

A mini-review on the microbial continuum: consideration of a link between judicious consumption of a varied diet of macroalgae and human health and nutrition

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Abstract As the primordial, prokaryotic inhabitants on Earth, microbial entities were responsible for significant influences on the pathways taken in the development of life as we know it. The manifestation of numerous pathologies in humans is considered to be intrinsically associated with microbial dysbiosis in the gut (i.e. a poorly balanced microbiota). Such adverse health conditions include obesity, chronic fatigue syndrome, cancer, cardiovascular issues, neurological disorders, colitis, irritable bowel syndrome (IBS), and rheumatoid arthritis. Endosymbiotic events at the single cell level took place billions of years ago, eventually leading to eukaryotes, photosynthesis, and multicellularity. Macroalgae (seaweeds) were amongst the first organisms to develop these characteristics. Microbes and macroalgae interacted in a pattern of co-evolution, a process that applies to most, if not all living organisms. It is recognized that the normal human microbiome consists of over a trillion microorganisms, including about 2 000 commensal bacterial species typically stationed in the gut. Many of these live in the colon, where they function in the digestion of foods, releasing bio-available nutrients, bioactive molecules, and various metabolites. They mediate communication signals between the gut and the brain, and promote the normal development of immune function, metabolic activities, behaviour, and neurological stability. As very early humans foraged for food, some would have benefitted from coastal diets, rich in seaweeds and associated microbes. Such diets would have consistently provided all the nutrients essential for survival and growth, and as such, could have conveyed competitive advantages and contributed to enhanced cognitive sophistication. This mini-review article highlights studies regarding the health benefits of dietary fibres and the production of short chain fatty acids (SCFA). Insights are offered regarding the positive effects the inclusion of macroalgae into the standard, Western diet can deliver in terms of providing appropriate fodder for those microbial populations deemed beneficial to human health and wellness.

Keyword: microbiota; macroalgae; fibre; short chain fatty acids (SCFA); nutrition

1 INTRODUCTION

The prevailing theory that photosynthetic eukaryotes made their planetary debut when at least one heterotrophic eukaryote engulfed a cyanobacterium signifies a life-altering symbiotic relationship, and a prehistoric association involving a bacterial entity (Margulis, 1974, 1993; Collén et al., 2013; Nowack and Weber, 2018). As multicellularity

continued to evolve from this, and other endosymbioses, primitive marine macroalgae arose as being among the first organisms to have cellular interconnections (Cock et al., 2010; Knoll, 2011; Popper et al., 2011). As the massive primordial seas became home to a wide diversity of single celled organisms,

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plentiful opportunities to establish symbiotic relationships between, and among microbial populations and their hosts, including seaweeds, were exploited. Bacterial-eukaryotic interactions are ubiquitous, and the wide range of influences of bacteria on eukaryotes varies from subtle to profound. Secretions of a newly characterized marine bacterial chondroitinase (EroS), for example, acts like an aphrodisiac by inducing mating in *Salpingoeca rosetta* (a species of choanoflagellate), one of the closest living relatives to animals (Woznica et al., 2017). The growing realization that microbial influences are significant drivers of a myriad of life processes highlights the evolutionary importance of bacteria and other microbes (collectively called the microbiome) and their relationships to humans, animals and plants (Ikeda et al., 2010; Thomas et al., 2011; Flórez et al., 2015).

The likelihood that, by the very nature of its ready availability along shorelines 2.5 million years ago (mya), (when early human ancestors entered an era of brain development and enhanced cognitive sophistication (Schoenemann, 2006; Holloway et al., 2009; Cunnane and Crawford, 2014) seaweeds would naturally have been part of an increasingly diversified diet for some groups of people. Using a network-based analysis of RNA gene sequences from the fecal biota of a wide diversity of mammals, Ley et al. (2008) showed that herbivore microbiota contained the greatest variety of phyla, as compared to carnivores and omnivores. It is probable that the ancestors of early *Homo sapiens* were primarily tree-dwelling herbivores, before they became omnivores, and some groups would have also had access to coastal food resources (Verhaegen and Munro, 2011; Tattersall, 2014). The primitive human biome was developing in concert with a variety of microbes, influencing and adapting to every metabolic system. As a result of this dietary diversification, some gut microbes adapted to process a wider variety of carbohydrates, and many key gut bacteria became generalists, able to contend with an assortment of resources and their subsequent utilization (Stevens and Hume, 1998). Other members of the gut microbiota became specialists, only able to target a few select glycans, but all are elements of a metabolic network where substantial cross-feeding occurs as the by-products of one organism serve as important resources for another (Cockburn and Koropatkin, 2016). Lateral and horizontal gene transfers were, and still are phenomena enabling bacteria to evolve through the acquisition of genetic

material from other organisms, offering a competitive, fitness advantage and opportunities for the bacteria to increase in abundance. An extensive sequencing study by Moeller et al. (2016) revealed that clades of the *Bacteroidaceae* and *Bifidobacteriaceae* have been maintained exclusively within host lineages across hundreds of thousands of generations, indicating robust co-speciation, facilitated by strong vertical transmission. In addition, sequence analyses provided evidence for extensive sympatry between hosts and their colonizing microbial populations (Sonnenburg, 2010; Blaser, 2018). Hence, the co-evolution of eukaryotes and their commensal, or symbiotic microbial populations must play an important role in the adaptation and fitness of the host (Margulis, 1993; Zilber-Rosenberg and Rosenberg, 2008). Some of these keystone microbial relationships could well have been influenced by dietary seaweeds, highlighting the efficacy of marine macroalgae as a prehistoric and fundamental food.

Recent studies have established that human gut microbes play multiple and essential roles in securing the health and survival of their host (Donia et al., 2014; Cani and Everard, 2016). In addition, specific forms of dysbiosis are clearly associated with the expression of various pathologies, including, among others, inflammation, obesity, cardiovascular diseases, colitis, and neurological disorders (Mazmanian et al., 2008; Chow et al., 2010; Clemente et al., 2012; Le Chatelier et al., 2013; Roszyk and Puszczewicz, 2017). The impacts of the host/microbe interdependence are profound in their influence, encompassing food digestion, carbohydrate fermentation, energy harvesting and storage, gene expression, the secondary generation of beneficial compounds (i.e. cross-feeding), and the facilitation of metabolic functions. Considering the likelihood that seaweeds comprised a readily available and stable food source at the beginning of hominid development and migration (Dillehay et al., 2008; Cornish et al., 2017), it is feasible that the consumption of macroalgae by primitive foragers may have contributed to the establishment of a core group of residential gut microbes. Indeed, marine macroalgae have been challenged by microorganisms throughout their evolution and they continue to evolve in a world of microorganisms (Goecke et al., 2010). These particular microbes probably included members of *Firmicutes*, *Bacteroidetes*, and *Proteobacteria*, the latter two of which are known to digest the galactan sulphates commonly found in red algal cell walls

(Miranda et al., 2013). These taxa are also typically found in the healthy human microbiota, although their relative proportions can vary dramatically, depending upon numerous factors, including diet, local environment, genetic pre-disposition, and various personality characteristics associated with the individual (The Human Microbiome Project Consortium, 2012; Lloyd-Price et al., 2016; Davenport et al., 2017). Mammals have evolved an enormous range of digestive strategies and gastrointestinal structures, and in many cases, these anatomic variations are directly linked to the endogenous microbial communities (Stevens and Hume, 1998). Research has shown that microbial diversity in the gut, when low, is a risk factor (and a reliable biomarker) for diseases such as inflammation, obesity and insulin resistance (Le Chatelier et al., 2013). Alternatively, wide genetic diversity in the gut microbial communities is likely to extend the range of environments and resources within which the host can successfully forage for food. An enriched microbiota enhances opportunities for competition and favourable community development, providing important fitness advantages and a vehicle for out-competing pathogenic microbes (Martens et al., 2014; Sonnenburg et al., 2016).

Compounds produced from the microbial digestion or fermentation of macroalgae are important in the establishment and sustainability of the organisms that utilize them (Jiménez-Escrig et al., 2013). Short chain fatty acid (SCFA) contributions and adaptability programming enhanced by macroalgae in those earliest diets, potentially introduced keystone microbial consortia to the human microbiota. Where diet has such a profound effect on the microbial mix in the human gastrointestinal tract (GIT) (Wu et al., 2011; Sonnenburg et al., 2016), appropriate management of individual and collective food intakes deserves serious investigation. Seaweeds may be considered fundamental, yet complex foodstuffs with an ancient ancestry, and their more broadly-based utilization should be actively investigated. It is noteworthy that many factors can intrinsically influence both the bio-accessibility (release from the food matrix), and the bioactivity (uptake into tissues, metabolism, and physiological effects) of seaweed-derived food products, but little research has yet been done in this area (Wells et al., 2017). Furthermore, there is currently limited understanding of nutritional composition across algal species, geographical regions, and seasons, all factors that can substantially

influence quality and quantity of nutritive value (Stengel et al., 2011; Wells et al., 2017). Co-evolution of gut microbes and their hosts leads to an interdependence, as clearly demonstrated by the vast array of essential functions provided to the human host by its respective microbiota. Seaweeds were early contributors to the diets of *H. sapiens*, both directly, and through the animals that consumed macroalgae (Dillehay et al., 2008; Cunnane and Crawford, 2014; Kyriacou et al., 2014) and opportunities for their judicious and regularized utilization in global diets today is worthy of greater study and significance.

2 LITERATURE REVIEW

2.1 Macroalgae and their microbial relationships (co-evolution)

Primitive *H. sapiens*, as they diverged from their most recent common ancestor, began to develop, or acquire, an increasingly diverse gut microbiota as would be associated with fundamental changes in diet. Adapting to new foods and their associated microbiota is likely to have resulted in synergies leading to the utilization of non-selective energy sources within the host's gut microbiota. The most successful microbes can take advantage of rapid response times to environmental changes, and the ability to degrade a variety of resources. This would enable further GIT development through a system of integration and co-dependence whereby the gut microbiota enter into mutually beneficial partnerships with the host. The contribution of the gut microbiota to the host gene pool is estimated to be over 100 times more than that of the human genome (Qin et al., 2010). These genes encode a diverse array of functions which are actually absent from the human genome, including the considerable number of enzymes needed to process and utilize ingested carbohydrates (Muegge, 2013). Increasing diversity within the gut microbiota provided an increased likelihood of survival opportunities associated with the production of multi-functional metabolites and enhanced nutritional bio-availabilities (Duncan et al., 2008; Kovatcheva-Datchary et al., 2015). It is possible that marine macroalgae may have played a role in the early establishment of a complex, metabolically integrated microbiota, based on selective pressures of diet leading to the fixation of specific variants. These variants, as they increase in frequency, become part of the genetic make-up in the relevant population (Haygood et al., 2007). However, one must be

cognizant that accurate determination of the availability and subsequent uptake and utilization of nutrients from a given food matrix remains a significant challenge. This same difficulty exists with establishing the modes of action of the microbiota. Although research is increasingly making important progress, much more work in this area is required (Wells et al., 2017). Nonetheless, it is widely understood that a balance of nutritional inputs must be provided and processed in ways that sustain a synergistic and health-promoting portfolio of microbes necessary to meet the needs of the human host. Research has demonstrated the presence of microbial ecosystems with various species in important symbiotic relationships in plants, humans, and animals, indeed, in all living things (Long, 2001; Zilber-Rosenberg and Rosenberg, 2008; Blaser et al., 2016; Augustin et al., 2017). Gene sequencing and advanced data analysis capabilities are potent tools contributing to the explosion of research in this area regarding the microscopic dimensions of human health and wellness. The present mini-review will focus on those impacts which macroalgal components have had on gut microbiota, with some consideration given to those symbiotic relationships that could have been established early in the evolutionary timeline.

An example of one of the more striking aspects of the symbiotic relationships between algae and bacteria is the mutualism between vitamin B₁₂-synthesizing prokaryotes and certain B₁₂-dependent macro and microalgae (Croft et al., 2005; Croft et al., 2006; Kazamia et al., 2012). *Pyropia* (*Porphyra*) is considered one of the most ancient genera of macroalgae, belonging to the Order Bangiales, a primitive group of seaweeds, and quite feasibly the precursors to the red algal clade (De Clerck et al., 2012). *Pyropia* spp. have been demonstrated to be a viable dietary source of B₁₂ (Rauma et al., 1995; Watanabe et al., 2014), a vitamin essential to human health and development, but one which we are unable to produce ourselves. Scientists continue to question the processes underlying how species become dependent on an external source of essential micronutrients and the prevailing theory is that vitamin availability drives selection for vitamin dependence. This approach invariably links an organism's metabolic processes to its early environment (Helliwell et al., 2015), and offers some support regarding a dependable and long-term coastal diet for primitive *H. sapiens*. During the period of primitive brain development and enlargement, a

stable source of B₁₂, (cobalamin) essential for cognition and memory, could have been derived from a stable diet containing *Pyropia* spp. Prokaryotes are the only organisms that synthesize this important vitamin, and other sources at the time before the advent of tools and fire would include eggs, possibly scavenged meat, and fish, foods unlikely to be available on a long-term and consistent basis to early foragers. Although corrinoids are produced in the large intestine due to the activity of the gut microbiota, cobalamin produced here, where microbial numbers are highest, is not bioavailable because the receptors necessary for absorbing the vitamin are found in the small intestine, upstream of the site of corrinoid production (Seetharam and Alpers, 1982). In humans, the stomach releases an intrinsic factor that is essential for dietary vitamin B₁₂ absorption in the small intestine (Wells et al., 2017). Cobalamin has also been reported in other non-animal foods, such as mushrooms and other edible algae (Watanabe et al., 2014). Without an adequate supply of vitamin B₁₂, newborn infants express symptoms of cerebral and optic nerve atrophy, apathy and coma, hypotonia, and developmental delay (Von Schenck et al., 1997; Roumeliotis et al., 2012). Maternal intake must be sufficient during the nine-month human gestation period, and there remains a necessity for dietary replenishment during lactation. In a detailed chart review of 27 infants in India, Goraya et al. (2015) noted B₁₂ deficiency symptoms which included lethargy, irritability, feeding difficulties, refusal of solid foods, pallor, and failure to thrive, followed by neurodevelopmental regression. Thus, the historical importance of dietary seaweeds, which, while unlikely to be "proven", should not be dismissed.

Certain microbe/algal symbioses may contribute to improved growth rates, as in the case of *Bacillus* sp. WPySW2 and *Pyropia haitanensis* (Xiong et al., 2017), induced morphological changes (Provasoli and Pintner, 1980; Marshall et al., 2006), and effects on metabolic activities, defense mechanisms, hormone production, and oxidative imbalances (Garbary and London, 1995; Armstrong et al., 2001; Goeck et al., 2010; Singh et al., 2011; Singh and Reddy, 2014 and the references therein). An extensive evolutionary timeline has contributed to multiple opportunities for horizontal gene transfers to occur in macroalgae (Collén et al., 2013). This mechanism of transfer has also been discovered in humans whereby the gene encoding for specific seaweed carbohydrate-degrading enzymes has been acquired by the gut

bacterium *Bacteriodes plebeius* in certain groups of people (Hehemann et al., 2010; Rebuffet et al., 2011). An example of this became known among the general public as the *sushi factor* in the case of a common Japanese seaweed product *nori* produced by *Pyropia* spp. and often used for sushi. Hehemann et al. (2012), found that a portion of the Japanese population had gut enzymes that could break down porphyran from *Pyropia* whereas a population of North Americans did not. *Pyropia* is an ancient edible seaweed resource commonly consumed by people in Japan since the 6th century (Mouritsen, 2013). In a recent study by Kearney et al. (2018), *B. plebeius* was shown to colonize the mouse gut at high levels in the presence of an introduced, preferred substrate, i.e. *Pyropia* sp., with no evidence of competition for this substrate by native gut bacteria. The authors suggested that these results highlighted the possibility of seeding the gut microbiota with an appropriate substrate, matched with its microbial degradation partner through a process of re-programming a diet for therapeutic benefits.

Many diseases have been linked to the Western diet, and compared to more traditional food regimes, such a diet has led to a significant reduction in certain microbiota accessible carbohydrates (MACs) typically found in dietary fibres. Studies by Sonnenburg et al. (2016) using mice colonized with human gut microbiota illustrated an increasing loss of microbial diversity over generations as a result of dietary limitations of MACs, ultimately resulting in an unrecoverable loss of taxa, in particular, members of the *Bacteroidetes*. This preliminary research in mice led the authors to emphasize the importance of utilizing a variety of substrates for the maintenance of a diverse and healthy gut microbiota. They also suggested that as global initiatives to investigate precision medicine are launched (Riscuta et al., 2018), strategies to therapeutically target microbiota should involve the incorporation of MACs, as well as taxa not currently present in the Western diet. While numerous studies showed that short-term changes in diets can rapidly alter the GIT microbial populations, it is the long-term diet that better correlates to the specific enterotypes clustering in the human gut (Wu et al., 2011; Roszyk and Puszczewicz, 2017). It is the authors' view that marine macroalgae, with its long history of utilization as a natural and nutritional foodstuff within a wide variety of cultures (Mouritsen, 2013) should be given serious consideration as a standardized prebiotic. Obviously, research to further

verify this functionality must advance beyond animal models to include well-structured and focused human trials.

Of interest is the inability of humans to process a range of carbohydrates beyond starch, and simple sugars such as sucrose and lactose, and therefore we are dependent upon microbial degradation of most dietary polysaccharides to release essential metabolites and make available nutritional compounds (Stevens and Hume, 1998; Sonnenburg, 2010; Cantarel et al., 2012; El Kaoutari et al., 2013). The diversity and quality of marine macroalgal microbiomes present millions of years ago would set a precedent for human nutrition based upon a system of co-evolution in those groups of individuals with access to a shore-based diet. The fossil record indicates that humans diverged from a common ancestor approximately 5–7 mya (Holloway et al., 2009), and that macroalgae had been already prominent on the planet for at least 540 million years prior to that (Leliaert et al., 2016). In an extensive review of genomics sequencing data, Thomas et al. (2011) highlighted the diversity of *Bacteroidetes*, keystone, mutualistic members of the human GIT, equipped with numerous carbohydrate-active enzymes covering a broad spectrum of substrates, from plant, algal, and animal origin. The authors stated that this functional diversity had evolved through dynamic processes over evolutionary time, driven by highly frequent genetic rearrangements, gene duplications, and lateral gene transfers. Current science is only at the outer periphery of identifying and understanding all of the complex interactions and permutations of microbes and microbial enzymes within the GIT. For example, in a study analyzing the genetic composition of gastrointestinal bacteria of 397 people of various ages and nationalities, 850 bacterial genera that could potentially metabolize at least one foreign or exogenous substance were identified (Das et al., 2016). The ability to determine the precise bioavailability of macroalgal compounds in the human GIT may still be quite some time in the future.

2.2 Humans and gut microbiota

A well-functioning human body results from the culmination of ongoing interactions of numerous dynamic consortia of microbes, all members of communities or niches, often within other communities, and widely influenced by the host's diet. Other influential factors exist, such as genetics,

environment, antibiotic regime, and individual predisposition, but diet constitutes one of the most pertinent attributes leading to health management, and the food is processed and transformed into nutrients and bioactive compounds primarily via the gut microbiota. Extensive investigative studies are establishing the multiple roles played by gut microbes in the manifestation of human health and disease. Microbially-mandated immune functions have widespread biological and physiological impacts, and microbial dysbiosis in the gut underlies multiple human pathologies related to immunity, including rheumatoid arthritis, inflammatory bowel diseases (IBDs) such as Crohn's disease and ulcerative colitis (Elson, 2000; Mazmanian et al., 2005; Clemente et al., 2012; Nanjundappa et al., 2017; Roszyk and Puszczewicz, 2017). Other conditions leading to detrimental health issues have also been shown to be impacted by gut microbiota and the uncontrolled proliferation of unfavourable (pathogenic) species, as they gain an advantage and out-compete beneficial strains. This can result in metabolic disorders such as obesity, diabetes, blood flow regulation/hypertension, sleep deprivation disorders, and various forms of neurological dysfunction (Benedict et al., 2016; Cani and Everard, 2016; Thiba et al., 2017; Farzi et al., 2018; Jocken et al., 2018). Fundamental to the effective maintenance of a health-promoting microbial profile, is the appropriate management of that system through its energy/food source. As an example, the efficiency with which the microbiota degrade polysaccharides relates to the calories the host can extract from its diet, potentially influencing the survival and fitness of both host and microbiota, in a truly mutualistic association (Sonnenburg, 2010; Cockburn and Koropatkin, 2016). The nature of the metabolites produced by microbial degradation adds to the web of functional inter-dependence, and the product mix is dependent upon the substrates provided to the GIT.

An important health-promoting product of beneficial gut bacteria are the short chain fatty acids (SCFA), e.g. propionate, butyrate, and acetate, which are derived from dietary fibre (i.e. polysaccharides/oligosaccharides). These are normally resistant to digestion in the small intestine and are fermented in the large bowel. It is surmised that both the amount and relative abundance of SCFAs may be considered as biomarkers of a healthy status (Ríos-Covián et al., 2016). The nutritional substrates provided to the gut microbiota present multiple opportunities within the

microbiota, and these unicellular organisms switch metabolic status accordingly, so as to maintain their associated niche population homeostasis. To demonstrate this mechanism, an investigation into the effects of a food-grade antimicrobial agent on the gut microbiota in a mouse model ultimately revealed only a transient perturbation of the microbial community, indicating a dynamic but resilient microbiome (You et al., 2017). This plasticity of endogenous microbial populations in the gut is a strong selection factor related to host fitness. The ability of bacteria to multiply rapidly and to adapt to new environments is a well-known characteristic, and a highlight of their persistence and evolutionary success. Biological systems favour community robustness, which is often based upon various symbiotic relationships, and SCFAs play a major role as mediators of function and facilitators of the provision of energy. SCFAs are absorbed and used in different biosynthetic pathways by the host such as shaping the gut environment, thereby influencing the physiology and structure of the colon, acting as energy sources for host cells and the intestinal microbiota themselves, whilst also participating in different host-signaling mechanisms (Den Besten et al., 2013). SCFAs may also regulate cell proliferation through the release of growth factors or gastrointestinal peptides, or additionally, through the modulation of mucosal blood flow. SCFAs are also known to influence the genes regulating cell proliferation (Siavoshian et al., 2000; Blottière et al., 2003; Ríos-Covián et al., 2016).

Of utmost significance is the influence SCFAs have on brain function via the bi-directional hypothalamic pituitary adrenal (HPA) axis, sometimes referred to as the gut/brain/microbiota axis. These important fatty acids are critical factors in the maturation and function of microglia, which in turn acts as the primary form of active immune defence in the central nervous system (CNS) (Erny et al., 2015). Butyrate not only exerts anti-depressant effects in humans, it plays a significant role in the intervention of neuro-degenerative diseases and psychiatric disorders (Farzi et al., 2018). Both butyrate and propionate can modulate brain functioning, in particular appetite and energy homeostasis through the regulation of neuro-peptide production (Bourassa et al., 2016; Oriach et al., 2016). Mechanisms by which the microbiota influences the gut-brain axis include modification of autonomic/sensorimotor connections, immune activation, neuro-endocrine pathway regulations, and interactions between microbial metabolites and the blood-brain

barrier (Hoyles et al., 2018; Wang et al., 2018b). Furthermore, studies have shown that microbe-generated metabolites were intrinsically integrated within host cell biochemistry and physiology and SCFA-mediated cell-signaling is a key pathway used by microbes to communicate with the host (Cryan and Dinan, 2012; Moos et al., 2016 and references therein). However, abnormally elevated levels of certain SCFAs appeared to be linked to deleterious effects on human health and wellness, such as obesity and cognitive issues in autistic children (MacFabe, 2013; Perry et al., 2016), but, a definitive cause and effect has not yet been clearly identified, and research continues in this area. In the case of butyrate, for example, the general view was that sufficient butyrate production by the gut microbiota is a crucial component for maintaining host health, but chronic imbalances in its supply and utilization could facilitate the manifestation of disease. Key gut microbes critical to the production of butyrate encompass taxa from various *Firmicutes* families and some *Bacteroidetes* (Vital et al., 2017), which suggested that foods promoting the colonization and maintenance of these species were likely to also contribute to overall health benefits. Caution must be applied to such a simplified approach however, as excesses of gastrointestinal *Firmicutes* sp. have been associated with obesity, as is low bacterial richness in general, and research is still at the very early stages of providing an understanding of the various complexities around diet and microbial interactions (Ley et al., 2005, 2006; Davenport et al., 2017). For instance, we do not yet know whether the individual molecule, gene, pathway, strain, genus, family, consortia of co-operating species, or other combination is most relevant to human health and disease (Cani and Everard, 2016; Blaser, 2018). Research is responding, and Tramontano et al. (2018) have taken steps to determine the optimum nutrient requirements of a representative set of human gut microbes, 96 bacterial strains from 72 species over 19 different media. The results of that work highlighted robust growth in defined media, in many cases better in defined than in rich media, and interestingly, several species showed inhibitory responses to SCFAs and amino acids. The authors suggested that other factors could possibly account for this, such as an accumulation of toxic intermediates or pH imbalances, and further research is underway.

2.3 Dietary seaweeds

Metagenomic analysis of fecal DNA extracted

from 33 distinct mammalian species indicated that all gut microbiota appeared to share a large core group of genes, but that the host diet strongly influenced their relative abundance and functionality (Muegge, 2013). The data showed that total protein intake was significantly correlated with the functional profile of the community, whilst fibre intake was significantly related to both the species composition and SCFA production. Virtually all the SCFAs circulating in the bloodstream are microbial in origin. Changes in SCFAs would indicate activity of the gut microbiota, which in turn would be based largely on the substrates provided to it (Bourassa et al., 2016). Non-digestible soluble fibre, such as polysaccharides (and their oligosaccharides) constitute over half of the total fibre content in seaweeds (Lahaye, 1991), and its utilization in the large intestine has been demonstrated to provide butyrate, propionate, and acetate (Liu et al., 2015). These particular soluble fibres are termed 'functional fibres' because they confer health benefits in humans.

Algal-derived, marine oligosaccharides are broadly classified into different groups depending upon their chemical diversity. For example, there are chitosan-, laminarin-, alginate-, fucoidan(s)-, carrageenan(s)-, and ulvan-oligosaccharides (Jutur et al., 2016). However, many of these fibres are not completely fermented by colonic bacteria, but various degrees of fermentation do occur, and are likely to vary by seaweed species, polysaccharide portfolio, and presence or absence of appropriate colonic microbiota (Holdt and Kraan, 2011; Williams et al., 2013; Chen et al., 2018; Zhang et al., 2018). Carbohydrates are known to fuel the Acetyl Coenzyme A (CoA) pathway, and this pathway dominates butyrate synthesis (Vital et al., 2017).

Quantifying the bioavailability, or fraction of nutritional or functional components that actually have an effect in relation to their residence time in the digestive system remains a significant limitation, and a full understanding of the various processes and mechanisms is far from realization. For example, Salvia-Trujillo et al. (2015) compared bioavailability of fucoxanthin (an accessory pigment, a xanthophyll, found in most brown seaweeds) under in vitro and in vivo (rats) conditions using nano-emulsion delivery systems with different carrier oils. While the fucoxanthin was absorbed into the intestinal epithelium in the same order in rats as observed for the in vitro solubility tests, the serum concentration was similar for all carrier oils, suggesting unanticipated internal biological activities. Determining

bioavailability of specific nutrients remains a significant challenge regardless of food source.

The oligosaccharide components of marine macroalgae are both numerous and varied, and often influenced by season and other environmental factors, conditions of practical importance to commercial entities, and well known in general. Laminarin is a storage polysaccharide found exclusively in brown seaweeds. It is not hydrolyzed by the human endogenous digestive enzymes (Devillé et al., 2007), but it has been shown to be used by human intestinal bacteria in an in vitro fermentation study. The resultant SCFAs in this study were primarily acetic, propionic and butyric acids, i.e. 63.96%, 25.91%, and 8.16% respectively (Devillé et al., 2007). In a six week feeding trial, adult rats fed different rates of a mineral blend containing ingredients isolated from the red seaweed, *Lithothamnion* sp. showed differences in caecal SCFA composition. There was a significant increase in propionate with the 0.1% mineral blend over the control and a significant increase in butyrate in the 0.1% blend compared to those receiving the 0.2% rate. The 0.1% supplemented group also contained significantly more bacterial diversity than the control group (Crowley et al., 2018). Assessing the bioavailability of these ingredients from the whole algae in the diet is an area worthy of further research.

In one of the earliest studies to assess the prebiotic potential of the red seaweeds, *Chondrus crispus*, and *Sarcodiotheca gaudichaudii* in layer hens, Kulshreshtha et al. (2014) supplemented a standard poultry diet with powdered whole seaweed biomass (at rates of 0.5%, 1%, and 2% wt/wt) of each species. The seaweed diets were found to increase the abundance of beneficial bacteria, reduce the prevalence of pathogenic bacteria, and significantly increase the concentration of SCFAs in the cecal digesta. Acetic acid content was greater in the birds fed 1% *Sarcodiotheca gaudichaudii* or *Chondrus crispus* (52.21 mmol/kg; 51.53 mmol/kg, respectively) as compared to either the basal diet (29.94 mmol/kg), or the industry prebiotic standard, inulin (36.11 mmol/kg). The concentration of both propionic and butyric increased 2- to 3-fold in the seaweed treatments.

In a follow-up study to assess the prebiotic effects of a cultivated red seaweed, *C. crispus*, Liu et al. (2015) compared the results of supplementing rat feed with either 2.5%, or 0.5% dried, ground seaweed to diets including the same rates of fructo-oligosaccharide (FOS/inulin), with a standard basal diet as the control. In the 2.5% feed supplementation with

C. crispus, the concentration of the three primary SCFAs increased significantly, as compared to the control group, and similarly, acetic and butyric acids significantly increased in the 0.5% group. Fructooligosaccharide (FOS) supplementation also increased SCFA over the control, but that difference was not significant. Furthermore, in the seaweed supplemented diet, there was an increased abundance of beneficial colonic microbiota and a concomitant decrease in pathogenic microbes.

Kappaphycus alvarezii is a red seaweed typically grown for utilization in the food/hydrocolloid industry, generally as a cultivated biomass for the production of industrial gums (i.e. kappa carrageenan). However, recent initiatives to investigate other applications led to research indicating that this seaweed also has prebiotic potential. An in vitro colon model showed that *K. alvarezii* significantly increased total SCFA production, especially acetate and propionate, and it also significantly increased the *Bifidobacterium* sp. count, which are considered to be beneficial bacteria (Bajury et al., 2017). Feeding a supplement of dried and milled *K. alvarezii* (at 5% w/w) to rats receiving a high fat diet designed to induce metabolic syndrome symptoms demonstrated positive effects on their gut microbiota by selecting against increases in *Firmicutes* (excesses are also associated with obesity) and promoting *Bacteroidetes* (Wanyonyi et al., 2017).

Other research investigating the prebiotic effects of seaweeds or their extracts has focused on members of the Phaeophyta, which, in the case of *Saccharina latissima*, increased some of the SCFA content in healthy rats. Acetic and propionic concentrations in the seaweed-treated rats increased to 15.07 and 28.43 $\mu\text{mol/g dw}$ respectively, as compared to the control, 10.19 and 19.12 $\mu\text{mol/g dw}$ (Jiménez-Escrig et al., 2013). Other measures of the prebiotic potential of dietary seaweeds relates to modifications of microbial species in favour of those groups deemed beneficial to the host. An extract derived from *Laminaria digitata*, containing laminarin and fucoidan increased the digestibility of feed components and reduced pathogenic bacteria in newly weaned pigs, and these results also contributed to the overall health improvements of the pigs in this study after weaning (O'Doherty et al., 2010). Feed supplementation for rams with a commercial, air-dried brand of *Ascophyllum nodosum*, Tasco clearly modified their microbiota communities and reduced pathogenic bacterial levels (e. g. *E. coli*) (Zhou et al.,

2018). In addition, Okolie et al. (2017) published a review tabulating numerous trials indicating prebiotic activity and immune stimulatory responses to brown seaweed polysaccharides (BSP). These included β -glucans and laminarin from *L. digitata*, a fucoidan from *L. japonica*, low molecular weight polysaccharides from *A. nodosum*, and a range of BPS from *Ecklonia radiata*.

Kim et al. (2016, 2018) conducted studies on the impact of supplementing standard rat diets with *Undaria pinnatifida* or *Laminaria japonica* on the intestinal microbiota and the production of metabolites. The results of these studies indicated that adding those seaweeds to rat diets demonstrated multiple prebiotic effects including enhanced immune response and desirable changes in microbiota composition. Anti-obesity characteristics (proliferations of leanness-associated bacterial genera and increased production of butyric acid) were also apparent.

There are reports that seaweed polysaccharides are not fully fermentable in the large intestine (Holdt and Kraan, 2011), but evidence of increased levels of SCFAs in most investigations suggests reasonable functionality, at least in animal models. SCFA concentrations and bacterial composition are the most common prebiotic-based measures of the gut microbiota (Sawicki et al., 2017). However, it is also possible that dietary seaweeds could exert a positive impact on the microbial communities in the gut through other mechanisms, such as localized pH modifications, nutrient provision, regulation of gut metabolism, and by influencing cross-talk and general improvements in the GIT environment through increased hydration and enhanced surface area of the intestinal epithelium (Cian et al., 2015; Liu et al., 2015; De Jesus Raposo et al., 2016). Any selectively fermented ingredient that results in specific changes in the composition and/or activity of the GI microbiota and conferring health benefits upon the host is considered a prebiotic (Gibson et al., 2010). However, recent developments in community-wide sequencing and glycomic analyses have revealed that more complex interactions occur between putative prebiotic substrates and the gut microbiota than previously considered (Hutkins et al., 2016) and increased production of SCFAs is not the only measure of benefits. There are novel pathways by which gut microbes interact with host cells and *vice versa*, readily leading to changes in gut barrier and metabolic inflammation (Cani and Everard, 2016), and

components in dietary seaweeds are possible candidates for conferring positive influences. As sequencing technologies continue to advance, new species-level insights can be gained in the study of complex and therapeutically important microbial communities and their interaction with food-based substrates within the GIT. These should be carefully scrutinised over the coming years for leads related to the benefits of consumption of seaweeds on gut microbiota and human health.

3 DISCUSSION AND CONCLUSION

Scientists have now acquired a basic understanding of what constitutes a healthy human microbiome through cross-disciplinary studies correlating deviations from the healthy state to a wide range of known maladies. The impacts of gut microbiota are so extensive and widespread that the collective human microbiome itself may be considered as an “organ” that interacts with other metabolic systems in order to perform specific critical functions within the body (O’Hara and Shanahan, 2006). There is increasing evidence that the gut microbiota are an integral component of human physiology, with an important role in shaping both the innate and adaptive immune responses (Round and Mazmanian, 2009; West et al., 2015). The intestinal microbiota is also an important component of the mucosal barrier, the outermost layer of the intestinal epithelium and the largest area of the gut in contact with the external environment. In the mucosal layer, an effect of prebiotic administration enables the host to modify the intestinal microbiota through the production of mucus, secretory immunoglobulin, or anti-microbial peptides, while the microbiome shapes the immune response, interacting with receptors located in the intestinal epithelial cells, dendritic cells, or macrophages (Cian et al., 2015). Increased villi height and deeper crypt depth in the ileum are also beneficial effects of prebiotics (as demonstrated by red seaweed supplements in model animal trials), providing more surface area for housing innate populations of commensal microbial communities (Kulshreshtha et al., 2014). This is a microbially-mediated health benefit not only for the host, but also for the microbiota. The scientific world exploring the gut microbiota and humans has reached new dimensions, and definitions and terminologies continue to evolve in parallel. Ultimately, if a food enhances the gut microbiota in a way that is beneficial for the host, it remains a positive effect, regardless of the terminology

used to describe it. In the present review, the focus is supported by the current expert consensus for the definition of a prebiotic: 'a substrate that is selectively utilized by host microorganisms conferring a health benefit' (Gibson et al., 2017). A significant amount of published data already exists regarding the many health benefits attributed to the judicious intake of dietary seaweeds, but more cross-disciplinary studies are required to further assess the specific prebiotic effects in humans of this natural and ancient food in humans. In the Plant Kingdom, seaweed extracts have been shown to enhance the beneficial microbial communities associated with them, conferring fitness opportunities and productivity advantages (Alam et al., 2013, 2014; Wang et al., 2018a). The studies listed in this review clearly suggest that similar effects could apply to the microbiota co-inhabiting with humans and animals.

With such profound importance associated with the gut microbiota in relation to human health and wellness, and evidence for the detrimental loss of diversity (Moeller et al., 2016; Sonnenburg et al., 2016) within this 'forgotten organ' it would seem pertinent to investigate the offerings of the descendants of ancient seaweeds. An enlightening, newly developed database of intervention studies for applications of dietary fibres in human nutrition identified 188 studies, each with at least one outcome related to the gut microbiome. Results of this 'evidence map' identified 47 different fibre types, with oligosaccharides (i.e. 20% of the studies) the most frequently studied, followed by resistant starch (16%), chemically synthesized fibres (15%), inulin (13%), bran (13%), and cereal fibre (11%) (Sawicki et al., 2017 for further details). While it is possible that some macroalgal studies were included in these groups, it may also be unlikely, as seaweeds do not typically overly interest non-phycologists (yet), and there are currently some industrial limitations regarding standardized macroalgal products available to the western diet.

The widespread use of antibiotics in agriculture and healthcare has led to significant issues around antimicrobial resistance associated with perturbations of the innate microbial communities present in the GIT. The rise of antibiotic resistant pathogens also promotes microbial dysbiosis and allows opportunistic pathogens to flourish, to the detriment of the host. This is another arena where dietary seaweeds can play important roles, as they have co-evolved for millions of years in an environment rich in microbes which

were the first colonizers on earth, and numerous studies have demonstrated important *in vitro* antimicrobial activities of seaweeds (Cox et al., 2014; Kadam et al., 2015; Kausalya and Narasimha Rao, 2015; Pérez et al., 2016). While such effects are seemingly counter-intuitive to the promotion of dietary seaweeds as robust prebiotic resources, the field of microbiology in relation to diet and concomitant human health is extremely complex. Ultimately, it is the collaborative relationships microbial communities develop and maintain within an often loosely balanced, but dynamic system, which facilitate the expression of health and wellness for all participants. Human development (meat-eating, cooking, and consumption of highly processed foods) has significantly altered the innate microbial communities present in the GIT over the evolutionary timeline, particularly in westernized societies, but there may remain traces of those earliest inhabitants falling under the auspices of cryptic-genetic variation. This concept contends that the visible genetic diversity observed in populations is only a fraction of the potential diversity that standing genetic variation can produce, and environmental changes can stimulate expression of previously hidden phenotypes (Gibson and Dworkin, 2004). Viable methods to help detract societies from diets containing high fat, salt, and sugar components, and heavily processed foods must continue to be investigated in the interest of facilitating health and wellness. While still far from being scientifically proven, the addition of dietary seaweeds as a component of the Westernized diet may well provide functional benefits.

These are fascinating times when so many tools to investigate the myriad of relationships between humans and their microbiomes are becoming increasingly available and accessible. It is ironic that modern industrial societies appear to have lost more than half their GIT microbial diversity (Sonnenburg et al., 2016; Davenport et al., 2017), and at the same time developmental diseases related to inflammation, neurological irregularities, obesity, and immune deficiencies are increasingly prevalent. There is consensus within the scientific community that there must be great importance attached to the restoration of a diverse and well-balanced gut microbiome (Blaser and Falkow, 2009). This will be far from simple but a logical step in the right direction would point to the inclusion of a food such as seaweed, with a very long and positive history of co-evolution and consumption. Symbiotic (commensal) relationships

may have been established in the early hominid microbiota of those who consumed it as a dietary staple, as in the case of *B. plebeius* and porphyranase production (Hehemann et al., 2010; Rebuffet et al., 2011). As Blaser (2018) suggested, we may first need to prime our systems with seed, and then fertilize the true, and currently extinct, probiotic organisms with specific prebiotics in order to maintain and prolong our evolutionary fitness. Much akin to a re-set position to serve as the foundation upon which to build health and wellness truly from within, and based upon fundamental nutritional elements in terms of microbial substrate degradation. Consider, for example, that today, on a global scale, neuro-degenerative diseases such as Alzheimer's, dementia, depression, Parkinson's, etc., are on the rise, and these and other non-communicable diseases have surpassed infectious diseases as the principal cause of death, particularly in developed countries (Moos et al., 2016; Global Burden of Disease Collaborators, 2017; WHO (World Health Organization), 2018). There is evidence strongly linking these diseases to gut dysbiosis, and it is likely that a return to fundamental foods, including the types of nutritional resources early *H. sapiens* may have eaten during a time when brain size and its cognitive sophistication were expanding, is in order.

In this context, it is important to remark that with a diet that, due to the industrial processing of food, is increasingly more sterile and less contaminated with natural and environmental microorganisms, the diversity and robustness of the human microbiota is diminished. A similar remark is in order with regard to the reduced microbiota with newborn children who have been delivered under sterile conditions by a caesarian (Moya-Pérez et al. 2017).

It is exciting to read every day of new developments in this area of research, feeding the global knowledge-base, but the sheer magnitude of the number of variables may temporarily slow widespread therapeutic applications. However, there is significant interest, convincing rationale, and a certain sense of urgency to promote the judicious consumption of seaweed-based products for the establishment and maintenance of a healthy human microbiota. We suggest that this is a critical area for further human health, wellness, and nutritional research.

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