

# The Brown Alga *Ascophyllum Nodosum* As A Nutraceutical Useful for the Control of Type II Diabetes



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## Abstract

In the last few decades, diabetes has become a global health concern, due to its increasing prevalence in developed and developing countries. The most common form of diabetes is type 2 diabetes (T2D), characterized by an impairment of insulin in activating glucose transport system into the cells and an inappropriate hyper-insulinemia due to insulin resistance. The maintenance of normal blood glucose levels is one of the major goals in diabetes management and could be achieved by reducing the glycemic index (GI) of foods. The brown seaweed *Ascophyllum nodosum* is an easily available food traditionally used by coastal communities. *A. nodosum* contains numerous bioactive compounds with several health benefits for humans, i.e. the carotenoid fucoxanthin, phlorotannins, high molecular weight phenolics and simple phenolics, such as catechins, hydroxybenzoic acid, coumaric acid, cinnamic acid, and caffeic acid, all displaying anti-obesity, antidiabetic and antioxidant potential. The reduction and the delay of glucose absorption consequent to the inhibition of the digestive enzymes  $\alpha$ -glucosidase and  $\alpha$ -amylase induced by *A. nodosum* can significantly lower postprandial glucose levels by slowing the digestion of dietary starch, the major dietary source of glucose, and decreasing the rate of blood sugar absorption from small intestine. In conclusion, *A. nodosum* extracts could be administered before a meal to slow down the rate of carbohydrate digestion and assimilation and modulate the glycemic response to high glycemic index (GI) foods. This can help the management of T2D patients and could be use even in synergistic way with other pharmacological treatments.

**Keywords:** *Ascophyllum nodosum*; Brown seaweed;  $\alpha$ -Amylase;  $\alpha$ -Glucosidase; Type 2 diabetes; Antidiabetic effect

**Abbreviations:** GI: glycemic index; T2DM: Type 2 Diabetes; NASH: Non-Alcoholic Steatohepatitis

## Introduction

Diabetes is nowadays becoming a global health concern due to its increasing prevalence both in developed and developing countries [1]. In 2011, it has been estimated that 347 million adults were affected by diabetes mellitus with an expected increase by 50% in the next 20 years [2]. The most common type of diabetes is type 2 diabetes (T2D), a metabolic disorder of the endocrine system that could be described as the incapability of insulin to activate the glucose transport system into the cells and an inappropriate hyperinsulinemia, which is due to insulin resistance [3]. As a result, this uncontrolled chronic hyperglycemia is responsible for the development of several vascular complications, such as retinopathy, angiopathy, nephropathy, and neuropathy [3]. There is a general consensus that the maintenance of normal blood glucose levels is one of the major goals in diabetes, and this can be achieved either by stimulating insulin secretion through drug therapy or by means of dietary control [4-6]. The latter approach seems to be a safer

and complementary treatment for T2D patients. One of the most recommended nutritional treatments for T2D is based on the reduction of the glycemic index (GI) of foods. Moreover, dietary control could be used to obtain a synergistic effect with other pharmacological treatments [7-9]. The inhibition of carbohydrate digestive enzymes, such as  $\alpha$ -amylase and  $\alpha$ -glucosidase, represents an efficient strategy for the dietary control of T2D [5]. Indeed, it has been demonstrated that the inhibition of these digestive enzymes can significantly lower the postprandial glucose level by slowing digestion of dietary starch, the major dietary source of glucose, and decreasing the rate of blood sugar absorption from the small intestine [5]. In T2D patients, this approach seems to be more efficient than controlling insulin secretion, by the fact that it is economic, convenient, and with virtually no adverse reactions [4].

Since the majority of T2D patients under oral hypoglycemic therapy have hyperglycemia due to poor adherence to therapy

because of the side effects [10], there is a growing interest in the use of natural products with anti-diabetes activity [11]. Brown seaweeds, e.g. *Ascophyllum nodosum*, are easily available food traditionally used by coastal communities, especially in Asiatic countries [12]. *Ascophyllum nodosum* is a brown seaweed species belonging to the class of *Phaeophyceae*, which is commonly growing on the northeastern coast of North America and the northwestern coast of Europe [13]. It has been reported that *A. nodosum* contains several bioactive compounds with numerous health benefits for humans, in particular the carotenoid fucoxanthin [14,15], phlorotannins [16], both high molecular weight- and simple phenolics, like catechins [17], hydroxybenzoic acid, coumaric acid, cinnamic acid, and caffeic acid (Olivier Dumay et al. 2004). These bioactive compounds have anti-obesity, antidiabetic and antioxidant potential [14,18-21]. Moreover, brown seaweed extracts contain sulfated polysaccharides, called fucoidans [22], that have been demonstrated to display multiple pharmacological properties, such as anti-proliferative and anti-inflammatory activities, and help to slowdown food digestion, since they increase viscosity, thus decreasing the absorption of blood sugar and cholesterol [23-25]. Zhang and collaborators have demonstrated that the solvent extracts of *A. nodosum* have a high phenolic content, and their administration could be correlated with a reduction of blood glucose levels in rats [18]. Although in this study, ethanol, butanol, methanol, and acetic acid have been used as solvents to extract active compounds from this seaweed, a water-based extraction system would be more desirable for functional food application, because of the absence of solvent residues [13], as suggested by Apostolidis et al., who studied water extracts obtained from *A. nodosum* demonstrating that they have a significant inhibitory effect on carbohydrate digestive enzymes, which appeared correlated to their phenolic content [26].

Two of the key digestive enzymes involved in starch breakdown and absorption are  $\alpha$ -amylase and  $\alpha$ -glucosidase.  $\alpha$ -amylase is a calcium metalloenzyme, secreted from pancreas and salivary glands, that catalyzes the hydrolysis of the  $\alpha$ -D-1,4 glycosidic linkages of starch, amylopectin, amylose, glycogen, and many maltodextrins into shorter oligosaccharides.  $\alpha$ -glucosidase is responsible for the final step of the carbohydrate digestive process in the brush-border surface membrane of intestinal cells, catalyzing the hydrolysis of  $\alpha$ -1,4 linkage of complex carbohydrates and disaccharides and giving as final products absorbable monosaccharides, e.g. glucose. Kim and collaborators demonstrated that fucoidans extract obtained from *A. nodosum* were able to inhibit both  $\alpha$ -amylase and  $\alpha$ -glucosidase, but the concentration of the bioactive compounds required for  $\alpha$ -amylase inhibition were higher than those for  $\alpha$ -glucosidase inhibition [27]. Moreover, they speculated the presence of a correlation between the harvesting period of *A. nodosum* and the activity of the algal extracts on carbohydrate hydrolyzing enzymes. As a conclusion, they postulate that the best harvesting periods to obtain the highest  $\alpha$ -amylase inhibition were summer and

autumn, whereas the best harvesting period for  $\alpha$ -glucosidase inhibition was autumn [27].

The reduction and the delay of glucose absorption through the inhibition of digestive enzymes  $\alpha$ -glucosidase and  $\alpha$ -amylase induced by algal extracts obtained from *Ascophyllum nodosum* had already been demonstrated by several preclinical and clinical studies [13, 28-31]. In particular, Gabbia and collaborators have recently studied the inhibition of digestive enzymes in mice fed with a diet particularly rich in fat, which developed non-alcoholic steatohepatitis (NASH). They found that the administration of a phytocomplex obtained from both *Ascophyllum nodosum* and *Fucus vesiculosus*, which is another brown seaweed, caused both a delay in carbohydrate digestion and a significant decrease in their assimilation in these mice [28]. Moreover, these authors suggested that since NASH could be associated with T2D and insulin resistance, brown seaweed extracts may be useful for glycemic control and for prevention of the transition of NASH to T2D.

### Discussion and Conclusion

*Ascophyllum nodosum*, a seaweed found in abundance along the US Northeast coast, is currently considered one of the underutilized brown algal species that contains a wide range of bioactive compounds with different biological effects [13]. In particular, *A. nodosum* extracts contain fucoxanthins, catechins hydroxybenzoic acid, coumaric acid, cinnamic acid, and caffeic acid and sulfated polysaccharides, called fucoidans. Among all the beneficial activity of brown algae reported in literature, these bioactive compounds have anti-obesity and antidiabetic potential [14,18-21]. Some studies reported that an efficient strategy to control hyperinsulinemia in T2D patient is the inhibition of carbohydrate digestive enzymes,  $\alpha$ -amylase and  $\alpha$ -glucosidase [4,5]. Kim and collaborators reported that fucoidans from *A. nodosum* inhibited both enzymes, whereas that obtained from another brown alga, *Fucus vesiculosus*, inhibited only  $\alpha$ -glucosidase [22]. Since it has been reported that fiber consumption is related to a significant reduction of multiple chronic diseases, such as diabetes, obesity, and hypertension, fucoidans of *Ascophyllum nodosum* could represent a pharmacological potential for T2D patients [32].

In conclusion, the pre-prandial administration of *A. nodosum* extracts to T2D patients can be exploited as a strategy to slow down the rate of carbohydrate digestion and assimilation [33]. Thus, the glycemic response to high glycemic index (GI) foods, associated with high blood glucose and insulin resistance, could be modulated by these products into one typical of foods with lower GI [34]. This takes on importance in the management of T2D patients and could be even use in synergistic way with other pharmacological treatments, improving their efficacy.

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