Fucoidan - A valuable source from the ocean to pharmaceutical

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Abstract

Fucoidan is one of the most relevant polysaccharides synthesized by Phaeophyceae class (brown seaweeds). Previous research reveals widespread fucoidan bioactivity properties, like antitumoral, anti-inflammatory, antithrombotic or immunomodulatory.

Fucoidan extraction and purification methods are the current challenge, in order to obtain this biomolecule that presents different conformations within several seaweed species. The main goal of this mini review is to give an overview of fucoidan pharmaceutical applications research and to support the potential of this biomolecule to be explored by science and industry.

Introduction

Nowadays, the discovery of new biomolecules with bioactivities derived from natural sources is gaining more attention among the scientific community but it is important to promote eco-sustainability before the industry exploitation [1].

The relevance of marine resources, such as seaweeds, as a source of these bioactive compounds is attracting interest due to seaweeds’ fast growth rate, the myriad of chemical substances produced and its widespread applications.

The high variability of compounds synthesized by seaweeds is an outcome of the adverse conditions to which they are exposed in their natural habitats [2].

Macroalgae are categorized into the phylum Chlorophyta, Rhodophyta and Ochrophyta (class Phaeophyceae), accordingly to its taxonomy. Brown seaweeds (Phaeophyceae) are a valuable source of polysaccharides, such as fucoidan, alginate, cellulose, laminarin and mannitol [3]. Thus, the composition and quantity of this biomolecules range according to the species and can fluctuate seasonally [4].

From the chemical point of view, fucoidans are complex polysaccharides [5,6] and their bioactive properties are attracting interest due to their immunomodulation, anti-inflammatory, antitumor and antioxidant activities [7-9].

The main goal of this short review is to provide a general overview of fucoidan characterization and its pharmaceutical applications, including the most recent discoveries.

Fucoidan characterization

Seaweeds synthesize several polysaccharides with different conformations as main components of their cell wall [4,10]. Those which belong to class Phaeophyceae, particularly, synthesize fucoidan.

Fucoidan is a sulfated polysaccharide class that has the particularity of presenting a skeleton rich in fucose and composed by other sugars that differ between species (e.g.: mannose, galactose, glucose, xylose) (Figure 1) [11,12]. The first studies related to fucoidan chemical structure demonstrated that it was mainly a bone of (1→2) linked 4-O-sulphated fucopyranose residues. Yet, 3- linked fucose with 4-sulphated groups were afterwards described to be

![Figure 1. Idealized structure of the chemical units of Fucoidan](attachment://figure1.png)

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present around the fucose residues. Furthermore, it was determined to contain branches every 2-3 fucose residues [13].

Nevertheless, fucoidan represents a heterogeneous group of carbohydrates, comprised by galactose, mannose, xylose, uronic acid, sulphated and acetyl groups [1].

Seaweed derived fucoidans are heterogenic due to variations in the content of carbohydrate units (L-fucopyranose and non-fucose) and non-carbohydrate groups (mainly sulfate and acetyl). Thus, the accurate analysis of its backbone structures and the precise determination of the location of minor structural elements is a challenge. The position of sulfate groups is important to the biological activities of sulfated polysaccharides. The methods of determining the sulfate position include infrared spectroscopy, desulfation, stability of sulfate esters to alkali and methylation analysis [11].

Therefore, research of fucoidan backbones and branches is the main targets of structural analysis [6].

Fucoidan is a secondary metabolite, in which its structural differences allow the differentiation between seaweed species [14].

For instance, structural differences affect fucoidan bioactivity such as fucoidan acetylation degree [14,15], uronic acid and glucuronic acid concentration [3].

Monosaccharide backbone composition and other structural characteristics of the principal polymer chain (such as branching) are also relevant [16]. Fucoidan could be extracted and purified by several methodologies which influence its bioactivity [11,17]. Furthermore, during fucoidan extraction process, can occur the co-extraction of other compounds such as laminarin, alganic acid, proteins, terpenoids and polyphenols [18-21]. For this reason, the correct selection of algal species is a decisive factor to obtain fucoidan with a high yield of purity [22,23].

The physicochemical properties of fucoidan are ideal for an emulsifier agent because fucoidan tends to form viscous gel without gelling. Thus, fucoidan has been validated to have higher emulsification indexes than carboxymethyl cellulose materials, particularly hydrocarbons. In addition, the capacity of fucoidan to form and stabilize emulsions is specific for certain hydrophobic compounds [24].

Low-molecular weight polysaccharides as fucoidan have a higher solubility, which contributes to their penetration into the cell [25].

The dynamic viscoelasticity of the fucoidan goes down linearly with rise in temperature. Fucoidan may flow under shearing and angular forces in aqueous solution including at high concentration (1.5%) indicating that fucoidan properties are available for adhesion and connection on the surface of the materials. High values of the dynamic viscoelasticity in a large range of pH show that fucoidan molecules are stable in salts, acid and alkaline conditions [26].

This denotes that polymer of fucoidan is appropriate for commercial use in stabilizing, thickening and water holding agents in the food market, cosmetic and several more industries, for example, to stabilize protein oil-in-water emulsions [24,26].

The anti-adhesion feature of fucoidans is being utilized for the upgrade of oral hygiene and dental caries prevention [27].

In Japan fucoidan is commercialized as a component of drinks and tablets utilized as a nutritional supplement being manufactured on an industrial scale [26].

Pharmaceutical applications

Historically, seaweeds have a traditional usage, especially in Asian countries, as herbal medicine for the treatment of tumors, neurodegenerative diseases, urinary problems or gastrointestinal issues [2,28]. Brown seaweeds containing fucoidan are extensively used as part of the regular diet in East Asia, particularly in Japan, China, and Korea [29]. Despite their use in traditional Chinese and Japanese folk medicines, only in the current years they were commercialized as nutritional supplements and pharmaceutical products. They also began to be more studied and their compounds isolated [30].

Recently, fucoidan has been applied industrially in different sectors, such as cosmetics, dietary supplements and animal feeding supplements [8]. Still, fucoidan effects on terrestrial and aquatic animals have not been widely researched. In most of these studies was applied fucoidan crude extract, that can include non-fucoidan components (such as polyphenols and laminaran) with bioactivities which may interfere with the evaluation of bioactivities properties [5,7,8,29,31]. Table 1 shows several studies that point different seaweeds as a source of crude bioactive fucoidan and indicates that the average yield of extraction is around 1-20% [7]. It may therefore be necessary to consider that fucoidan diverse extraction and purification methodologies will present differences in their efficiency and yield [32].

There are new fucoidan based pharmaceutical products being developed to cardiovascular disease treatment and evaluated for its human safety before clinical trial (phase I) [33].

Nowadays, fucoidan is applied in some topical treatments and in other available dietary supplements. Furthermore, to evaluate the relevant fucoidan consumption and to aid in production, new measuring techniques have been developed. Due to the need of alternative approaches to antibiotic utilization in the food chain, microbiome modulation and anti-pathogenic effect are hopeful applications for fucoidans [9].

In vitro and in vivo tests were performed and confirmed antitumoral properties in fucoidans and an anti-metastatic effect in the development of cancer [34-39]. Nevertheless, the comparison of the available data is complex, due to the heterogeneity of these intricate polysaccharides, the strong influence of collecting and processing conditions, and the lack of tests with standardized purified products [38]. However, immune modulation is one of the most promising areas for the anticancer efficacy of fucoidan [39-41].

Fucoidan biological activities are wide, ranging from anticoagulant and anti-inflammatory, to antiviral, hepatoprotective and neuroprotective [8,42,43].

Recent studies confirm the potential of fucoidan in tissue and bone engineering. Even in low concentrations, it could induce osteoblasts differentiation from stem cells. For instance, regenerative property of fucoidan is associated with its content of L-fucose and with the sulfate ester group in its polysaccharide skeleton [44-46].

Conclusion

It is important to consider that fucoidan yield falls within the selected extraction and purification methodologies. It is also necessary to consider methods suitable for scale-up, considering the costs, safety and its sustainability.

In future prospection, industrial fucoidan application will pass by the research of extraction methods and purification techniques that
allow chemical structure stability. Fucoidan is a promising natural compound targeted by the biomedical and pharmaceutical industries because of its promising therapeutic properties. Its low toxicity and wide bioactive components have already been confirmed in several in vitro and in vivo studies."

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Table 1. Bioactive fucoidan dry weight yield of extraction from brown seaweeds (Phaeophyceae)

| Species | DW Yield (%) | Bioactivity | Concentration | Model | Ref. |
|---------|--------------|-------------|---------------|--------|------|
| Cladosiphon sp. | 20 | Anti-inflammatory; Anti-cancer | 2% of high-molecular-weight fucoidan; 6 g per day up to 13 months | Rat; Human | [7,47,48] |
| Macrocytis pyrifera | 7.59 | Immunomodulatory | 50 ml of a drink that contained 1.5 g of fucoidan twice daily for 6 months | Human | [32,39,49] |
| Ecklonia radiata | 3-5.4 | n.d. | n.d. | n.d. | [32] |
| Sargassum sarsi | 1.24 | n.d. | n.d. | n.d. | [32] |
| Saccharina latissima | 5.3 | Antitumor | 1–1000 µg/mL | Raji cells (Burkitt lymphoma; B-lineage) | [19,22] |
| Fucus vesiculosus | 2.6 | Neuroprotection; Anticoagulant; Antitumor | Between 12.5 to 100 µg/mL; c: 0-5 µg/ 300 µl/100 µg/mL | PC-12 cells; Normal pooled human plasma; MDA-MB-231 cells | [6,9,22] |
| Fucus serratus | 2.9 | Antitumor; Antithrombin | 100 µg/mL/100 µg/mL | MDA-MB-231 cells; Human platelets | [6,22] |
| Fucus evanescens | 4.5 | Antioxidant; Antithrombin | 1 mg/mL;2 mg/mL; 250 µg/mL/100 µg/mL | ABTS, TAC DPPH assay; Human platelets | [6,22,50] |
| Fucus distichus | n.d | Antithrombin; Antitumor | 1–200 µg/mL | RAW 264.7 cells | [38] |
| Fucus spiralis | n.d | Antifungal Antioxidant | 10 to 250 mg; 0.75 mg/mL | C. lucigenarium, depsipeptide flavis (fungi); DPPH, FRAP | [51,52] |
| Laminaria digitata | 2.2 | Antitumor; Antithrombin | 100 µg/mL/100 µg/mL | Human platelets MDA-MB-231 cells | [6,22] |
| Dictyopteris delicatula | 2.0 | Anticoagulant | 125.5 µg/mL | Normal pooled human plasma | [22] |
| Dictyopteris delicatula | n.d | Anticoagulant, Antioxidant, Antitumor | 100 mg/mL | Citrate-treated normal human plasma; HRSa, Superoxide Radical Scavenging, Ferric Chelating; HeLa cells | [53] |
| Undaria pinnatifida | n.d | Neuroprotection; Anti-inflammatory | Between 12.5 to 100 µg/mL | PC-12 cells | [9] |
| Laminaria japonica | 16 | Antitumor; Antioxidant; Antimicrobial | 0 to 2.0 mg/mL; 0.5 to 8 mg/mL; 250-5 mg/mL 2500 mg | HeLa cells; DPPH, HRSa; Adult horses | [29,54] |
| Durvillaea potatorum | 6.3 | n.d | n.d | n.d | [32] |
| Sargassum sp. | 19 | Antioxidant | 5 mg/mL; 0.25 to 5 mg/mL; 250 µg/mL | TAC, FRAP, HRSa | [24] |
| Ascyphochyphus nodosum | 20 | Antitumor | 3 mg/mL | DPPH | [55] |
| Padina boryana (formerly Padina commersonii) | 8-12 | Anti-inflammatory | 1–200 µg/mL | RAW 264.7 cells | [38] |

*n.d: nothing to declare
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