Review

New insights into the boron essentiality on humans and animals

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Abstract: Boron (B) is considered a prebiotic chemical element with a role in both the origin and evolution of life, as well as an essential micronutrient for plants, some bacteria, fungi, and algae. B has beneficial effects on the biological functions of humans and animals, such as reproduction, growth, calcium metabolism, bone formation, energy metabolism, immunity, brain function, and steroid hormones. In the future, naturally organic B (NOB) species may become promising novel prebiotic candidates. We included the most relevant works about NOB species, starting from our 30-year research experience. NOB-containing compounds have been shown essential for the symbiosis between different kingdoms. New insights into the essentiality of NOB species for healthy symbiosis between the human/animal host and the microbiota will determine the use of natural B-based nutraceuticals to target the colon (colonic foods). The mechanism of action (MoA) of NOB species is related to both the B signaling molecule [autoinducer-2–borate (AI-2B)], as well as the fortification of the colonic mucous gel layer with NOB species from the specific prebiotic boron-rich diet. Therefore, both microbiota and the mucous gel layer of the colon become the NOB species' target. This paper reviews the evidence supporting the essentiality of the NOB species on the symbiosis between the microbiota and the human/animal host with the stated aim of highlighting the MoA and target of these species.

Keywords: naturally organic boron containing compounds; prebiotic candidate; microbiome; intestinal microflora; symbiosis

1. Introduction

In science, boron (B) is considered a prebiotic chemical element with a role in both the origin and evolution of life [1–4], as well as an essential micronutrient (meaning that life cannot be sustained without it) for plants [5, 6], some bacteria [7, 8], fungi and algae [9]. Moreover, B is considered beneficial in human and animal nutrition [10, 11]. B has not been classified as an essential micronutrient for humans and animals because its biological role has not been clearly identified [12–14]. However, B has beneficial effects on the biological functions of humans and animals, such as reproduction, growth, calcium metabolism, bone formation, energy metabolism, immunity, brain function, and steroid hormones, including vitamin D and estrogen [11, 15–17].

As a scientific term, the word "prebiotic" has two meanings: (*i*) in the origin and evolution of life, "prebiotic" means either the chemical molecules essential for the evolution of life or the raw constituents from which these molecules were formed [3, 18]; (*ii*) in nutrition, "prebiotic" today means "a substrate that is selectively utilized by host microorganisms (thereby) conferring a health benefit" on the host itself [19]. The latest data on the accepted definition of prebiotics from nutrition and regulations have been very well reviewed [20]. Currently, prebiotics are based on microbiota-accessible carbohydrates (MACs) [21], but also on other natural phytochemicals, such as polyphenols [22, 23], polyunsaturated fatty acids (PUFAs) [24, 25], lactose and lactose derivatives [26]. The prebiotics' effects on human/animal health are increasingly being investigated, with many scientific papers published in this field [27]. Presently, the demonstrated prebiotic effects on health involve mainly benefits for the gastrointestinal (GI) tract, innate and adaptive immune homeostasis, cardiovascular metabolism, mental health and bone health [28–30].

MACs are the most important carbon source for bacteria within the colon, as they promote the growth of healthy bacteria, and the production of short-chain fatty acids (SCFAs) that can have multiple interactions with host tissues [31]. A diet low in MACs favor bacteria that degrade mucus and result in decreased diversity of bacteria with irremediable loss of beneficial bacterial strains; MACs also contribute to decreased epithelial integrity of the colon, favoring increased mortality and disease development, as proved within various preclinical and clinical research work [32]. The MAC class also includes the microbiota-accessible naturally organic B (NOB), which naturally occur in plants [33] and have been found in fruits, vegetables, herbs, nuts and seeds regular to the human nutrition [34, 35].

Various studies [36–38] have shown that sugar-alcohol B esters (SBEs) as NOB species are crucial in plant development. However, more recently, SBEs have been proved to be potential modulators of health in humans [33, 39–41]. The identification of the health benefits of SBEs and the further clinical recognition of their importance have become a novel direction of research into the science of NOB compounds.

To date, out of all SBEs, only fructoborate (FB) has been clinically tested, proving to have beneficial and quantifiable activity for humans [17, 33, 34]. The main physiologically stable phyto-SBE compounds are B pectic polysaccharides ramnogalacturonan II (RG-II) [42], glucose and fructose borate esters, *bis*-sucrose esters and borate polyalcohols (containing minimally digestible carbohydrates, such as sorbitol, mannitol, dulcitol) [41, 43–45] and recently discovered, chlorogenoborate diester (DCB) [46]. In the future, all these compounds may be promising novel prebiotic candidates. SBEs and DCB (detected in green coffee bean) are found in numerous vegetables and fruits ingested by humans and animals and from a biochemical point of view they are indigestible and microbiota accessible.

Recent studies have shown that since the *pKa* of SBEs is around 4.0, then their indigestibility is maximum above the postprandial pH (4.5) of the stomach [17, 33]. In the human cell, there are no known biochemical mechanisms that require B and, therefore, B has not found a specific status in the world of nutraceuticals. As the mechanism of action (MoA) of B has not been identified in human/animal cellular metabolism, the market for B nutraceuticals does not yet distinguish between NOB compounds (*e.g.*, SBEs, DCB) and naturally inorganic B compounds [boric acid (BA), borates].

There is a major scientific gap between the use of B compounds in human and animal diets and the MoA of B and its target in the body [11]. However, the latest investigations show that in bacteria, the signaling molecule containing B, furanosyl borate diester [autoinducer-2–borate (AI-2B)], contributes to the host health (*via* intestinal flora) and its protection against pathogens [17, 33, 47]. Because SBEs are similar to AI-2B, it has been claimed [33] that they can also increase the beneficial capabilities in some bacteria and reduce virulence in others. Considering the above developments, new insights into the essentiality of B species in humans and animals are emerging. This paper reviews the evidence supporting the essentiality of the NOB species on the symbiosis between the microbiota and the human/animal host, with the stated aim of highlighting the MoA and target of these species.

2. New insights into essentiality of boron species on symbiosis between kingdoms

Symbiosis is described as "the close relationship between two organisms of different species, with benefits for one or both individuals" [48]. Symbiosis is any kind of long-term and close biological interaction between two various biological organisms, be it parasitic, commensalic or mutualistic. These close interactions between species are often long-term and, for the most part, beneficial to symbionts [49].

B plays an essential role in several symbioses between plants/animals and bacteria such as:

(*i*) *Rhizobium–legume symbioses*: In micromoles concentrations, B has been recognized as a key element (essential micronutrient) in the formation of a symbiosis between legumes and a group of bacteria called nitrogen-fixing bacteria (*Rhizobium*, *Azorhizobium* and *Bradyrhizobium*) [50, 51], although these bacteria have not shown that B is essential for them. These findings show that when B lack exists, rhizobia–legume "dialogue" disappears, and the bacterium is identified as a pathogen agent by the plant with disastrous consequences for symbiosis. The unanimously accepted MoA is that arabinogalactan-protein extensin (AGPE), a hydroxyproline-rich glycoprotein, forms a B complex, while rhizobia cells are separated from it by an exopolysaccharide capsule [7, 52]. The existence of a bacterial exopolysaccharide capsule is necessary to prevent the attachment of the AGPE glycoprotein matrix to the surface of the bacterium [53].

(*ii*) *Arbuscular mycorrhizal (AM) symbiosis*: It is well known that a considerable natural accumulation of B in certain parts of plants (especially roots and leaves) is controlled by the presence of several mycorrhizal and saprotrophic species [54]. Recently, the mycorrhizal symbiosis has been shown to be essential for most plant species to acquire nutrients from the soil [55]. Although B does not play a key role in fungi, some of them are carriers for organic B species, consequently these fungal species has been assumed to function as agents for ameliorating B toxicity and regulating the amount of B species in plants [56]. An interesting fact is that some fungal species accumulate B, while other species exclude it, which suggests that B has specific functions among fungi [9]. Recent research has revealed the useful effect of the AM symbiosis by diminishing B toxicity in roots and leaves in a citrus rhizome. AM symbiosis is improving the tolerance of *Carrizo citrus* to excessive source of B by reducing the concentration and toxicity of B in leaves and roots [57]. It is believed that mushrooms do not require B for their own metabolism; the first hypotheses about B in fungi indicated that B could be sequestered as SBEs in forms unavailable to fungi. At present, not much information is available about the role of organic B species in AM symbiosis, but future research may clarify the essentiality of B in plants extending beyond the essentiality of B in symbiosis between mycorrhizae and plant [58].

(*iii*) *Actinorhizal symbiosis*: A nitrogen-fixing bacterium with structure and functionality similar to heterocyst cyanobacteria is *Frankia* strains, actinomycete symbionts of actinorhizal plants. *Actinomyces* species are ubiquitous in the soil and in animal microbiota, including human microbiota [52]. Certain species are commensal in the flora of the skin, the oral flora, the intestinal flora and the vaginal flora of humans and animals and it is assumed that they need B for symbiosis with the host (human/animal) [59].

(*iv*) *Algal–bacterial symbiosis*: B-vibrioferin (a borate–siderophore complex), was separated from the specific environment of a bacterial "symbiont" from a toxic marine dinoflagellate, indicating B as having a possible biological function for the symbiosis of the algal partner [60].

(*v*) *Animal kingdom–bacterial symbiosis*: At present, although there is scarce scientific evidence to show that B deficiency adversely affects the symbiosis between animal kingdom host and its microbiota, they still provide strong and sufficient arguments for B's importance in microbiota health, such as be:

(*a*) Recent data show that in microbiota bacteria, the signaling molecule containing B, AI-2B (furanosyl borate diester) contributes to the health of the host (*via* intestinal flora or microbiota) and its protection against pathogens [47]. There is a growing body of scientific work showing that the "language" of bacteria using AI-2 with B is a "language" both between species and within the same species, as well as between different kingdoms (the bacterial kingdom and the animal kingdom, in this case) [61].

(*b*) Orally administered, in toxic concentrations, for the *Blattella germanica* (L.) insects, BA caused the dysbiosis of the intestinal microbiota (IM) [62].

(*c*) B is essential for symbiosis (parasitic) between nematodes and microbiomes in mice. Low or marginal dietary intake with B may affect the establishment and survival of parasites through its effects on the intestinal microflora [63].

(*d*) Significant induction of *Xenopus laevis* tadpole larval growth has been shown to be correlated with changes in the host's intestinal microbial communities. These changes in host physiology are due to indirect effects of B that could stimulate bowel maturation, with a beneficial effect on bacteria that promote host metabolism [64, 65].

(*e*) Tartrolon is a natural B compound found in some species of bacteria and has been detected in marine bivalve mollusks of the *Teredinidae* family (a group of saltwater shells found in symbiosis with the *Teredinibacter turnerae* bacterium). Together with the *T. turnerae* bacterium, the marine bivalve mollusks are achieving the digestion of cellulose and nitrogen fixation. The antibacterial tartrolon produced by mollusk symbionts, located in their gills, helps suppress pathogenic bacteria in the mollusk's gut and allows the host to maximize the efficient absorption of glucose released by the breakdown of lignocellulose [66].

(*f*) For chickens, it was observed that B based nutrition (as BA, but in a diet rich in carbohydrates and phenolic acid and a simple calculation shows that 0.1% BA can be totally complexed by fructose and phenolic acids from the diet) helped to regulate the microbiota following the attack of pathological bacteria. The study suggests that B maintains intestinal homeostasis and is effective in controlling *Salmonella enteritidis* infection through the microbiota [67].

(*g*) Dietary B addition proved an influence related to dose on protozoan's abundance and rumen microbial fermentation in one-year-old rams. The higher B content in the feces could be explained by its availability for the microbiota, B is not being accumulated in any internal organ, but only in the intestine. The concentration of B in the rumen fluid was lower than in the feces [68].

(*h*) Other animal tests showed that, after five days of feeding the sheep with B, the feces had a high concentration of B (250 ppm), higher than in the urine (140 ppm), this experiment demonstrating the large capacity of the large intestine to "sequester" B [69].

(*i*) It has recently been found that when the indigestible B in the nutrition ingested by African ostrich chicks reaches the colon, it interacts with the microbiota, thus stimulating apoptosis and cell proliferation. The proliferation of intestinal cells is determined by the relationship between B and microbiota [70].

(*j*) B in oral washes has been noted to positively influence the periodontal health. During a specific experiment in which B was administered by gavage, B addition did not influence the dentin and enamel of rabbits given a high-energy nourishment [71].

(*k*) Moderate supplementation of dietary B has improved growth performance, digestibility of crude protein and diarrhea index in weaned pigs, regardless of health status [72].

(*l*) In humans, a natural diet rich in B has led to an improvement in the oral microbiota and, most importantly, to a decrease in thyroid-stimulating hormone (TSH), which is generally a consequence of dysbiosis. At the same time, the ability to buffer saliva increased significantly after a diet rich in B, the B level of decayed teeth was lower than that of healthy teeth [73]. Increased B in saliva has a positive effect on dental and oral health and may decrease the formation of cavities and show a potential as a treatment option for gingivitis and periodontitis [74]. Important changes in salivary buffering capacity and TSH during a natural B-rich diet are of clinical importance, with dysbiosis being a common finding in thyroid disorders [73]. Recent work also reveals that B-rich foods result in cardioprotective effects and longevity, improving long-term survival among patients with kidney transplantation (KTR)

[73]. Other recently work shows that B-rich foods determine low risk of mortality and a favorable cardiometabolic risk profile [75].

All these data show that mainly B organic species appeared to be essential for the symbiosis between the different kingdoms.

3. AI-2B is essential quorum sensing in symbiosis between microbiota and its host?

Quorum sensing (QS) is described as a bacterial communication activity, which determins competence, bioluminescence, sporulation, antibiotic production, virulence factor secretion, as well as biofilm evolution in bacteria. Recent study has proved that the breadth of QS includes inter-kingdom communication, intermediated by many newly determined extracellular signaling molecules called autoinducers (AIs) [76].

To date, two types of AI-2 structures were reported: (2*S*,4*S*)-2-methyl-2,3,3,4-tetrahydroxy-tetrahydrofuranborate (*S*-THMF–borate, AI-2B) in *Vibrio harveyi* and (2*R*,4*S*)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran (*R*-THMF, AI-2) in *Salmonella typhimurium* [77, 78]. AI-2 has been suggested to promote communication between interspecies bacteria in mammalian gut [79]. AI-2 is also playing an essential role in probiotic functionality and intestinal colonization [80], and is also correlated to gut dysbiosis [81, 82]. AI-2 concentration was correlated with gut microbial disorder, so that AI-2 can be considered a new biomarker for dysbosis [83].

AI-2B has a recognized role in bacterial communication (intra- and interspecies). The recent findings show that cross-communication inter-kingdoms (*i.e.*, bacteria and eukaryotic cells) takes place *via* the bacterium AI-2B quorum detection system [84]. The limit of detection for AI-2B can be from 35 nM to 0.4 μM. A bigger concentration of AI-2B could not cause luminescence, subsequently BA hinders AI-2B signaling [78, 85]. Still, at an AI-2B level of 70 μM, luminescence restriction happened. As shown, AI-2B from gut may modify the constitution of the microbe population from gut, improve dysbiosis caused by antibiotics and develop a healthy microbiota [86].

There is evidence that B is essential for the development of certain types of bacteria, such as heterocyst cyanobacteria and actinomycetes of the genus *Frankia*. Also, many other bacteria are tolerant to large amounts of B, although its essentiality has not yet been demonstrated for them. For example, 15 strains of bacteria (*Arthrobacter, Rhodococcus, Lysinibacillus, Algoriphagus, Gracilibacillus*, and *Bacillus* taxa) were isolated and then shown to have tolerance to high concentrations of B [87].

In symbiosis with other kingdoms, bacteria use the ability of B to attach to glycoproteins, thus blocking the bacterium from infecting the host of the symbiosis. In addition, the discovery of bacteria containing one B-signaling molecule (an AI-2 self-inducer, identified as furanosyl borate diester) revealed a surprising role for B in detecting the bacterial quorum. AI-2B is a new signaling molecule serving as a universal bacterial signal for communication between species and between kingdoms [88].

IM is distributed across the whole GI tract in a heterogeneous way. Collectively in humans, it is an ecosystem typically weighing 1.5 kg, being formed of more 1500 bacteria and more 1000 other species (for instance: viruses, fungi, parasites, phages, archaebacteria) [89, 90]. The most important bacterial phyla of a healthy IM are *Firmicutes* and *Bacteroidetes*, followed by *Fusobacteria*, *Actinobacteria* and *Proteobacteria*. Since the most important species are *Faecalibacterium*, *Bacteroides* and *Bifidobacterium*, IM achieves several functions, such as maintaining metabolic homeostasis, nutrient absorption, defense against infections, and the development of mucosa and systemic immunity. AI-2B could influence bacterial behaviors to maintain balance between *Bacteroidetes* and *Firmicutes* species. AI-2B is generated by multiple bacterial phyla found in the GI tract, such as *Bacteroides* spp., *Eubacterium rectale*, *Ruminococcus* spp. and *Lactobacillus* spp. [47, 91].

These remarks support the hypothesis that AI-2B is an essential signaling molecule that might regulate bacteria, community dynamics and behavior in the microbiota and could also modulate the composition of the microbiota under dysbiosis conditions. The AI-2B production by one phylum may affect the expression of genes of other species and can promote communication between species, allowing bacteria to change their behavior, namely virulence, luminescence, and biofilm formation between different species [92–94]. This feature makes AI-2B a great candidate for modulating interactions between cells in mammalian intestines, where thousands of bacterial phyla coexist and communicate [95]. An example of the protective role of commensal microbes against pathogenic bacteria is the following: AI-2B produced from *Ruminococcus obeum* can confuse *Vibrio cholerae*, resulting in premature repression of AI-2B quorum sensing-mediated virulence and decreased colonization in the intestine [96].

4. NOB species are essential for a healthy human/animal microbiome symbiosis?

Nutritional essentiality was clearly established as a concept about 100 years ago. It resulted from the observation that certain pathologies may be stopped by including a specific food in the diet. Physiological essentiality and nutritional essentiality are two different concepts. Physiological essentiality means an indispensable material for life, while nutritional essentiality means an indispensable material in the diet [97]. A substance is usually considered to be nutritionally essential if a substance deficiency from the diet results in a biological dysfunction. The higher intake of that substance prevents the biological dysfunction or makes it reversible. Below, we are trying to prove the nutritional essentiality of NOB species based on standard criteria of nutritional essentiality [97]:

(i)"The substance is necessary in the diet for growth, health and survival". B species as carbohydrates esters are needed for healthy symbiosis between human/animal host and the microbiota. The literature holds evidence that certain bacteria need B (AI-2B), a B carbohydrate, for communication, and our preliminary data show that the colonic mucus gel layer of rats also contains B (**Figure 1**). Our recent discovery of the presence of B within the colonic mucus will need to be confirmed by other laboratories. This not withstanding, glycoproteins containing B are used in all symbyosis processes between kingdoms in which B is involved, and in controlling the interaction between the two entities taking part in the symbiosis process [51].

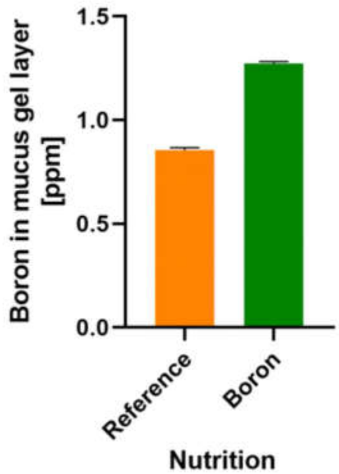

Figure 1. Boron detection in the rat's colonic mucus gel layer. Reference: normal diet [98]. Boron: CaFB (NOB) supplemented diet. Boron detection has been performed by UHPLC/MS method [99]. (Part I – Supplementary Material). CaFB: Calcium fructoborate; NOB: Naturally organic boron; UHPLC/MS: Ultra-high performance liquid chromatography/mass spectrometry.

(*ii*) "*Its absence from the diet or inadequate intake results in characteristic signs of a deficit disease and, ultimately, death*". The absence of B species from the diet could be a determinant, in our hypothesis, of the permeability of the intestine ("leaky gut syndrome") and dysbiosis. Dysbiosis and permeability of the intestine cause serious pathologies that lead to death, including inflammation, cancer, heart and brain diseases, arthritis, bone diseases [100, 101]. In most diseases, the composition of the microbiota is altered, causing pathophysiological diseases in vital human organs. The complex interactions between the IM and the host immune system influence the body's functions, resulting in the formation of an "axis" between the IM and various organs [102]. The "host–microbe" metabolic axis is a systemic multidirectional communication from the cellular pathways of the host's and different microbial phyla in the microbiota. Within these axes, various microbes sequentially regulate metabolic reactions, producing bile acids, choline, and SCFAs, which are vital to human/animal health. These metabolites bring their contribution to the metabolic phenotype of the host and the risk of developing the disease [103]. In our view, B deficiency from the symbiosis process may lead to dysbiosis and gut permeability by decreasing the concentration of AI-2B. At the same time, decreasing the concentration of B in the colonic mucus induces the formation of bacterial metabolites and proinflammatory cytokines, which could help the osteoarthritis (OA) pathophysiological mechanisms [104–106]. This mechanism could explain why in the areas with high content of B, people have a low OA index [107]. In our opinion, in the future, B analysis from the feces and colonic mucus could become an important marker indicating the B lack from nutrition and a predictive factor for several diseases resulting from unhealthy symbiosis.

(iii) "Growth failure and/or characteristic signs of deficiency are prevented only by the nutrient or a specific precursor of it, not by other substances". NOB species are prebiotic candidates that may help bacterial communication by AI-2B [33] and fortify the colonic mucus gel layer (**Figure 1**). Consequently, the effects of B species deficiency in the microbiota will could be: (a) Dysbiosis, an alteration of the symbiosis

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between the human/animal host and the microbiota. In our opinion this is happening due to the lack of B, which results in the deficiency of the AI-2B signaling molecule [17, 33]; (b) Increased intestinal permeability ("leaky gut syndrome") and translocation of the IM from the gut lumen to the systemic circulation, due to the lack of B in the structure of the mucin gel. It is well known from mucins separation techniques that the interaction of B with glycosylation sites within mucins, O-glycosylated linear glycoproteins, is known [108]. The B deficiency thus determines the interaction of the bacterial biofilm directly with the membranes of the host cell and, therefore, the infection of the host. Since 2008, B-stabilized glycoproteins have been claimed to be seemingly crucial for signaling during the symbiosis at plants. The description of MoA for B-stabilized glycoproteins created the probability that identical membrane constituents in animal cells may have a similar role due to B [109]. In all symbiosis processes in which B is essential, this cannot be replaced by any other supporting symbiosis [5].

(iv) "Below some critical level of intake of the nutrient, growth response and/or severity of signs of deficiency are proportional to the amount consumed". There is a direct correlation between the amount of B species ingested, the amount of B in the feces [69, 110, 111] and the level of B in the gel layer of colonic mucus following the NOB-supplemented diet in rats (**Figure 1**). It is known that in OA, diet modification by increasing B amount is resulting in diminishing OA severity depending on the ingested B amount [107, 112].

(v) "The substance is not synthesized in the body and is therefore required to be obtained from the diet for some critical function throughout life". Human and other animal cells do not have a metabolic pathway to synthesize organic B compounds, so these must be taken from plants. Although the World Health Organization (WHO) has not still accepted that B can be an essential element for humans with an important role in the human metabolism, this may change as our insights are confirmed by other laboratories. Further, confirmation would vindicate Newnham's recommendation, 28 years ago, to use B to prevent and manage arthritis and osteoporosis [107].

5. NOB species are novel prebiotic candidates?

When discussing B essentiality, we must consider not the element itself, but the molecular species that incorporates it [17]. A few essential B species were detected in bacteria as the AI-2B, in fungi as SBEs, and in higher plants as SBEs. Recently, a DCB was discovered in green coffee beans [46].

Essentiality should be correlated with one specific kind of speciation for the same element. In our view, NOB complexes (*e.g.*, B–RG-II complex, SBEs, organic polyhydroxy acid borate esters, *bis*-sucrose borate complexes, amino acid borate esters and recently, DCB) may be prebiotic candidates in human/animal nutrition. This is different from the BA/borates, which cannot be prebiotic compounds, as these inorganic compounds are digestible and toxic to the microbiota [33]. In general, in the acidic stomach medium, soluble and insoluble organic B species degrade into B monoesters and diesters [17, 33]. As natural B monoesters and diesters (polyalcohols, organic acids sugars, DCB) have *pKa* from 2.5 to 5, many of these do not degrade and therefore remain mainly in organic form of B. At the same time, because BA could be associated with *cis*-diol organic compounds (fructose, ribose, glucose, phenolic acids), probably that in the superior part of the digestive tract the NOB species are reconstituted even at pH 4.5 (postprandial) [17].

Our 30-year research has attempted to fill this scientific gap by studying the many chemical and biochemical reactions in which B is involved [3, 4, 17, 33, 34, 40, 74, 113–121]. Recently, we analyzed some of our old animal studies and found that at the beginning of the B diet, the increase of B concentration in feces could be explained by NOB species indigestibility, then NOB is released into the colon where the microbiota needs it [122–125]. We have evaluated *in vivo* the ability of a protein concentrates additive, enriched in NOB (as FB) in diminishing the toxic effect of a corn-based diet contaminated with *Fusarium* toxins in starter pigs. FB has been hypothesized to have stimulated the activity of intestinal microflora knowing that mycotoxins can disrupt the IM by altering the relative abundance of the commensal bacteria [126, 127]. The natural explanation hypothesis for these experiments was: the human/animal body did not need B, but the IM needed B to create a healthy symbiotic relationship with the host.

Subsequently, the MoA of NOB species is the following: supply with NOB species of bacteria that require B to communicate (AI-2B) and the fortification of colonic mucus layer with organic B esters (this is similar to plant symbiosis, in order to protect the host from bacterial infection). Consequently, NOB compounds are both a source of B (essential for symbiosis) and a source of carbon for the specific nutrition of the microbiota.

Giving the above-mentioned MoA, both microbiota and the gel layer of the colonic mucus become the NOB species target. Therefore, in the future, NOB species may become promising novel prebiotic candidates. For instance, in the acidic gastric environment, the NOB species (as FB) have about *pKa* 4.0, so these do not dissociate in the postprandial upper gastric system (**Figure 2**; **Tables 1 and 2 – Supplementary Material**) [33, 128]. In addition, indirect evidence of B presence in the gel layer of colonic mucus is the probable result of B "sequestration" in the colon during B nutrition in animals [69].

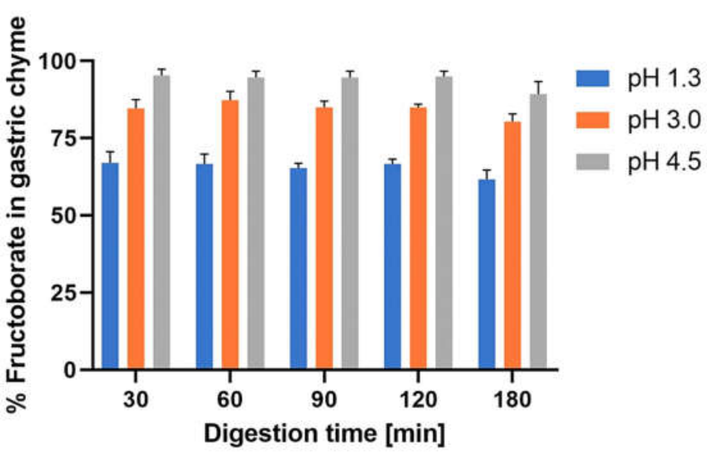

Figure 2. ***In vitro*** **simulation of gastric digestion of NOB species**. (Part II – SI; Tables 1 and 2 – Supplementary Material). NOB: Naturally organic boron.

6. Perspectives

New discoveries about metabolism and molecular nutrition have increased the details of our understanding of the relationship between colon and human health. As this understanding improved, the colon came to be recognized as the optimum location to improve the bioavailability of food due to its distinct features, including its nearly neutral pH, its low enzymatic activity, and its long transit time [129]. Ideally, nutraceuticals should be preserved in the rough medium of the superior GI tract, and then released into the colon to achieve a successful distribution in the colon and to obtain their full bioavailability [130].

Establishing essentiality of NOB species for a healthy relationship between microbiota and their human/animal hosts will mark a new approach to the use of these as prebiotic candidates in human and animal nutrition. The literature explains that the health of the human/animal organism depends on the health of the microbiota [131], supporting a view that NOB species role is crucial for the health of the human/animal organism [33]. This role has resulted from many scientific experiments that have shown that NOB species increase the buffering capacity of saliva [73, 74], have a positive impact on the intestinal and oral microbiome [70], protect important probiotic bacteria, *Bifidobacterium* spp. and *Lactobacillus* spp. [132–134], improve SCFAs production [68], are essential for improving the integrity and impermeability of the intestinal barrier [70], and improve the immunity, anti-inflammatory and antioxidant actions of the microbiota [135]. The microbiota influences the health of the body through the "axes" already formulated and studied in the literature: "gut–brain" axis, "gut–immunity" axis, "gut–bone" axis, "gut–cartilage" axis, "gut–heart" axis, "gut–lung" axis, "gut–thyroid" axis [103, 136]. This may explain the beneficial role of B in preventing certain diseases, such as OA [107], osteoporosis [137], rheumatoid arthritis [138], cardiovascular inflammation [17, 118, 139], depression [140], neurodegenerative diseases [136], obesity [141], diabetes [142], viral and bacterial infections [120, 143], thyroid diseases [144].

7. Conclusions

New insights into B essentiality to animals and humans suggest that a new hypothesis might be required to understand the the role of B in health: "Naturally occurring B species are essential for human/animal host healthy microbiome symbiosis". This, in turn, will drive new insights into the essentiality of NOB species for healthy symbiosis between the human/animal host and the microbiota, which in turn will guide the use of natural B-based nutraceuticals to target the colon as "colonic foods". The MoA of NOB species may be primarily related to B molecule signaling (AI-2B), but also may fortify the colonic mucus with B from the specific prebiotic diet.

Subsequently, the key aspects of NOB species' use in nutrition are:

(*i*) NOB species are novel and potential prebiotic candidates.

(*ii*) NOB species are needed for the symbiosis between bacteria and the human/animal host and are not necessary for the human cell metabolism.

(*iii*) NOB species can be considered effective novel prebiotic because they reach the colon more than 95%, they do not dissociate in the form of inorganic B (**Figure 2**; **Tables 1 and 2 – Supplementary Material**).

(*iv*) BA, borax and all inorganic B salts are not prebiotics because they are digestible, leading to B dissociation and have shown cytotoxic and genotoxic activity for microbiota [145–147]. The BA is highly available in the bloodstream, while NOB species are indigestibles and therefore reaches the colon.

(*v*) NOB species are likely to function as carriers for: (*a*) carbon to support microbiome growth and (*b*) the essential B element needed for healthy symbiosis.

From the practical point of view, the essentiality of NOB species will open up new opportunities for supplementing B in human/animal nutrition to stay healthy and live long [17, 33, 75, 148]. New knowledge about the essentiality of NOB species for a healthy symbiosis between human/animal host and microbiota will lead to the use of natural B-based nutraceuticals to target the human/animal microbiome (gut, oral, vaginal, skin, and scalp microbiome). Out of these, gut microbiome is the most important for human health. Subsequently, NOB species become novel prebiotic candidates and are targeting the colon as novel colonic foods. Moreover, NOB species target the colon nutrition, resulting in a healthy gut microbiome, as well as healthy microbiome in mouth, vagina, skin, and scalp.

In conclusion, NOB species are novel prebiotic candidates ("a prebiotic is a substrate that is selectively utilized by host microorganisms conferring a health benefit") [20], they are indigestible, they do not dissociate postprandial at pH 4.5 in the upper gastric system (**Figure 2**). An increasing number of studies show that nutrition may influence gut microbiota and the human health is crucially dependent of the healthy microbiota [149]. The prospective nutrition will be personalized depending on microbiota type for every human being [150]. Thus, NOB species will become essential for the personalized nutrition, as further novel prebiotic microbiota-accessible candidates. Moreover, supplements containing naturally occurring B should be taken preventively at any time, because these supplements ensure the capture and extinction of increased radiation from the living environment. Therefore, these supplements are effective as chemical protection against radiation, in conditions of natural radioactivity in soil and water or/and nuclear disasters (nuclear accidents or attacks with nuclear bombs) [151–153]. Recently, intestinal microbiota and its associated metabolites has been proved to play a major role in high dose radiation protection [154]. Researchers noticed that only a group of mice resistant to radiations had two main important classes of bacteria in their gut: *Lachnospiraceae* and *Enterococcaceae*. These bacteria need B for the biosynthesis of AI-2B and the MoA that we proposed for NOB complexes could explain why these complexes ensure absorption of neutrons and gamma-radiation when they reach the colon [125, 155, 156]. Also, in areas where the natural radiation of the soil is increased, the concentration of B in the blood of animals and humans is very low, because B in the body is consumed by natural radiation from the environment and transformed into lithium and helium. In these areas, people have very advanced OA (over 70%) [157–160].

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Data availability: Data described in the manuscript will be made publicly and freely available without restriction at https://docs.google.com/document/d/1LXqh6cYozOZSCsq9R4TyTBqv5lawr-ZG/edit?usp=sharing&ouid=110601923775251692590&rtpof=true&sd=true.

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