Fucoidan Structure

Subjects: Pharmacology & Pharmacy

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Fucoidans are complex polysaccharides derived from brown seaweeds. The search for novel and natural bioproduct derived drugs (due to toxicity issues associated with chemotherapeutic drugs) has led to an extensive study of fucoidan, as it has several bioactive characteristics. Among the various bioactivities of fucoidan, antidiabetic and anticancer properties have received extensive attention. However, the elucidation of the fucoidan structure and its biological activity is still vague. In addition, research has suggested that there is a link between diabetes and cancer; however, limited data exist where dual chemotherapeutic efforts are elucidated. This review provides an overview of glucose metabolism, which is the central process involved in the progression of both diseases. Potential therapeutic targets are highlighted and the relevance of fucoidan and its derivatives as a candidate for both cancer and diabetes therapy is shown.

Keywords: antidiabetic ; anticancer ; fucoidan ; glucose metabolism ; natural bioproducts

1. Introduction

Fucoidan is a complex sulphated polysaccharide found mainly in various species of brown seaweeds [1][2]. To date, fucoidans from various brown seaweeds have been partially characterised and studied for their potential bioactivities [3][4]. The bioactivity of fucoidans is linked to their degree of sulphation, monosaccharide composition and molecular weight. Fucoidan composition is varied in different species, although extraction methods and seaweed harvest time may also influence the structural composition of the bio-compound extracted from the same species [5]. Despite the increased interest in brown seaweeds as sources of fucoidan, there are some gaps linking improved yield, composition and structure to bioactivity [6]. Furthermore, to date, there are only a few commercially available fucoidan extracts, limited to those isolated from *Fucus vesiculosus, Macrocystis pyrifera* and *Undaria pinnatifida*, yet a vast biodiversity of unexplored seaweeds exists. Fucoidan's numerous bioactive properties have been noted in both *in vivo* and *in vitro* studies. These bioactivities include: anti-oxidant, anti-coagulant, anti-thrombotic, anti-inflammatory, anti-viral, anti-lipidemic, anti-metastatic, anti-diabetic and anti-cancer activities [7]. Importantly, fucoidan has been reported to exhibit anticancer properties in both *in vivo* and *in vitro* studies. The mechanisms of action of exactly how fucoidan inhibits the metabolic pathways of tumour cells have been shown and are relatively well understood [8][9]. Although several studies have focused on pathways that destroy or slow down cancer progression, very few have focused on glucose metabolism pathophysiology, which is essential for the survival of cancer cells and a determining factor in diabetes progression.

Furthermore, fucoidan has been implicated as a plausible antidiabetic agent as some fucoidans have inhibited the primary starch digesting enzymes; amylase and glucosidase, directly linked to postprandial hyperglycaemia [10]. Nevertheless, a limited number of studies have investigated the potential therapeutic effects of fucoidan on several possible control points of glucose metabolism. Notably, diabetes and cancer progression are linked with shared factors which involve glucose metabolism pathophysiology [11].

2. Fucoidan Structure

2.1. Fucoidan Backbone & Monosaccharide Composition

Fucoidans vary in their structure and composition but are primarily composed of a pentose sugar backbone comprised of fucose residues that are linked by α-(1–3), α-(1–3)-α-(1–4) or α-(1–3)-α-(1–2) linkages. Fucoidans are heterogeneous in their monosaccharide composition with different monosaccharides occurring in different fucoidans extracted from various species and their proportions varying depending on the extraction process that is employed. The numerous neutral monosaccharides reported to constitute fucoidans include glucose, galactose, xylose, mannose and rhamnose [12]. Furthermore, fucoidan may contain acetate and uronic acids, including glucuronic acid and galacturonic acid [13][14]. The monosaccharide units may substitute molecular entities on the fucoidan structure or may represent contamination of the fucoidan extracts with other polysaccharides.

2.2. Sulphate Content and Position

The sulphate content and overall degree of sulphation in fucoidans vary significantly between species. Variations in fucoidan sulphate content as a function of harvests over different seasons have also been reported numerous times in literature. For instance, varying sulphate content was reported among three species, namely, *F. serratus*, *F. vesiculosus* and *A. nodosum,* and within species harvested in different seasons [15]. The study further noted that the fucose and sulphate contents varied proportionally to each other and were inversely proportional to the total fucoidan content. A study on the galactofucans from *Saccharina longicruris* reported a 1.6% increase in sulphate content between March and November 2005, while the sulphate content decreased by 7.2% between November 2005 and June 2006 [15]. Sulphate group positioning is also one of the main qualities of fucoidan that determines its structural and functional capabilities [16]. It has been established that single and double sulphate group substitutions occur at the C-2 or C-4 positions of furanose residues constituting two types of fucoidan chain structures (the (1→3)-α-L-fucopyranose residues and α-L-fucopyranose residues linked by (1→3) and (1→4) glycosidic bonds [16]. Moreover, sulphate substitutions in fucoidans also occur at the C-2 and C-3 positions of other monosaccharide residues [17]. The methodologies employed in the determination of sulphate content within fucoidans include infrared spectroscopy (IR), de-sulphation, the stability of sulphate esters to alkali and methylation analysis. Nuclear magnetic resonance (NMR) and mass spectroscopy can also be used to analyse the presence and positioning of sulphate residues on fucoidan.

2.3. Molecular Weight

The molecular weight of fucoidans has been one of the many factors affecting their functional properties. Fucoidan size varies from 10 kDa to about 10,000 kDa depending on the fucoidan source - with the average size being approximately 20 kDa. [17]. The considerable variation in the size of fucoidans has led to the categorisation of fucoidans; low molecular weight fucoidan (LMWF) when <10 kDa in size, medium molecular weight fucoidan (MMWF) if between 10 and 10,000 kDa in size and high molecular weight fucoidan (HMWF) when >10,000 kDa in size. Native fucoidan is known to have a high molecular weight, which results in low cell membrane permeability, low bioavailability, efficiency, and potential clinical efficacy [18]. There is a lot of variation in fucoidan characteristics (Table 1) due to various species, extraction protocols, and techniques used to determine traits. For example, determining the fucose content varies when less specific methods like the phenol sulphuric acid, which measures total carbohydrate content, are used—compared to more specific methods, including enzymatic assays and HPLC. These discrepancies make comparison very difficult.

Table 1. A sample of partially characterised fucoidan studied for antidiabetic and anticancer potential.

Source	M_w (kDa)	Sulphate Content (*w/w*)	Fucose Content (*w/w*)	Monosaccharide Composition (*w/w*)	Polyphenol Content (*w/w*)	References
Fucus vesiculosus	98	15.5 ± 1.1%	94.8%	2.3% xylose, 1.9% galactose	ND	[19]
Ascophyllum nodosum	420	20.6 ± 0.3%	80.1%	14.3% xylose, 5.6% galactose	ND	[20]
Sargassum wightii	637	36 ± 0.60%	53 ± 0.52%	ND	ND	[21]
Sargassum honeri	ND	ND	32.5%	23.2% mannose, 27.6% galactose, 4.2% xylose	ND	[4]
Ecklonia maxima	470	6.01 ± 0.53%	4.45 ± 0.25%	12.78% fructose,1.44% galactose, 26.55% glucose, 4.3% mannose, 0.78% xylose	0%	[22]

Turbinaria ornata	ND	33 ± 0.42%	59 ± 0.69%	ND	ND	[14]
Undaria pinnatifida	378	15.02%	39.24%	28.85% xylose, 26.4% galactose, 5.04% mannose, 0.95% glucose	ND	[23]

ND: Not determined.

Depolymerisation of high-molecular-weight fucoidan to synthesise oligomeric components has recently gained attention as it may solve problems associated with the high molecular weight of native fucoidan [18]. For instance, native fucoidan (5–100 kDa) from *Undaria pinnatifida* had minimal anti-tumour activity compared to its depolymerised counterpart (490 kDa) [17]. Furthermore, a fucoidan fraction with a molecular weight range of 0.05–100 kDa was reported to be a potential anticoagulant, while fractions >850 kDa lacked activity [17]. Similarly, low molecular weight fucoidans (from 4.58 to 6.5 kDa) displayed high anticoagulant and antioxidant activity, which was explained by their greater solubility and bioavailability [18]. Therefore, it is evident that molecular weight is a vital factor in the bioactivity and bioavailability of fucoidan. Hence depolymerisation processes that will not cleave functional fucoidan side chains are necessary.

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