protein carboxylation, lipid oxidation, and eventually cell death, a mechanism that causes the progression of human neurodegenerative diseases [150]. The induction of phosphorylation of the Tau protein [151], the accumulation of β-amyloid peptides [134], or the formation of neurofibrillary tangles [152], can also be stimulated inducing neuroinflammation, another hallmark of Alzheimer's disease (Figure 5. Other neurodegenerative diseases such as Parkinsonism may also be induced in zebrafish by exposure to certain toxins or chemicals, such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) [153] which leads to loss of dopaminergic neurons in the midbrain with resulting Parkinsonian symptoms.

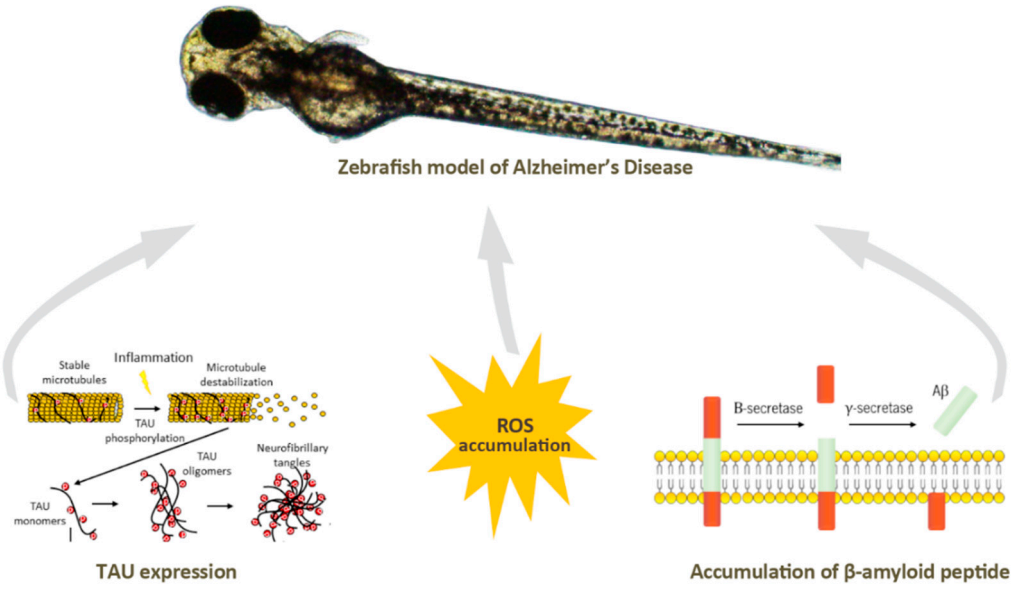


Figure 5. The main hallmarks of Alzheimer's disease can be mimicked in zebrafish model, namely the induction of TAU expression, and ROS or β-amyloid peptide accumulation.

Zebrafish disease models are thus upcoming as valid, interesting alternatives for screening both toxicity and bioactivity of new therapeutic compounds and/or formulations currently being developed to tackle neurodegenerative diseases.

4. Conclusions and Future Perspectives

It is recognized that bioactive compounds derived from macroalgae with neuroprotective activity are mostly associated with brown algae (57.6%), followed by red (28.3%) and green (14.1%) algae [154]. Many studies have been performed searching for molecules

with neuroprotective effects by acting against oxidative stress, reduction of Aβ-induced cell death, inhibition of pro-inflammatory cytokines production, among others (reviewed in [155]). Additionally, some studies can be found in the literature combining the use of NPs with bioactive compounds, such as fucoidan, most of the time commercially acquired. However, to the best of our knowledge, there is lacking information on the use of NPs for delivery of natural compounds extracted from brown algae, namely *Cystoseira* spp., alone or in combination with other chemicals, for the prevention and treatment of neurodegenerative diseases. We strongly believe that some of the compounds described in this review present biological activities that can help to reduce neuroinflammation and oxidative stress, both hallmarks of these pathologies. Moreover, the combination of these bioactive compounds with nanotechnology will reduce any associated toxicity or side effects and improve their high circulation time. Furthermore, the use of NPs will also enhance the desired effect by improving the ability of the compounds to reach the target site by crossing the BBB. However, and despite nanotechnology being a solution to overcome some problems in drug delivery, as already mentioned above, this physical barrier remains one of the biggest roadblocks in accelerating of clinical trials, since in vivo, a large percentage of studies fail to show clear therapeutic efficacy.

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