Bioactive Compounds in Cystoseira Extracts for Neurodegenerative Disorders

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In the last decades, marine macroalgae have drawn attention mainly due to their bioactive components, which have a wide range of biological activities, such as anti-inflammatory and antioxidant potential. Phlorotannins, fatty acids, sterols and carbohydrates are some of the compounds present in brown algae and *Cystoseira* extracts responsible for such activities, representing enormous importance for the management of neurodegenerative diseases, such as Alzheimer and Parkinson's, with neuroinflammation and oxidative stress as hallmarks.

brown algae | Cystoseira | antioxidant activity | anti-inflammatory activity | neurodegenerative diseases

1. Phlorotannins

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 [1]. Bearing in mind that neuroinflammation and oxidative stress are hallmarks of neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases [2], phlorotannins, fatty acids, sterols and fucoidans compounds can be used as potential sources in medicine, to treat these conditions.

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 [3]. 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 [4][5]. 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][6]. 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 [7][8]. 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 [9][10][11]. 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) [8]. LPS is one of the main components of the membrane of Gram-negative bacteria [12] capable of promoting the secretion of pro-inflammatory cytokines [13] and NO [14]. 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 [8]. Furthermore, the antioxidant activity of purified phlorotannins extracts was also confirmed in the same *Cystoseira* species enunciated above [15]. 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 [15] and Barbosa [16] 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 [17], thus evidencing a correlation between antioxidant activity and phenolic content.

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* [6][18][19][20]. 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 [21]. 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) [19][22]. 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) [23]. Furthermore, they stimulate the production of anti-inflammatory cytokines and inhibit the migration and accumulation of neutrophils and macrophages at the infection site [24]. Fatty acids can also be part of human diet, providing neuroprotection and reducing the risk of incident Alzheimer's disease [25][26]. Andrade [6] 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.

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* [6]. 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 [27]. 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 [28][29]. Neuroprotective functions of sterols extracted from marine organisms have already been confirmed [6][30], although there are few studies with seaweed extracts.

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 [31]. The chemical composition varies according to the species of algae and can vary within the same species [32].

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 [32]. 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 [33].

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