Artículo de Revisión / Review Article

Role of the consumption of fucoïdians and beta-glucans on human health: An update of the literature

Rol del consumo de fucoidanos y betaglucanos en la salud humana: Artículo de actualización

ABSTRACT

Bioactive compounds are substances present in low doses in foods mostly from the plant kingdom. Their consumption can influence physiological or cellular processes and has a beneficial effect on health. Fucoïdians and beta-glucans are bioactive compounds that share the characteristic of being carbohydrates of the polysaccharide type, specifically of the soluble fiber kind. These compounds can be found in foods available in Chile and part of the Chilean diet; foods include, brown algae and some cereals. The concentration of these compounds in foods is variable, and depends on factors like season, cultivation, germination, and method of preparation and conservation. The current literature shows the potential beneficial effects of fucoïdan and beta-glucans compounds in human health, which include: anticoagulant, immunomodulator and antidiabetic and immunomodulating. The effects depend, among other factors, on their bioavailability and molecular weight. The objective of this review was to describe the potential beneficial effects of these bioactive compounds, analyze their characteristics and properties, and provide consumption recommendations that may lead to achieving the expected beneficial effects. To that end, relevant and recent scientific literature was analyzed.

Keywords: Beta-glucans; Bioactive compounds; Fucans; Fucoïdians; Immunomodulation; Soluble fiber.

RESUMEN

Los compuestos bioactivos corresponden a aquellos elementos presentes en los alimentos, que influyen en procesos fisiológicos o celulares, cuyo consumo produce un efecto beneficioso para la salud, encontrándose en alimentos principalmente del reino vegetal y cuyas concentraciones en los alimentos son en mínimas dosis. Los fucoidanos y los beta-glucanos, son compuestos bioactivos que comparten la característica de ser un carbohidrato, de tipo polisacárido, específicamente fibra de tipo soluble, encontrándose presente en alimentos disponibles en nuestro país y que son parte de nuestra dieta, como las algas pardas y algunos cereales. La concentración de estos compuestos en los alimentos, es fluctuante y depende de factores como la estacionalidad, cultivo, germinación,

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Este trabajo fue recibido el 30 de marzo de 2019.
Aceptado con modificaciones: 30 de julio de 2019.
Aceptado para ser publicado: 13 de agosto de 2019.

método de preparación y conservación. En la bibliografía actual, se evidencian los potenciales efectos beneficiosos de fucanos y beta-glucanos para la salud humana como anticoagulante, antidiabético e inmunomodulador, la intensidad de estos efectos dependen de su biodisponibilidad y del peso molecular. El objetivo de esta revisión fué profundizar respecto a los potenciales efectos beneficiosos de estos compuestos bioactivos, analizar sus características, propiedades, además de relacionar una recomendación de consumo que permita alcanzar los efectos beneficiosos esperados. Para ello se analizó la bibliografía científica atinente, relevante y reciente.

Palabras clave: Beta-glucanos; Compuestos bioactivos; Fibra soluble; Fucoïdianos; Inmunomodulador.

INTRODUCTION

Fucans, also called fucoidans or fucoids, refers to a type of polysaccharide, which contains substantial percentages of L-fucose and sulfate ester groups, mainly derived from brown seaweed. For the past decade, fucoidan has been extensively studied due to its numerous interesting biological activities¹. Similar fucan sulfates were isolated from marine invertebrates (the jelly coat of sea urchin eggs and the body wall of sea cucumbers)². The nomenclature and the purity of these compounds have always had observations linked with algal fucoidans, because the initial preparations had large amounts of sugars other than fucose, like galactose, mannose, xylose, or uronic acid, and sometimes even proteins. Furthermore, their composition changes according to the alga species, the extraction process, the harvesting season, and the local weather conditions. That is why some authors have proposed suggesting the term fucoidan and using the term fucan as a generic name of the polysaccharides rich in L-fucose³, but currently, according to the International Union of Pure and Applied Chemistry IUPAC recommendations, the name fucoidan is preferred for fucans coming from algae⁴. The total content of fucoidans in algae varies between 2% and 4% per dry weight of algae, with a higher concentration in the leaves than in the thallus and showing great seasonal variation⁵.

Brown algae, whose taxonomic name is Phaeophyta, corresponds to an extensive group of marine algae whose exact number of species is unknown⁶. Their pigmentation varies from brownish yellow to dark brown, and they have the characteristic that their species produce a large amount of protective mucus. Among this brown algae group, the best known in Chile are *Macrocystis pyrifera* (huito), *Lessonia nigrescens* (huito negro), and *Durvillaea antarctica* (cochayuyo)⁷. From the nutritional standpoint, the algae share attractive characteristics like a low calorie content and amino acid⁸ composition, as their proteins are rich in the amino acids glycine, arginine, alanine, and glutamic acid⁸. The protein content in brown algae varies from 10.4 to 13.2% and its amino acid composition depends on the type of algae. For *Macrocystis pyrifera* (huito), glutamic acid, aspartic acid, valine and methionine predominate, and in *Durvillaea antarctica* (cochayuyo) amino acids such as glutamic acid, histidine, alanine and glycine predominate⁹. Furthermore, they have additional contributions of vitamins, minerals, and dietary fibers^{6,7,8,9,10}.

Consumption of algae in Chile, which are popularly believed to have multiple health benefits, is increasing, but we do not yet have figures that allow the quantification of consumption patterns in the population, as algae were not included in the lastest National Food Consumption Survey of Chile¹¹. Table 1 shows the content of dietary fiber and the ratio between soluble and insoluble fiber in marine algae.

According to the different types of algae analyzed, *Grateloupia turuturu* is the seaweed with the highest soluble fiber content, followed by the *Durraea Antarctica*¹² and finally by the *Ulva Clathrata*¹³. On the other hand, *Durvillaea*

Antarctica has the highest insoluble fiber content⁷, followed by the *Ulva lactuca*⁷. The greatest relationship between soluble and insoluble fiber content is found in *Grateloupia turuturu*¹² algae, followed by *Himathalia elongata*¹⁴.

The bioactive compound fucoidan is found in soluble fiber, so this compound is neither digested nor absorbed, and it behaves as a soluble fiber acting on the microbiota as a prebiotic. The marine environment is an untapped source of bioactive compounds. Specifically, marine macroalgae (seaweeds) are rich in polysaccharides such as fucoidans that could potentially be exploited as prebiotic functional ingredients for both human and animal health applications¹⁵, providing individuals with multiple benefits presented by the consumption of this type of fiber. However, due to its molecular weight, its access to the lymphatic circulation is limited. Fucoidans enter blood circulation¹⁶ and, in this way, achieve a systemic distribution effect. There is no data available on the concentrations that reach a systemic level, likely due to the fact that this is a relatively incipient area of research. The plasmatic level required for human benefit effects is also unknown. During several decades, there has been interest in determining the potential positive effects of fucoidans for human health. In Japan, there is the NPO Research Institute of Fucoidan, which for more than 20 years has been devoted to characterizing the molecule and measuring its interactions. However, in consultations made with the Institute, they point out that unfortunately they have never measured the interaction between fucoidans and other nutrients, so they can not give a precise answer on whether it interacts positively or negatively, affecting or reinforcing bioavailability. However, since fucoidan has negative charges, it is believed that there are possibilities that it may interact with positively charged molecules, while in molecules with negative charges, like omega-3 fatty acids, probability that they interact is very low¹⁶.

On the other hand, beta-glucans are natural polysaccharides not digestible by human beings as there are no digestive enzymes capable of degrading them. Thus, they are not classified as soluble dietary fiber, present in the cell wall of food like oats, barley, mushrooms, and some algae¹⁷. In cereals, beta-glucans are found mainly in the cell walls of the grain's endosperm, with oats in the first place, followed by barley as the cereals with the highest concentrations of beta-glucans¹⁸. Concentration of the compound in food depends on the conditions of cultivation, growth, germination¹⁹, and the food's preparation and conservation techniques²⁰, and even the genetic modifications to which the seeds have been subjected (in the case of the cereals)¹⁸. Table 2 presents the concentration of beta-glucans in cereals and greenhouse and wild mushrooms. The highest content of beta-glucans is found in wild mushrooms²¹, followed by oat bran²⁰, wheat also represents a source of beta-glucans, but at a low rate.

Considering that oats, among the cereals group, is the best provider of beta-glucans, it should be noted that reports point out that the beneficial effects to human beings

Table 1. Dietary Fiber Content and its S.F. / I. F. ratio.

Scientific Name of Marine Algae	Soluble Fibe g/100 g	Insoluble Fiber g/100 g	S.F./I.F. Ratio	Reference
<i>Grateloupia turuturu</i>	48.1 ± 1.0	12.3 ± 1.2	3.9	12
<i>Ulva clathrata</i>	21.9 ± 0.9	18.7 ± 2.1	1.2	13
<i>Ulva lactuca</i>	27.2 ± 1.2	33.3 ± 0.3	0.8	7
<i>Durvillaea antarctica</i> (leaves)	27.7 ± 1.2	43.7 ± 0.3	0.6	7
<i>Durvillaea antarctica</i> (talus)	24.2 ± 2.5	32.2 ± 0.7	0.8	7
<i>Himanthalia elongata</i>	23.6 ± 0.5	13.51 ± 0.45	1.7	14
<i>Laminaria saccharina</i>	17.1 ± 0.8	13.11 ± 0.56	1.3	13

Each value is the mean ± standard deviation, n= reference. S.F.= soluble fiber. I.F= insoluble fiber.

Table 2. Beta-glucans concentration in cereals and mushrooms (dry base).

Cereal	Beta-glucans (g/100g)	Reference (n)
Oat bran	9.7	20
Oat flakes (average of four samples)	6.4	20
Barley (average of ten samples)	5.6	20
Oatmeal	3.8	20
Wheat (average of five samples)	0.6	20
Greenhouse mushrooms	8.4+ 0.9*	21
Wild mushrooms	10.1+ 2.1*	21

*Each value is the mean ± standard deviation, n= reference.

are differentiated depending on the molecular weight of beta-glucans, as weight affects the physical properties, the solubility and the viscosity²². Thus, beta-glucans with high (around 2000 kDa) and medium (greater than 500 kDa) molecular weights may have an approximately 5% decrease of low density lipoproteins (LDL) (in both cases), while beta-glucans with low molecular weights (210 kDa) would have less impact in the reduction of LDL (2.5% reduction)²². Therefore, to produce the expected reduction of plasma cholesterol it is necessary for the molecular weight of the beta-glucan from oats to be at least 1,200 kDa. Accordingly, molecular weight is a factor to consider together with the amount of beta-glucan to be ingested^{22,23}. Another important factor when evaluating the bioavailability of the compound is the degree of processing, since roasting and cooking foods containing beta-glucan from oats increases

the solubility and viscosity of the compound, increasing its bioactivity²⁴.

Due to its potential effects on health, the food industry has been increasingly using beta-glucans to develop functional foods. Furthermore, its rheological properties have stimulated its addition to different food matrices with the purpose of improving the food's stability, texture, and useful life, replacing some artificial additives or texturing agents²⁵.

The objective of this review is to update the existing information among the scientific community with respect to these two bioactive compounds and go deeper into the potential beneficial effects for human health associated with their periodic consumption as part of the habitual diet. For this article, a bibliographic search was carried out in English and Spanish, using the descriptors: *Fucans*, *Fucoidans*,

Beta-glucans, probiotics, fiber, others, in the global impact scientific search engines such as ScienceDirect, Springerlinks and Scielo. Scientific articles were selected mainly *in vitro* and *in vivo* studies.

Bioactive Compounds

The main research shows that the use of bioactive compounds derived from plants as a source of functional ingredients in food products can reduce the risk of cardiovascular and neurodegenerative diseases. Fucans and beta-glucans obtained from vegetable sources can be considered bioactive compounds due to the positive effects on human health.

Bioactive compounds are those compounds present in small concentrations in foods mainly derived from plants that have an influence on physiological or cellular processes, whose consumption has a beneficial effect on health²⁶. For compounds to have the expected physiological effect, they must reach the tissues and get to the action site through the blood stream. Hence, bioavailability is influenced by many factors belonging to the individual, the food in which they are found, and the intestinal microbiota of the host²⁷. *In vitro*^{28,29} and *in vivo*^{30,31} evidence suggest that beta-glucans can be used as prebiotics²¹ due to their ability to promote the growth of beneficial microorganisms of the intestinal microbiota such as *Lactobacillus* and *Bifidobacterium*.

It is important to mention that although at times the initial molecule existing in the food may not be absorbable, the intestinal microbiota of the host modifies the molecule, turning it into a new metabolite. These modifications sometimes result in compounds, which can now be bioavailable and exert a physiological effect³².

Potential Role of the Consumption of Fucoidans and Beta-glucans on Human Health

Fucoidans

Various *in vitro* and *in vivo* studies indicate that the fucoidans have an antitumor³³ or antineoplastic activity^{34,35}, and these findings indicate that this property can be associated with a significant increase of the cytolytic activity of natural killer cells³⁶ caused by the increase of the production of molecules signaling the immune response mediated by macrophages^{37,38} (e.g., interleukins L-2, L-12)³⁷, induction of cell apoptosis³⁹, decrease of tumor angiogenesis⁴⁰, and immunopotentialization^{33,39,41}, since in tumor-bearing rats it was seen that the fucoidans seem to act by potentiating the immune response against A20 leukemia cells and decreasing the size of tumors in transgenic rats³⁷.

In vitro studies determined that the low molecular weight fucoidan extracted from the brown alga *Laminaria japonica* had an important antioxidant activity⁴². In addition to the antiinflammatory role⁴³ determined by the molecular weight of the studied fraction, i the ability to inhibit nitric oxide synthetase (ONS) and cyclooxygenases activity was observed, suggesting its use in acute inflammatory alterations⁴⁴.

Studies on rats measured coagulation times after the intraperitoneal injection of a fucoidans dose of 5 mg/kg, in mice whose weight fluctuated between 18-20 g. After 15 min, a coagulation times were 3.3 and 4.7 higher than normal values, evaluated by the Activated Partial Thromboplastin Time (TTPa) and the Thrombin Time (TT), respectively⁴⁵. Furthermore, it was found that in rats with damaged gastric mucosa induced by aspirin, fucoidans had a gastroprotective effect against ulceration induced by this compound. This may be due to a decreased elevation of pro-inflammatory cytokines IL-6 e IL-12⁴⁶.

Otherwise, *in vivo* studies determined that the potential anticoagulant role of fucoidans is due to the fact that they have a structure similar to that of heparin, so it takes part in the intrinsic pathway of coagulation, causing an inhibition of coagulation factors (VII, IX, XI and XII)⁴⁷.

Because cancer treatments have known undesirable side effects and long-term complications⁴⁸, attention has recently been centered on the potential beneficial effects provided by bioactive compounds present in foods, specifically in marine algae⁴⁹.

According to the reviewed studies, one of the most frequent pathways through which fucoidans can inhibit the general growth of cancer is via cell apoptosis. It has been shown that different types of fucoidans can induce apoptosis in melanoma cells³⁹, HT-29 colon cancer cells, MCF-7 human breast cancer cells⁵⁰, and HS-Sultan lymphoma cells⁵¹. A study was carried out to determine the apoptosis inducing activity of fucoidan in cultured HT-29 and HCT116 human colon cancer cells and revealed that fucoidan reduced the viability of tested cells in a dose-dependent manner through the inhibition of both tumor necrosis factor and caspase-induced cell signaling⁵².

Beta-glucans

A study in rats analyzed the effects of beta-glucans extracted from baker's yeast (*Saccharomyces cerevisiae*) (BBG) on inflammatory responses induced by lipopolysaccharides (LPS) in RWA264.7 mouse macrophages. The findings showed that BBG inhibited nitric oxide production stimulated by LPS. BBG also suppressed the mRNA and protein expression of LPS-induced inducible NO synthase and mitogen-activated protein kinase phosphorylation, but not the activation of NFκB⁵³.

The potential beneficial effects of the consumption of beta-glucans are due to the fact that, similar to other soluble fibers, they form gels in the digestive tract, which slow down gastric emptying. This also creates difficulty for the digestive enzymes to reach and digest the nutrients, slowing down these processes and the absorption of nutrients⁵⁴, increasing the excretion of bile acids⁵⁵, and preventing their reabsorption (enterohepatic circulation). In this way, elimination is caused through the feces, forcing the liver to synthesize new bile salts from circulating cholesterol, which thereby reduces plasma levels of cholesterol and decreases the risk of a cardiovascular events and the

associated clinical effects⁵⁶.

Another potential action studied is the antidiabetic effect⁵⁷, which is mainly due to the fact that these types of fibers form a barrier on the intestinal walls that prevent the absorption of glucose and cholesterol, thus improving plasma insulin levels⁵⁸. Furthermore, for the same effect, another study mentions that beta glucans may act by activating metabolic pathways (PI3K/Akt) with a key role in the pathogenesis of diabetes as the metabolic route. It is hypothesized that beta-glucans on this pathway decrease the production of hepatic glucose and glucogenolisis and increase the synthesis of glucogen and synthesis of fatty acids⁵⁹. Another contribution of beta-glucans is the reduction of the glycemic index of foods⁶⁰, but their use is controversial due to the large response variability within and between individuals. Variability occurs because of the amount of carbohydrates present in the food, thus, the application of this concept can lead to making unbalanced nutritional recommendations⁶¹.

Beta-glucans are also attributed the role of substance immune potentiating, since they promote immunomodulation of CD4+ T cells and the infiltration of neutrophils in tumors, leading to the inhibition of tumor growth. This finding may position beta-glucans as efficient agents for the immunotherapy of cancer⁶². In the case of the beta-glucans from mushrooms, a recognized property is that of modulating the immune system^{63,64}, which may be due to the ability to stimulate the innate immunity against viruses, bacteria, yeasts, and molds, contributing to the recognition and elimination of these pathogens⁶⁵. These receptors are present in the membrane enterocytes of M and dendritic cells, improving the phagocytic activity of macrophages and the antimicrobial activity of mononuclear cells and neutrophils⁵³.

Recommended Consumption

An important aspect related to associating nutrients or compounds with potential beneficial effects for humans is the concept of recommended daily consumption. Consumption or recommended dietary allowance is defined as the nutrient-level daily intake which meets the needs of 97-98% of a given population⁶⁶. To this concept is added that of compound bioavailability and factors that modify it, like chelating agents or compounds with synergistic effects. In this regard, the daily dose recommended by the NPO Fucoidan Research Institute of Japan is 1-2 g of fucoidans/day for fighting everyday diseases, preventing chronic diseases and 3-6 g of fucoidans/day to attenuate the complications and symptoms associated with cancer treatment¹⁶. No details were found on the recommended daily intake in published scientific literature analyzed in this review. An important aspect when talking about daily recommendations of this compound is to mention that it is recommended to distribute the daily dose ingested four times per day (morning, mid-morning, afternoon, and night), which allows for stable levels of the compound in circulation¹⁶. In

Chile, there are currently no functional foods that contain such compounds in the expected concentrations. In other countries, mainly in Europe and Asia, there are nutraceuticals based on fucoidanes in powder, liquid and capsules format, in concentrations that, with multiple doses, can achieve recommended daily ingestion.

With respect to beta-glucan, the recommended ingestion is 3 g/day, as part of a habitual diet which also considers low saturated fat and cholesterol content, which may contribute to decrease the risk of coronary disease^{67,68}, as approved by various regulating agencies (e.g., Food and Drug Administration of the United States⁶⁹ and the European Food Safety Authority)⁷⁰.

Doses of 6 g/day or doses larger than 3 g/day for a longer period are sufficient to improve the ranges of plasma glycemia and lipids in those with diabetes mellitus, while low doses of beta-glucans for a minimum of 12 weeks also had beneficial metabolic effects⁵⁶.

If we consider that ¼ cup is equivalent to 20 g of oats, it should be noted that such an amount could provide a range of 1.1 to 1.51 g of beta-glucans per portion of oats consumed¹⁹. Slightly greater amounts are contributed by 20 g of mushrooms, with ranges of beta-glucan contribution of approximately 1.68 g to 2.02 g, considering the contribution of greenhouse and wild mushrooms, respectively²¹.

The recommendations of the European Food Safety Authority state that the consumption of 5-15 g/day of soluble fiber from food containing oats may be beneficial for reducing total cholesterol⁷⁰, while the FDA recommends consuming 10-25 g/day of soluble fiber⁶⁹.

CONCLUSIONS

Fucoidans and beta-glucans are carbohydrates, specifically non-digestible polysaccharides (i.e., soluble fiber), which are considered bioactive compounds due to benefits to human health associated with habitual consumption. Fucoidans and beta-glucans are present in foods such as brown algae and cereals, with oats being a good source of beta-glucans. The amount recommended for consumption, associated with the beneficial effects pointed out in this review, is 1-2 g/day in the case of fucoidans for the prevention of everyday diseases and chronic illnesses. One kg of brown algae provides 2-4 g of fucoidans, thus it can be concluded that it is difficult to follow this recommendation by direct consumption, despite the high availability of foods containing this compound. Thus, the consumption of functional foods that contain fucoidans and/or the use of nutraceuticals based on this compound, provided they are backed by the corresponding effectiveness and biosafety studies and the approvals of the competent organizations, is important. It is also essential to encourage the food industry to produce and process this type of algae in order to allow more people to have access to these foods in a varied and natural way. Preserving active principles in the production of these foods presents challenges in the development and innovation of products. No intake recommendations were found for fucoidans. Japan is one of

the countries with the greatest scientific focus on fucoidans. The main role of the consumption of fucoidans on human health are anticoagulant, antineoplastic, immunomodulator, and antioxidant activity.

The recommended consumption of beta-glucans is 3 g/day, an amount that can be covered by healthy and balanced food. For example, with a daily consumption of 1-2 portions of 20 g of oats, ideally whole-wheat, or otherwise with 1-1.5 portions of 20 g of mushrooms per day. Furthermore, it should be mentioned that oats are included in multiple other foods part of the regular diet, like breads, cookies, cereal bars, etc., and mushrooms are being given greater nutritional, gastronomic, and culinary value. However, it is important to consider factors that influence and modify the bioavailability of beta-glucans, such as, the processing, cooking, baking, and freezing of foods, among others. The main benefits of beta-glucan consumption for human health include the ability to decrease plasma cholesterol, the antidiabetic and immunomodulating role, that it is common to beta-glucans and fucoidans.

In both cases, the potential beneficial effects of the consumption of these bioactive compounds relate to the main causes of morbidity and mortality in our population. Thus, promoting their consumption as part of a normal diet may contribute to decreasing the consequences of the main non-transmissible chronic diseases prevalent in Chile. Therefore, it is vital to educate the population concerning the consumption of foods containing these bioactive compounds, and in this way make people aware of the importance of including them in the regular diet by means of a wide range of preparations.

In Chile, as well as in neighboring countries, there is a scientific basis for studies in animals and humans with respect to beta-glucans. On the other hand, local scientific evidence on fucoidans is limited, with more information and experimental analysis available from Western countries. In conclusion, it is feasible to consider a diet rich in beta-glucans and, in the same way, include fucoidans in eating recommendations for the Chilean population, given the availability of locally sourced foods currently generated as waste or non-exploitable marine material.

Acknowledgments. This update article was funded by Fondo de Fomento al desarrollo Científico y Tecnológico FONDEF ID17AM0009 and the University of Santiago of Chile (USACH).

Conflicts of interest. The authors declare no conflicts of interest.

REFERENCES

- Li B, Lu F, Wei X, & Zhao R. Fucoidan: structure and bioactivity. *Molecules* 2008; 13(8): 1671-1695.
- Berteau O, Mulloy B. Sulfated fucans, fresh perspectives: structures, functions, and biological properties of sulfated fucans and an overview of enzymes active toward this class of polysaccharide. *Glycobiology* 2003; 6: 29-40.
- Nardella A, Chaubet C, Boisson C, Blondin P, Durand J. Anticoagulant low molecular weight fucans produced by radical process and ion exchange chromatography of high molecular weight fucans extracted from the brown seaweed *Ascophyllum nodosum*. *Carbohydr Res* 1996; 289: 201-208.
- iupac.org. [web]. USA Research Triangle Park. 2019. [updated 31 July 2019; citado 31 July 2019] available in: <https://iupac.org/what-we-do/nomenclature/>
- Ragan M, Jensen A. Widespread distribution of sulfated polyphenols in brown algae. *Phytochemical* 1997; 18: 261-262.
- Quiral V, Morales C, Sepulveda L, Schwartz M. Nutritional and health properties of seaweeds and its potential as a functional ingredient. *Rev Chil Nutr* 2012; 39: 196-202.
- Ortiz J, Romero N, Robert P, Araya J, Lopez-Hernández J, Bozzo C, Navarrete E, Osorio A, Ríos A. Dietary fiber, amino acid, fatty acid and tocopherol contents of the edible seaweeds *Ulva lactuca* and *Durvillaea antarctica*. *Food Chem*. 2006; 99: 98-104.
- Rajapakse N, Kim S. Nutritional and digestive health benefits of seaweeds. *Adv Food Nut Res* 2011; 64: 17-28.
- Ortiz J. Nutritional and functional composition of Chilean brown algae: *Macrocystis pyrifera* and *Durvillaea antarctica* [Internet]. Santiago, Chile: University of Chile -; 2011 [cited: 2019, August]. Available in: <http://repositorio.uchile.cl/handle/2250/121459>
- Dawczynski C, Schubert R, Jahreis G. Amino acids, fatty acids and dietary fibre in edible seaweed products. *Food Chem* 2007; 103: 891-899.
- Amigo H, Bustos P, Pino P. Food and nutrition of Chileans. National survey of food consumption [Internet]. Santiago, Chile: University of Chile; 2018 [cited: 2019, March]. Available in: <http://repositorio.uchile.cl/handle/2250/149966>
- Denis C, Moránçais M, Li M, Deniaud E, Gaudin P, Wielgosz-Collin G, Barnathan G, Jaouen P, Fleurence J. Study of the chemical composition of edible red macroalgae *Grateloupia turuturu* from Brittany (France). *Food Chem* 2010; 119: 913-917.
- Peña A, Mawhinney T, Ricque D, Cruz E. Chemical composition of cultivated seaweed *Ulva clathrata* (Roth) C. Agardh. *Food Chem*. 2011; 129: 491-498.
- Gómez E, Jiménez A, Rupérez P. Dietary fibre and physicochemical properties of several edible sea- weeds from the northwestern Spanish coast. *Food Res Int* 2010; 43: 2289-2294.
- O'Sullivan L, Murph, B, McLoughlin P, Duggan P, Lawlo, PG, Hughes H, Gardiner GE. Prebiotics from marine macroalgae for human and animal health applications. *Mar Drugs* 2010; 8(7): 2038-2064.
- Research Institute of Fucoidan of Japan - NPO [internet]. Japon. 2019. [actualizado 2019, citado: 2019, Marzo]. Disponible en: <http://www.fucoidan-life.com/esp/faq/>
- Volman J, Mensink R, Ramakers J, Winther M, Carlsen H, Blomhoff R. Dietary (1→3), (1→4) Beta-D-glucans from oat activate nuclear factor-kappa B in intestinal leukocytes and enterocytes from mice. *Nutr Res* 2010; 30(1): 40-48.
- Fujita A, Figueroa M. Nutrient profile and b-glucans content in cereal seeds and foodstuffs contain them. *Ciênc Tecnol Aliment* 2003; 23: 116-120.
- Wood P. Cereal β -glucans in diet and health. *J Cereal Sci* 2007; 46(3): 230-238.
- Áman P, Rimsten L, Andersson R. Molecular weight distribution

- of beta-glucan in oat-based foods. *Cereal Chem* 2004; 81(3): 356-360.
21. Park Y, Ikegaki M, Alencar S, Aguilar S. Determination of concentration of musegeguan in mushroom agaricus blazei murill by enzymatic method. *Cienc. Tecnol Food* 2003; 23(3): 312-317.
 22. Wang Q, Ellis P. Oat beta-glucan: physico-chemical characteristics in relation to its blood-glucose and cholesterol lowering properties. *Br J Nutr* 2014; 112(2): 4-13.
 23. Kim H, White P. Interactional effects of beta-glucan, starch, and protein in heated oat slurries on viscosity and in vitro bile acid binding. *J Agric Food Chem* 2012; 60(24): 6217-6222.
 24. Regand A, Tosh S, Wolever T, Wood P. Physicochemical properties of beta-glucan in differently processed oat foods influence glycemic response. *J Agric Food Chem* 2009; 57(19): 8831-8888.
 25. Pizarro S, Ronco A, Gotteland M. β -glucans: what types exist and what are their health benefits? *Rev Chil Nutr* 2014; 41(3): 439-446.
 26. Biesalski H, Dragsted L, Elmadfa I. Bioactive compounds: definition and assessment of activity. *Nutrition* 2009; 25(11-12): 1202-1205.
 27. Lutz M. Bioavailability of bioactive compounds in food. *Perspect Nutr Human* 2013; 15: 217-226.
 28. Jaskari J, Kontula P, Siitonen A, Jousimies-Somer H, Mattila-Sandholm T, Poutanen K. Oat beta-glucan and xylan hydrolysates as selective substrates for *Bifidobacterium* and *Lactobacillus* strains. *Appl Microbiol Biotechnol* 1998; 49(2): 175-181.
 29. Kontula P, Jaskari J, Nollet L, De Smet I, von Wright A, Poutanen K, et al. The colonization of a simulator of the human intestinal microbial ecosystem by a probiotic strain fed on a fermented oat bran product: effects on the gastrointestinal microbiota. *Appl Microbiol Biotechnol* 1998; 50(2): 246-252.
 30. Dongowski G, Huth M, Gebhardt E, Flamme W. Dietary fiber-rich barley products beneficially affect the intestinal tract of rats. *J Nutr* 2002; 132(12): 3704-3714.
 31. Snart J, Bibiloni R, Grayson T, Lay C, Zhang H, Allison GE, et al. Supplementation of the diet with high-viscosity beta-glucan results in enrichment for lactobacilli in the rat cecum. *Applied Environm Microbiol* 2006; 72(3): 1925-1931.
 32. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr* 2005; 81: 230-242.
 33. Alekseyenko T, Zhanayeva S, Venediktova, A, Zvyagintseva, T, Kuznetsova T, Besednova N, Korolenko T. Antitumor and antimetastatic activity of fucoidan, a sulfated polysaccharide isolated from the Okhotsk Sea *Fucus evanescens* brown alga. *Bull Exp Biol Med* 2007; 143: 730-732.
 34. Cho M, Lee B, You S. Relationship between oversulfation and conformation of low and high molecular weight fucoidans and evaluation of their in vitro anticancer activity. *Molecules* 2011; 16: 291-297.
 35. Synytsya A, Kim W, Kim S, Pohl R, Synytsya A, Kvasnicka F, Copikova J, Park, Y. Structure and antitumor activity of fucoidan isolated from sporophyll of Korean brown seaweed *Undaria pinnatifida*. *Carbohydr Polym* 2010; 81: 41-48.
 36. Tutor M, Mikkelsen J. Important determinants for fucoidan bioactivity: a critical review of structure-function relations and extraction methods for fucose-containing sulfated polysaccharides from brown seaweeds. *Mar Drugs* 2011; 9: 2106-2130.
 37. Maruyama H, Tamauchi H, Hashimoto M, Nakano T. Antitumor activity and immune response of Mekabu fucoidan extracted from Sporophyll of *Undaria pinnatifida*. *In Vivo* 2003; 17: 245-249.
 38. Takahashi M. Studies on the mechanism of host mediated antitumor action of fucoidan from a brown alga *Eisenia bicyclis*. *J Jpn Soc Reticuloendothel Syst* 1983; 2: 269-283.
 39. Ale M, Maruyama H, Tamauchi H, Mikkelsen J, Meyer A. Fucoidan from *Sargassum* sp. and *Fucus vesiculosus* reduces cell viability of lung carcinoma and melanoma cells in vitro and activates natural killer cells in mice in vivo. *Int J Biol Macromol* 2011; 49: 331-336.
 40. Hlawaty H, Suffee N, Sutton A, Oudar O, Haddad O, Ollivier V, Laguillier-Morizot C, Gattegno L, Letourneur D, Charnaux N. Low molecular weight fucoidan prevents intimal hyperplasia in rat injured thoracic aorta through the modulation of matrix metalloproteinase-2 expression. *Biochem Pharmacol* 2011; 81: 233-243.
 41. Cho M, Lee D, Kim J, You S. Molecular characterization and immunomodulatory activity of sulfated fucans from *Agarum cribrosum*. *Carbohydrate Polymers* 2014; 113: 507-514.
 42. Wang J, Zhang Q, Zhang Z, Song H, Li P. Potential antioxidant and anticoagulant capacity of low molecular weight fucoidan fractions extracted from *Laminaria japonica*. *Int J Biol Macromol* 2010; 46: 6-12.
 43. Semenov A, Mazurov A, Preobrazhenskaia M, Ushakova N, Mikhaïlov V, Berman A, Usov A, Nifant'ev N, Bovin N. Sulfated polysaccharides as inhibitors of receptor activity of P-selectin and P-selectin-dependent inflammation. *Vopr Med Khim* 1998; 44: 135-144.
 44. Siqueira R, Da Silva M, Alencar D, Pires A, Alencar N, Pereira M, Cavada B, Sampaio A, Farias W, Assreuy A. In vivo anti-inflammatory effect of a sulfated polysaccharide isolated from the marine brown alga *Lobophora variegata*. *Pharm Biol* 2011; 49(2): 167-174.
 45. Kuznetsova T, Besednova N, Mamaev A, Momot A, Shevchenko N, Zvyagintseva T. Anticoagulant activity of fucoidan from brown algae *Fucus evanescens* of the Okhotsk Sea. *Pharm Toxicol* 2003; 5: 471-473.
 46. Raghavendran H, Srinivasan P, Rekha S. Immunomodulatory activity of fucoidan against aspirin-induced gastric mucosal damage in rats. *Int Immunopharmacol* 2011; 11: 157-163.
 47. Zhu Z, Zhang Q, Chen L, Ren S, Xu P, Tang Y, Luo D. Higher specificity of the activity of low molecular weight fucoidan for thrombin-induced platelet aggregation. *Thromb Res* 2010; 125: 419-426.
 48. Schneider U, Stippler A, Besserer J. Dose-response relationship for lung cancer induction at radiotherapy dose. *Z Med Phys* 2010; 20: 206-214.
 49. Jiao G, Yu G, Zhang J, Ewart S. Chemical structure and bioactivities of sulfated polysaccharides from marine algae. *Mar Drugs* 2011; 9: 196-223.
 50. Yamasaki-Miyamoto Y, Yamasaki M, Tachibana H, Yamada K. Fucoidan induces apoptosis through activation of caspase-8 on human breast cancer MCF-7 cells. *J Agric Food Chem* 2009; 57: 8677-8682.
 51. Aisa Y, Miyakawa Y, Nakazato T, Shibata H, Saito K, Ikeda Y, Kizaki M. Fucoidan induces apoptosis of human HS-sultan cells accompanied by activation of caspase-3 and down-regulation of ERK pathways. *Am J Hematol* 2005; 78: 7-14.
 52. Rajapakse N, Kim SK. Nutritional and digestive health benefits of seaweed. *Adv Food Nutr Res* 2011; 64: 17-28.
 53. Xu X, Yasuda M, Mizuno M, Ashida H. β -Glucan from *Saccharomyces cerevisiae* reduces lipopolysaccharide-induced

- inflammatory responses in RAW264.7 macrophages. *Biochim Biophys Acta* 2012; 1820(10): 1656-1663.
54. Tiwari U, Cummins E. Meta-analysis of the effect of beta-glucan intake on blood cholesterol and glucose levels. *Nutrition* 2011; 27(10): 1008-1016.
55. Andersson M, Ellegard L, Andersson H. Oat bran stimulates bile acid synthesis within 8 h as measured by 3 H-alpha-hydroxy-4-cholesten-3-one. *Am J Clin Nutr* 2002; 76(5): 1111-1116.
56. Poli A, Visioli F. Pharmacology of Nutraceuticals with Lipid Lowering Properties. *High Blood Press Cardiovasc Prev* 2019; 26(2): 113-118.
57. Cugnet-Anceau C, Nazare J, Björklund M. A controlled study of consumption of β -glucan-enriched soups for 2 months by type 2 diabetic free-living subjects. *Br J Nutr* 2010; 103: 422-428.
58. Liatis S, Tsapogas P, Chala E, et al. The consumption of bread enriched with betaglucan reduces LDL-cholesterol and improves insulin resistance in patients with type 2 diabetes. *Diabetes Metab* 2009; 35: 115-120.
59. Chen J, Raymond K. Beta-glucans in the treatment of diabetes and associated cardiovascular risks. *Vasc Health Risk Manag* 2008; 4: 1265-1272.
60. Francelino E, Vieira R, Vasques T, Zangerônimo M, Sousa R, Pereira L. Effect of beta-glucans in the control of blood glucose levels of diabetic patients: a systematic review. *Nutr Hosp* 2015; 31(1): 170-177.
61. Pi-Sunyer X. Glycemic index and disease. *Am J Clin Nutr* 2002; 76(1): 290-298.
62. Zou S, Duan B, Xu X. Inhibition of tumor growth by β -glucans through promoting CD4+ T cell immunomodulation and neutrophil-killing in mice. *Carbohydr Polym* 2019; 213: 370-381.
63. Volman J, Ramakers J, Plat J. Dietary modulation of immune function by β -glucans. *Physiology Behavior* 2008; 94(2): 276-284.
64. Wang Y, Zhang L, Li Y, Hou X, Zeng F. Correlation of structure to antitumor activities of five derivatives of a β -glucan from *Poria cocos sclerotium*. *Carbohydrate Res* 2004; 339(15): 2567-2574.
65. Călugăru A, Cremer L, Lupu A, Bădulescu M, Apetrei N, Moscovici M, et al. Recognition and modulation of Dectin-1 and TLR-2 receptors by curdlan derivatives and purified natural extracts. *Roum Arch Microbiol Immunol* 2009; 68(3): 119-124.
66. H Araya, M Ruz. Risk assessment for vitamins and minerals in fortified foods. Santiago, Chile: University of Chile -; 2007 [cited: 2019, August]. Available in: <https://www.minsal.cl/portal/url/item/62cdc6f7a6951bdb04001011e015a76.pdf>
67. Whitehead A, Beck E, Tosh S, Wolever T. Cholesterol-lowering effects of oat beta-glucan: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2014; 100(6): 1413-1421.
68. Vizuite A, Ortega R. Effects of oat beta-glucan consumption on blood cholesterol: a review. *Rev Esp Nutr Hum Diet* 2016; 20(2): 127-139.
69. FDA. [Internet]. United States. [cited: 2019, August]. Available in: <https://www.fda.gov/food>
70. EFSA. [Internet]. United States. [cited: 2019, August]. Available in: <http://www.efsa.europa.eu/>