Design of low glycemic response foods using functional ingredients from seaweed.

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Abstract

Several aspects offoods affect starch digestion and glycemic response, including food's physical/chemical structure and the presence of anti-enzymatic compounds. The complex relationship between food properties, metabolism and diseases implies that designing foods with a consistent lower glycemic response turn challenging.Edible seaweedsare rich in several bioactive compounds -particularly polyphenols-, which can be used to develop new low glycemic response foods.This paper reviews what is known about functional ingredients found in seaweeds that may help to design lower glycemic response foods through mainly the inhibition of digestive enzymes related with the breakdown of glycemic carbohydrates. A global viewpoint is exposed, covering aspects related with seaweed's polyphenols compositionand application of such compounds to design new products.

Keywords: seaweeds; anti-enzymatic compound; polyphenols; glycemic response; functional food.

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1. The problem of high glycemic response foods

Cumulative scientific evidence suggests that the change blood glucose after food ingestion is an important indicator of carbohydrate qualityregarding its nutritional/healthy value (FAO/WHO, 1998). After meal, carbohydrates are catalyzed until simple molecules that can either be absorbed in the small intestine, contributing to the increase in blood glucose concentrations (postprandial glycemic response), or pass throughout the digestive tube until the large intestine, where gut microbiota can eventually ferment them (Englyst and Englyst, 2005; Cummings and Englyst, 1995).

The problem with foods producing high postprandial glycaemia, such as gelatinized starch-richfoodstuffs, derives from the fact that glucose causes a metabolic stress when present in the blood at elevated levels.Thus, it is accepted that diets producing constantly high postprandial blood glucose concentration are associated with increased risk of type 2 diabetes and cardiovascular diseases (Cavalot et al., 2006; Bonora& Muggeo, 2001), which are among the main causes of death worldwide(http://www.who.int/mediacentre/factsheets/fs317/en/; http://www.who.int/mediacentre/factsheets/fs312/en/).In turn, lower glucose and insulin levels have been associated with an improved metabolic profile of high-density lipoprotein cholesterol, glycosylated proteins, oxidative status, hemostatic variables and endothelial function, as well as protect against obesity, colon cancer and breast cancer(Brand-Miller, 2003; FAO/WHO, 1998). It has been suggested that adherence to low glycemic-index diets may be a valid strategy for achieving such low glucose and insulin levels (Solomon et al., 2010), although there should be considered that the actual effect of a diet on specific disease or its complicationsdepends on several other factors, including genetic ones, as has been described, for example, to age-related macular degeneration (Chiu and Taylor, 2011).

2. Starch, its digestion stages and enzymes involved

Human is an omnivorous beingthat requires, togetherwith an adequate physical activity, the consumption of a combination of macro- and micronutrients in the form of several foodstuffs to achievea healthy status, avoiding chronic diseases and increasing the wellbeing (US Department of Health and Human Services and US Department of Agriculture, 2015). Among macronutrients, starch is the major carbohydrate and represents the principal source of energy worldwide, being its consumption part of a healthy diet (Björck et al., 1994; Frost and Dornhorst, 2000; Copeland et al., 2009).

Starchis constituted by glucose units forming two types of biopolymers: amylose, which is linear (glucose with α-1,4 bonds) and amylopectin, which presents branches and a much higher molecular weight (glucose units linked by two types of bond: α-1,4 in the linear sections, and α-1,6 in the branching points). For each botanic origin, both polymers are present forming granules of different sizes, shapes and amylose/amylopectin ratios depending on the specific plant (Sajilata et al., 2006; Copeland et al., 2009). These granules (in natural form or "raw") present a compact semi-crystalline structure, showing low accessibilityto enzymes and consequently limited degradation rate and release of total sugars during gastrointestinal digestion (Chung et al., 2006). This low digestibility turns the native starch a poor source of energy. However, if the granules are heated in the presence of abundant water, as it is the case for most processed foods, gelatinization, i.e., transformation from a semi-crystalline to amorphous state,takes place, making the starch fully digestible. Heating provides energy to break the hydrogen bonds that stabilize thestarch chains in native granules, thus exposing polar groups that become available for interactions with water molecules. This means that starch molecules turnhighly disordered, making the granule much more accessible for the digestive enzymes (Osorio-Díaz et al., 2003; Tester et al., 2004; Han et al., 2006).Interestingly, after heating and due to thermodynamic processes, starch chains do not keep fully disordered (amorphous)for a long time, but rather tend to re-crystallize partially. This process takes place through the simultaneous generation of hydrogen bonding between chains and loss of water from the fine

structure; this phenomenon is called retrogradation and its degree depends ontemperature, time, and molecules size/branching(Sajilata et al., 2006; Copeland et al., 2009). Overall, this re-crystallization diminishes the digestibility of starch since the resulting structure is less accessible to enzymes, thus generating more moderated glycemic responses after intake than gelatinized starch (Parada and Aguilera, 2011).

Additionally, it should be considered that starch is not present as an isolate structure within the food matrix. In contrast, it is closely associated with other macronutrients, such as lipids or proteins; different microstructural interactions have been reported between these food constituents (Parada and Santos, 2016). Thus, this should also be considered when evaluating starch disposition in a given foodstuff.

Simple carbohydrates, such as glucose and fructose, do not require additional digestion stages after they have been released from the food matrix. In contrast, when consumed, starch is digested both in the mouth and in the small intestine by the action of several enzymes. The glucose produced from the starch digestion in the small intestine brush border is then absorbed and transported by the bloodstream to the tissues for its use or storage (Santos et al., 2012; Nichols et al. 2009). Throughout this process, α-amylase and α-glucosidase are the two key enzymes involved in starch breakdown and intestinal absorption. α-amylase is secreted by the salivary glands and the pancreas and it catalyzes the hydrolysis of α-D-(1-4) glycosidic linkages of starch (amylose and amylopectin), generating shorter oligosaccharides (Santos et al., 2012). α-glucosidase completes the starch digestion catalyzing the hydrolysis of complex carbohydrates and disaccharides into absorbable monosaccharides in the brush-border surface membrane of intestinal cells (Kim, Nguyen, Kurihara, and Kim, 2010).

Depending on starch digestion speed, several starch types can be identified: “Slowly digestible starch”, digested in 20 to 120 min andproducingslow/moderate changes in the postprandial glycaemia; “Rapidly digestible starch”, digested in less than 20 min, and producinglargechanges in

100 the glycaemia, even as high as those produced by simple sugars; and "Very rapidly digestible
101 starch", which is hydrolyzed in few minutes. The latter is digested during the first digestion stage
102 (e.g. mouth), and its effect on the postprandial glycaemia is not clear yet (Parada and Santos, 2016).
103 A separate category is undigested starch ("resistant"), which is not digested by either salivary or
104 pancreatic amylases and it passes to the large intestine, where it may be fermented by the
105 microbiota (Dona et al., 2010; Cummings and Englyst, 1995).

106 Thus, starch may exhibit quite different digestion kinetics, whichvaries according to the
107 specificfood properties. Briefly, this will depend on: (1) the molecular arrangement of the starch
108 granule, (2) the presence of substances that inhibit the action of the digestive enzymes (i.e. anti-
109 enzymatic compounds), (3) the food matrix (microstructure) which controls the accessibility to the
110 substrate and the mobility of enzymes in the food bolus throughout the digestion process, and (4)
111 the intimate interactions of starch with other components present in the bolus, which preclude the
112 direct contact between starch and enzymes during digestion(Parada and Aguilera, 2011).

113 In additionto thesefood properties, starch digestion and glycemic response also depend on the
114 profile of each consumer, including their genetic background, metabolic status or presence of
115 certain diseases, among others. For instance, a genome-wide association study with more than
116 13,000 subjects found that a variation in the glucose transporter gene SLC2A2 was associated with
117 the glycemic response to metformin, the first-line antidiabetic drug (Zhou et al., 2016).Also,
118 increasing physical activity has been suggested as a valid strategy for improving glycemic response
119 (Bidwell et al., 2014). Even particle size after mastication may affect the glycemic response,
120 showing the complexity of this process (Ranawana et al., 2010).

121 **3. The complicated relationship between starch digestibility and glycemic response.**

122 It is widely accepted that lower starch digestibility at gut level will inducea lower glycemic
123 response. However, scientific evidence refutespartially this idea (Parada and Santos, 2016;

Eelderink et al., 2012a,b), suggesting that glycemic response is a multifactorial phenomenon. Figure 1 shows a simplified diagram summarizing the main steps and enzymes related with food digestion and glycemic response. Note the complexity of the system, even though the diagram omits many details.

For example, Mandel and Breslin (2012) reported that high endogenous salivary α-amylase activity (due to a high copy-number of *AMY1* genes) was associated with improved glycemic homeostasis and a lower glycemic responsefollowing starch ingestion in healthy, normal-weight adults. This apparent discrepancy would possibly be due to early release of starch digestion products in the oral cavity; this processwouldprepare the body for incoming starch and the ensuing glucose through the vagal activation, resulting in an early insulin release that can be termed preabsorptive (or cephalic phase) insulin release. According to the authors,individuals with low activity of salivary α-amylase may be at a greater risk for glucose intolerance after chronic ingestion of starch-rich diets. Additionally, Butterworth et al. (2011) suggested that the detection by upper section gastrointestinal receptors, of maltose released during oral starch digestion may influence control of gastric emptying, insulin secretion and appetite, therefore modulatingpostprandial glycemic homeostasis. Moreover, it has been reported that the consumption of slowly digestible starch does not always result in a low glycemic response. If glucose enters the circulation at a slower rate, less insulin will be secreted to keep glucose concentrations below an acceptable limit, resulting in a slower uptake of glucose into tissues, then leading to a high glycemic response (Eelderink et al., 2012a,b).

Therefore, these data show that the association between starch digestion and glycemic response is much more complex than initially thought. Thus, much more research, including an interdisciplinary approach (for instance, interrelating studies on food structure, physiology), is necessary for a full understanding of the actual relationship between starch digestion and glycemic response.

4. Polyphenols as natural anti-enzymatic compounds

Anti-enzymatic components are molecules that diminish enzymatic efficacy during the digestion processin the gastrointestinal tract. In the context of the control of the glycemic response, it has been suggested that the inhibition of enzymes such as α-amylase or amyloglucosidase could diminish the postprandial glycemic response to starchy food (Kwon, Apostolidis, and Shetty, 2008).Foodstuffs contains several enzyme inhibitors, such as abscisic acid (a plant hormone especially important in the response to environmental stresses), phytic acid (a saturated cyclic acid, which is the principal storage form of phosphorus in many plant tissues, especially bran and seeds) and lectins (carbohydrate-binding proteins, which are ubiquitous in nature and are found in many foods) (Tester et al., 2004; Sajilata et al., 2006; Zocchi et al., 2017). Polyphenols, a large and heterogeneous group of phytochemicals containing phenol rings, are particularly relevant anti-enzymatic food components.

Several mechanisms of action explaining the polyphenols health effects have been suggested. Even though they are mostly known as antioxidants, they may also stimulate insulin secretion and reduce hepatic glucose output, as well as enhance insulin-dependent glucose uptake, activate 5’ adenosine monophosphate-activated protein kinase (AMPK), modulate the microbial population in the large intestineor show anti-inflammatory effects (Kim, Keogh, and Clifton, 2016).In the context of starch digestion, their widely known ability to become associated with proteins becomes especially relevant, since this means they can also associate with enzymes, lowering their efficacy (Parada and Aguilera, 2011). Thus, dietary polyphenols may inhibit, at different extents,all key enzymes related with carbohydrate digestion, i.e., α-amylase, α-glucosidase, maltase or sucrase (Williamson, 2013). Moreover, they also inhibit glucose absorption in the intestine by affecting several sodium-dependent glucose transporters (GLUT), such as GLUT2, GLUT5, GLUT7; interestingly, selective inhibition for each one of these transporters have been recently reported for the different polyphenol classes (Gauer et al., 2018).

The ability of polyphenols to inhibit certain enzymes is related to their well-documented interaction with macromolecules (proteins, but also polysaccharides), especially in processed foods. They can be either non-covalent interactions (mainly derived from hydrogen bonds and hydrophobic interactions) or covalent ones, including processes such as the oxidation of phenolic compounds or the cleavage of procyanidin interflavanic bonds to form carbocations (Bourvellec and Renard, 2012; Zhu, 2018). Phenolic compound scan also form an inclusion complex with starch in the form of amylose single helices facilitated by a hydrophobic effect (Zhu, 2015). All these interactions and their impact on food properties, such as phenolic compounds bioaccessibility, bioavailability, and even their actual anti-enzymatic effect, appear to be dependent on the type and structure of both phenolic compounds and macromolecules, as well as the processing (Ribas-Agustí, 2017). Nonetheless, the impact of these interactions on starch digestion remains as an unexplored research field.

Since this effect of polyphenols on the activity of digestive enzymes is largely associated with their interaction with proteins, it seems logical that it has been mostly observed for the polyphenols class known to be especially prone for this kind of interactions, i.e, tannins. Thus, several *in vitro* studies have reported the enzyme inhibitory activities of condensed tannins or proanthocyanidins from different sources (persimmon, sorghum, rowanberry or almond seed skin, among others), with different monomeric units (catechin, epicatechin, epigallocatechin, epicatechin-gallate, robinetinidol or fisetinidol) or inter-monomeric linkages (A-type and B-type) on α-amylase and α-glucosidase. These inhibitory activities have also been reported for hydrolysable tannins, being dose-dependent, as well as for phlorotannins present in seaweeds- this aspect will be discussed separately. Nevertheless, such effects have also been reported for other phenolic compounds, such as anthocyanins. Indeed, the main structural aspects of polyphenol contributing to their potential as inhibitors of digestive enzymes have been reported.

5. Seaweeds as a source of anti-enzymatic polyphenols

198 Seaweeds are among the several natural sources of anti-enzymatic compounds, although knowledge
199 about them is limited.Edible marine macroalgae (or seaweeds) are consumed around the world, and
200 they have especially been used in the Far East (Chan, Ho, and Phang, 2006). They have also been
201 applied as thickeners and gelling agents, as well as fertilizers and cosmetic ingredients (McHugh,
202 2003). Seaweeds have been classified based on pigmentation into brown (Phaeophyta), red
203 (Rhodophyta) and green (Chlorophyta) types, and contain several potentially healthy components,
204 including dietary fiber, polyunsaturated fatty acids, mineralsand certain vitamins (Brownlee et al.,
205 2005; MacArtain et al., 2007; Rodriguez-Bernaldo de Quiros, Lage-Yusty, and Lopez-Hernandez,
206 2010).

207 But the most relevant aspect of seaweeds regarding starch digestion is their high polyphenol content.
208 Indeed, seaweeds are characterized by specific polyphenols classes, not found in other vegetables.
209 Brown seaweeds contain phlorotannins, polymeric structures constituted by units of phloroglucinol;
210 depending on the linkages between the units, phlorotannins are divided in fucols, phlorethols,
211 fucophlorethols, fuhalols and eckols (Martínez and Castañeda, 2013).Red and green seaweeds
212 contain bromophenols, complex structures originated by different combinations of the structural
213 units 2,4-dibromophenol and 2,4,6-tribromophenol (Zhao et al., 2018).However, it should not be
214 disregarded that seaweeds also contain those polyphenol classes commonly found in vegetal
215 materials, such as phenolic acids and flavonols (Rajauria, 2018). There is an increasing interest on
216 the study of specific seaweed polyphenols (Martínez and Castañeda, 2013), and advanced analytical
217 techniques have contributed to their characterization (Heffernan et al., 2015; Steevensz et al., 2012);
218 still, much more information is needed about these complex structures.

219 Several studies have explored the enzymatic inhibition activities of extracts rich in seaweed specific
220 polyphenols. Thus, bromophenols from red seaweeds such as *Gratelopupia elliptica* or
221 *Symphyiocladia latiuscala* have been shown to inhibit α-glucosidase, sucrase, maltase and aldose
222 reductase (Wang et al., 2005; Kim et al., 2008), while phlorotannins from brown seaweeds such as

Eisenia bicyclis, *Ecklonia cava*, *Ascophyllum nodosum* or *Fucus vesiculous* are able to inhibit α-amylase and α-glucosidase (Okada et al., 2004). The inhibitory capacity of each seaweed may not be the same for all enzymes, but rather specific depending on the seaweed's polyphenolprofile. Thus, while extracts from*Ascophyllum nodosum* had the strongest α-amylase inhibitory effect, the extracts from*Fucus vesiculosus* were found to be potent inhibitors of α-glucosidase (Lordan et al., 2013).

It seems that, in addition to phlorotannins or bromophenols, other polyphenols found in seaweeds possess anti-enzymatic activity. For example, chlorogenic acid, which is abundant in potatoes, has also been found in red seaweeds (*Acanthophora spicifera* and*Gracilaria edulis*),green seaweeds (*Ulva fasciata* and *Enteromorpha flexuosa*) and brown seaweeds (*Padina gymnospora*) (Abirami & Kowsalya, 2017). This compound has shown, in *in vitro* studies, the ability to inhibit enzymes related to starch digestion andto regulate intestinal glucose transport (Karim et al., 2017; Moser et al., 2015).Probably, the combination ofmechanisms of action of phenolic compounds present in other natural sources with those specific of seaweeds, is behind the reported beneficial effect in blood glucose after supplementation with seaweeds in different animal models (Lauritano and Ianora, 2016).

A promissory group of bioactive seaweeds compounds are macromolecular antioxidants (or non-extractable polyphenols). These are either high molecular weight phenolic compounds or small polyphenols (eventually also carotenoids) associated with macromolecules of the food matrix, which are not present in the supernatants of the aqueous–organic extractions, so they are not commonly analyzed (Pérez-Jiménez and Saura-Calixto 2015). These compounds, scarcely explored in vegetal materials, have also been commonly ignored in research on seaweeds phenolic compounds. Nevertheless, some studies have reported the presence of this insoluble fraction of phenoliccompounds in species such as *Fucus vesiculosus*, *Halimeda opuntia* or *Halimeda monile* (Koivikko et al., 2005; Vidal et al., 2009).Sanz-Pintos et al. (2017) studied several edible seaweed

248 species collected in Chile and showed that macromolecular antioxidants are a major polyphenol
249 fraction (42% in average of the total polyphenol content); hydroxycinnamic acids, hydroxybenzoic
250 acids and flavonols were the main constituents, and this fraction exhibited remarkable antioxidant
251 capacity. Most macromolecular antioxidants are closely associated with dietary fiber; in the case of
252 seaweeds, many of these compounds are associated with alginic acid, a constituent of cell wall,
253 through ester or hemiacetal bonds (Arnold and Targett, 2003; Koivikko et al., 2005), both covalent
254 linkages. This originates a two-way feedback between the specific effects of polyphenols and those
255 of dietary fiber (Pérez-Jiménez et al., 2013). Therefore, it is worth exploring how macromolecular
256 antioxidants can also be a source of anti-enzymatic compounds related to starch digestion.

257 As described above,the main mechanism of regulation of starch digestion by seaweeds seems to be
258 enzymatic inhibition by intact phenolic compounds in the digestive tube. However, it should not be
259 disregarded that metabolites derived from seaweed specific polyphenols may ultimately affect
260 glucose homeostasis. It has been reported that phenolic metabolites from vegetal materials, once
261 absorbed, affect insulin signaling pathways (Scazzocchio et al., 2015). In the case of phlorotannins,
262 the information on their metabolic fate is still scarce, although some specific metabolites have been
263 reported (Corona et al., 2016; Corona et al., 2017). *In vitro* studies have shown that bromophenols
264 are able to inhibit aldose reductase (Wang et al., 2005), a cytosolic enzyme target for diabetes
265 prevention, so it would be relevant to determine whether absorbed bromophenol metabolites are
266 also able to induce this effect. Overall, more *in vivo* studies on the metabolic transformations of
267 phlorotannins and bromophenols -considering the particularly high inter-individual variability that
268 these compounds seem to show (Corona et al., 2017)- will help to obtain a complete overview of
269 the transformation of seaweed polyphenols, identifying potential metabolites involved in the
270 regulation of glucose homeostasis after absorption.

271 Finally, a key missing aspect for fully understanding the potential role of seaweeds in the
272 modulation of starch digestion is the development of clinical trials in subjects at different risk stages

and using realistic doses. Thus, although dozens of *in vitro* or preclinical studies on the potential effect of seaweeds in relation to diabetes prevention have been published (Lauritano and Ianora, 2016), to the best of our knowledge only two clinical trials have been performed (Paradis et al., 2011; Lee and Jeon, 2015). These studies (with *Ascophyllum nodosum, Fucus vesiculosus* and *Ecklonia cava*) showed promising results in relation to postprandial insulin and glucose levels, as well as on C-peptide concentration, but much more evidence should be provided.

6. Polyphenols from seaweed for the development of functional foods

In the last few decades,the interest and researchregarding the so-called functional foodshas increased strongly. These may be briefly defined as foods containing bioactive compounds, or phytochemicals, which may benefit health beyond the role of basic nutrition, either helping the promotion of optimal health conditions or reducing the risk of non-communicable diseases (Doyon and Labrecque, 2008). The development of functional foodsinvolves mainly the addition ofthe so-called functional ingredients to foodstuffs to enhance their health properties. Development and validation of functional foods is a complex process comprising, among others, chemical characterization of natural sources, optimization of the process of extraction and purification of the bioactive compounds, food design aspects, technological and sensorial research and, finally, *in vivo* validation of alleged health claims (Granato et al., 2017; de Boer et al., 2016).

In the case of seaweeds, their use as natural sources for the development of new functional foods focused on the regulation of starch digestion is a promising field, as described above. Nevertheless, this should be approached by an integral point of view, considering four different areas, with multiple interactions among them: seaweed research, process research, food research and nutrition research. An overview of the complexity of this approach is shown in Figure 2.

First, if seaweeds are to be considered as raw material for bioactive compounds, it is important to increase the basic biological studies on these natural products. This should include advances in the

297 identification of edible species as well as in the characterization of their polyphenols profile.
298 Moreover, engineering research on seaweeds should ensure the design of sustainable production
299 systems, suitable to get appropriate volumes of biomass, with minimum environmental damages,
300 and reaching a stable algal composition (Michalak and Chojnacka, 2015; Little et al., 2016).

301 Given the wide variability of polyphenols from seaweed, their extraction requires the development
302 and optimization of suitable and reproducible protocols to extract the desired specific group.The
303 most common methods of extraction for food applications are Soxhlet extraction, ultrasound-
304 assisted extraction, accelerated solvent extraction, and shake extraction,among others, which have
305 been used to obtain several types of compounds, including polyphenols (da Silva et al., 2016).In
306 recent decades,methods which avoid the use of toxic solvents, such asextraction by pressurized
307 water and supercritical fluid, have become increasingly relevant and can even be more effective
308 than conventional methods (e.g. methanol extraction) for the recovery of compounds such as
309 polyphenols. Water appears to be a suitable extraction solvent possessing several advantages: easily
310 accessible, non-toxic, environmentally friendly, and non-hazardous to operator health (Çam and
311 Hışıl, 2010). These novel extraction systems should be specifically explored in the case of seaweeds;
312 for instance, it was observed that pressurized hot water extraction of *Gracilaria*
313 *chilensis*polyphenols yielded higher antioxidant capacity than conventional aqueous-organic solvent
314 extraction (Sanz-Pintos et al., 2017). Nevertheless, in other seaweed species (*Ascophyllum nodosum*,
315 *Pelvetia canaliculata*, *Fucus spiralis* and *Ulva intestinalis*) pressurized liquid extraction did not
316 lead to higher antioxidant capacity than traditional solid liquid extractions, showing the relevance of
317 the optimization of specific protocols for the different seaweeds. For instance, a particular
318 pressurized liquid extraction protocol (ethanol:water 95:5 at 160ºC) was found as the best procedure
319 for extracting phlorotannins from *Sargassum muticum* collected on North-Atlantic coasts, without
320 further improvement when it was combined with enzymatic treatments. These studies have focused

on phlorotannins; to the best of our knowledge, pressurized liquid procedures have not been evaluated for extracting bromophenols from seaweeds.

Seaweed extracts, once obtained, may need the application of further purification techniques, such as chromatography (commonly with Sephadex LH-20 columns), ultrafiltration (using membranes with cut-off between 100 and 5 KDa) or liquid–liquid fractionation (for instance, with ethyl acetate). Another strategy recently reported for the purification of phlorotannins from *Macrocystis pyrifera* was theadsorption on macroporous resins (Leyton et al., 2017).Further technological advances are also needed in this area.

For some applications, the whole matrix of seaweeds (commonly after drying) may be used as source of bioactive compounds, without the need of extraction or purification processes. This is particularly relevant considering the complex formed between macromolecular antioxidants and dietary fiber, which may represent a major percentage of the dry matter in certain seaweeds (Sanz-Pintos, 2017). Similar strategies for using the whole material as food ingredient have been suggested for other natural products such as grape pomace from wine making (Martínez-Maqueda et al., 2018). Nevertheless, in the case of seaweeds, their known high content in certain minerals, such as iodine or certain heavy metals, should be considered for discerning when it is better to adopt a strategy of whole material or when it is preferable to obtain extracts rich in specific compounds.

Extensive research on the field of food science is also a key step for a successful development of new functional foods using seaweeds. Theapplication of algal phenolic extractsin “real” foods is limited by their unpleasant taste; however,the use of technologies of encapsulation appears to be effective to alleviate these deficiencies. Among these techniques, the most common are spray drying (the most used), coacervation, liposome entrapment, inclusion complexation, co-crystallization, nanoencapsulation, freeze drying, yeast encapsulation and emulsion (Fang and Bhandari, 2010). This kind of processes may also ensure the stability, bioactivity and bioavailability

of phenolic compounds. Overall, the application of these technologies for the development of functional ingredients from seaweeds is still a pending task.

A key aspect for the successful application of seaweeds in the modulation of starch digestion is related to the validation of their beneficial effects. Thus, a specific effort towards the exploration of selective effects on enzyme inhibition, due to their potential health implications described above, should be developed. For this, *in vitro* studies are still the first necessary stage, particularly useful for wide screening of seaweed species, although analytical optimization for avoiding potential interferences are still under development (Nyambe-Silavwe et al., 2015). These studies must be combined with preclinical and, particularly, clinical trials, aiming at elucidating both the metabolic fate of seaweed polyphenols and their ultimate biological activities.

Conclusions

The relationship between food composition, starch digestibility, glycemic response, and development of diseases appears to be complex and needs multidisciplinary research to understand and design healthier foods. Specifically, there is a potential benefit for the selective inhibition of enzymes related to the breakdown of starch. Seaweeds are an important source of functional ingredients related to the management of postprandial glycemic response of starchy foods, particularly phenolic compounds. An integrative approach for the successful development of new functional foods for seaweeds aiming to modulate the glycemic response is needed, including: biological and chemical sciences related with seaweed; chemical and engineering aspects related to the extraction and purification of polyphenols; food technology for the stabilization of phenolic extracts and the design of new food products; as well asnutrition studies to validate the health claims of the final foods.

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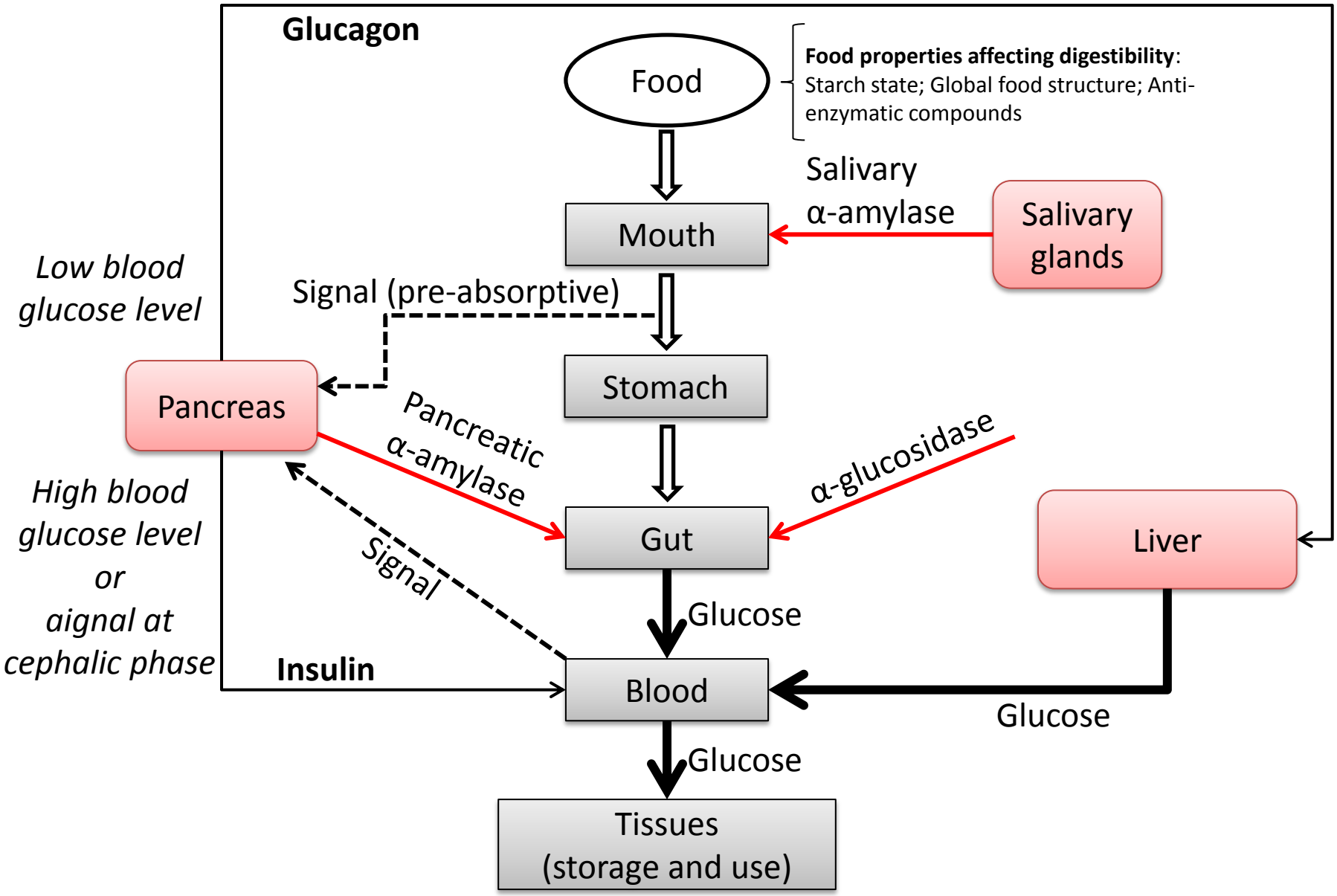
635

636 **Figure Captions**

637 **Figure 1.**Global process of starch metabolic fate. In red, key enzymes are shown affecting the
638 glycemic response.

639 **Figure 2.**General stages in the development of functional foods using seaweed as source of
640 bioactive polyphenols, from an integral point of view.



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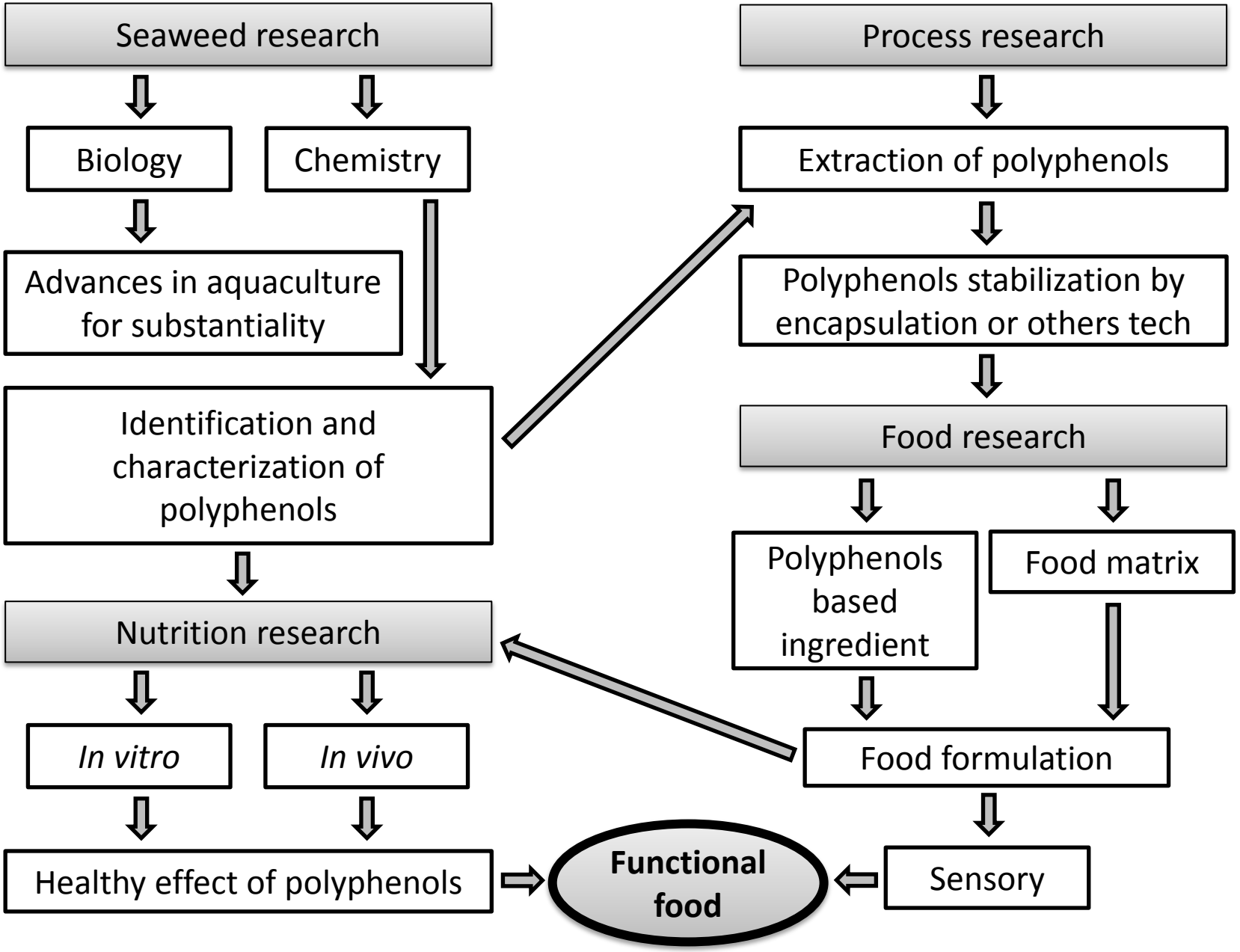

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