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Critical Review

B-Group Vitamins as Potential Prebiotic Candidates: Their Effects on the Human Gut Microbiome

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A B S T R A C T

In recent years, thousands of studies have demonstrated the importance of the gut microbiome for human health and its relationship with certain diseases. The search for new gut microbiome modulators has thus become an objective to beneficially alter the gut microbiome composition and/or metabolic activity, which may modify intestinal physiology. Growing evidence has shown that B-group vitamins might be considered as potential candidates as gut microbiome modulators. However, the relationship between the B-group vitamins and the gut microbiome remains largely unexplored. Studies have suggested that non-absorbed B-group vitamins administered orally can reach the distal intestine or even the colon where these vitamins may have potential health benefits for the host. Clinical trials supporting this effect are still limited. In this review, we discuss evidence regarding the modulatory effects of B-group vitamins on the gut microbiome with a focus on their potential role as prebiotic candidates.

Keywords: B-group vitamins, B-group vitamin bacterial producers, intestinal microbiome, microbiome modulators, prebiotic

Introduction

B-group vitamins are a set of water-soluble organic compounds that act as coenzymes in several metabolic processes, carrying chemical groups and electrons [1,2]. The functional roles of B-group vitamins are related to cellular energy production, methyl donor generation, neurotransmitter synthesis, immune functions, 1-carbon metabolism, cell signaling, and nucleic acid biosynthesis [3]. Current evidence also points to another important role of these vitamins: the modulation of the composition and function of the gut microbiome [4]. However, the relationship between the B-group vitamins and the gut microbiome has not been fully elucidated yet.

A dynamic and varied ecosystem of trillions of microorganisms, known as the microbiota, is found in the human body. These microorganisms include bacteria, fungi, in addition to viruses and archaea, and reside in almost every niche of the organism [5]. The majority of these microorganisms, which contain >1000 bacterial species, reside in the gastrointestinal tract (GIT) [5,6]. The gut microbiota and their genes, known as the gut microbiome, include >100 times more genes than the complete human genome [5].

The main bacterial phyla that have been identified in the human intestine are *Actinomycetota* (previously *Actinobacteria*), *Pseudomonadota* (previously *Proteobacteria*), *Bacteroidota* (previously *Bacteroidetes*), and *Bacillota* (previously *Firmicutes*), with ~90% of the microbial population belonging to the *Bacillota* and *Bacteroidota* phyla [7]. These phyla are differentially dispersed throughout the gut and regulate the microbial ecosystems [7,8]. The distribution of different species in the community is measured by the microbial diversity. Moreover, during gut dysbiosis this diversity is reduced. To the contrary, a healthy gut is the result of a richness of species [6].

The gut microbiome plays key roles in several aspects of the host physiology such as modulation of the immunologic system;

Abbreviations: GIT, gastrointestinal tract; HMP, pyrimidine; IBD, inflammatory bowel disease; LAB, lactic acid bacteria; THZ, thiazole; TPP, thiamine pyrophosphate.

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protection against numerous pathogens; removal of exogenous toxins; regulation of bowel function; and nutrient synthesis, absorption and metabolism [5]. For example, the gut microbiota can produce important amounts of several vitamins, particularly vitamin K and B-group vitamins, and helps uptake and absorption of minerals including iron and calcium [9].

Dysbiosis of the human intestinal microbiota may be related to several diseases, such as obesity, type 2 diabetes, cardiovascular, autoimmune, and intestinal inflammatory diseases [10,11]. Changes in the composition or metabolic signatures of microbial populations are possible via dietary and non-dietary interventions [12]. Emerging evidence has shown the potential beneficial role of vitamins, including B-group vitamins, as gut microbiome modifiers [4,13]. Nevertheless, the way vitamins modulate the gut microbiome and associated health benefits still need to be clarified [11].

Microbiome modulation can take place through 2 mechanisms of action: *1*) direct (action of nutrients on the composition and metabolic activity of the microbiome) or *2*) indirect (changes in the gut physiology leading to modification in the environment of the intestinal lumen, thus generating modifications in the microbiome) [14].

Several mechanisms might explain why vitamins could be considered as good candidates as microbiome modulators. Some vitamins (for example, vitamins A, B-6, C, and E) may have direct antimicrobial effects on the gut microbiome [14]. Vitamins that act as cofactors in energy generation could contribute to the energy metabolism of bacteria and stimulate some microorganisms, leading to an increase in their prevalence or an improvement in their biologic functions [14,15]. Moreover, indirect mechanisms related to the modulation of the host susceptibility to infection and to immunologic response could also lead to effects on the gut [14]. Additionally, the gut microbiome acts as a vitamin producer, helping to provide micronutrients for the host and the intestinal microbial communities [14,16,17]. In this context, vitamins may have simultaneous effects in 2 directions, acting both directly and indirectly on the gut microbiome, and these effects are not associated to their use as an energy source [14].

Furthermore, emerging evidence has suggested that compounds such as vitamins might play beneficial effects by modulating the intestinal microbiota and might be qualified as prebiotics [18]. The current definition updated by the International Scientific Association for Probiotics and Prebiotics in 2016 defines a prebiotic compound as "a substrate that is selectively utilized by host microorganisms conferring a health benefit." This definition allows us to consider the use of new substrates (for example, conjugated linoleic acid, polyunsaturated fatty acid, human milk oligosaccharides, phenolics, and phytochemicals), in parts of the body other than the GIT, including skin, the oral cavity, and urogenital areas, and varied types other than food [12]. However, this definition does not include substrates such as vitamins, antibiotics, minerals, and bacteriophages, which may influence the composition of the microbiota by mechanisms that are not associative with the selective use by host microorganisms [12]. According to Cunningham et al. [19], non-fermentable modulators of the microbiome, such as vitamins, are adjacent to the prebiotic concept and will play a role in the future of microbiome modulation. Although further *in vivo* studies are mandatory to support the role of vitamins as prebiotic candidates, these compounds are emerging for use through the indigenous microbiome and may have potential health benefits for the host [19].

Controversies about the prebiotic effect of vitamins are due to the fact that they are normally absorbed in the proximal small intestine, not reaching the distal GIT [19]. However, studies have suggested that when supplied in large amounts or as colon-target delivery systems, vitamins may directly modulate the colonic microbiome [18–21]. Research using vitamins in high doses or formulations targeting the colon have led to the conclusion that vitamins, including riboflavin and niacin, can modulate the intestinal microbiota [18,20,21]. Moreover, indirect modulation of the gut microbiome by vitamins might occur through the systemic circulation, which could influence the host`s health [21].

Although a growing number of studies have indicated B-group vitamins as potential modulators of the gut microbiome, clinical trials supporting this effect are still limited [4,14]. Therefore, in this narrative review, the current scientific evidence is discussed regarding the modulatory effects of B-group vitamins on the gut microbiome to support the discussion about B-group vitamins as novel prebiotic candidates.

Human Gut Microbiome as a Source of B-Group Vitamins for the Host

B-group vitamins are crucial micronutrients for several metabolic and regulatory pathways necessary for the human health [1,2,22]. They are a group of 8 water-soluble vitamins and are cofactors that play important roles such as in the fat and carbohydrate metabolism and the DNA synthesis in the human metabolism [15]. The collection of B-group vitamins includes vitamins B-1 (thiamin), B-2 (riboflavin), B-3 (nicotinic acid/-niacinamide), B-5 (pantothenic acid), B-6 (pyridoxine), B-7 (biotin), B-9 (folate), and B-12 (cobalamin). Despite having similar water solubility, these vitamins are a set of micronutrients with diverse metabolic roles in terms of energy production, protein metabolism, and hemopoiesis [14].

It is important to point out that the majority of B-group vitamins can be similarly absorbed in 2 ways: *1*) at small concentrations by an active transport system that helps absorption and *2*) at higher concentrations by passive diffusion [14]. Moreover, excess B-group vitamin ingestion may result in vitamins reaching the large intestine [13]. However, the studies on the roles played by B-group vitamins in the gut microbiome are still scarce [13,14].

Because human cells cannot synthesize B-group vitamins in satisfactory quantities to avoid deficiencies, these micronutrients must be acquired either from the diet or by production from the gut microbiome [6,15]. B-group vitamins are present in several foods, particularly animal-based foods, leafy green vegetables, beans, and peas; however, because they are water soluble and thermolabile, these vitamins can be easily lost and degraded during the cooking process [6,15,23,24]. For this reason and owing to low vitamin intakes, the fortification of some food products with chemically synthesized vitamins is mandatory in many countries, including Argentina, Brazil, Canada, and United States [25].

As previously mentioned, the intestinal microbiome can produce vitamins, contributing to the supply of these

micronutrients and the stability of the intestinal bacterial community [16,26]. Regarding the production of vitamins by the gut microbiome, it has been shown in germ-free animals as they lack a microbiota needed to produce vitamin K and certain B-group vitamins, whereas in conventional rodents, their microbiota provides these essential micronutrients [27,28].

In general, some bacterial genera present in the distal intestine, such as *Bacteroides* spp., *Bifidobacterium* spp., and *Enterococcus* spp., are recognized as producing vitamins [28,29]. According to Engevik et al. [28], microorganisms of the human intestinal tract may produce certain B-group vitamins, including vitamins B-1, B-6, B-9, and B-12. Using metagenomic analyses, Das et al. [30] estimated that vitamin-related pathways are verified in 49% of the phylum *Bacillota*, followed by 19% of *Pseudomonadota*, 14% of *Bacteroidota* 14%, and 13% of *Actinomycetota*.

Even though the gut microbiome produces B-group vitamins, knowledge about the contribution of the gut microbiome to the host requirements and status of these vitamins is limited [14]. Evaluating the extent to which the gut microbiome contributes to the vitamin status of the host is difficult [21,26]. Along this line, Magnúsdóttir et al. [15] evaluated the genome of 256 common human intestinal bacteria for the presence of B-group vitamin biosynthesis pathways (biotin, cobalamin, folate, niacin, pantothenate, pyridoxine, riboflavin, and thiamin). The authors predicted that these vitamins were synthesized by 40%–65% of the 256 human genome gut microorganisms and riboflavin and niacin were the most synthesized vitamins, with 166 and 162 predicted producers, respectively. The authors also estimated the maximum percentages of the daily reference intake of the 8 B-group vitamins that might be provided by the human intestinal microbiota. They concluded that 86% of pyridoxine could be provided, in addition to 37% of folate, 31% of cobalamin, 27% of niacin, 4.5% of biotin, 2.8% of riboflavin, 2.3% of thiamine, and 0.78% of pantothenic acid [15]. It is important to point out that these results do not include an estimate of how much vitamins would be consumed by the nonproducing microbiota [31]. Additionally, the distribution of biosynthesis pathways presented a varied pattern; some genomes showed all 8 biosynthesis pathways, whereas others did not contain all of the *de novo* synthesis pathways [15]. The analysis performed by Magnúsdóttir et al. [15] suggested that human intestinal bacteria actively exchange B-group vitamins with each other, thus allowing the survival of microorganisms that do not produce any of these important cofactors [15,21,26]. Therefore, these results indicated that human intestinal microorganisms actively produce B-group vitamins and deliver these micronutrients to the bacteria that are close to them by symbiotic relationships [15,21].

In this context, the cross-feeding interactions in the gut microbiome (the sharing of intermediary and end point metabolites among different microorganisms) play important roles in the stability of gut microbial communities, which might influence the host's health [32]. B-group vitamins are suitable for inter-microbial cross-feeding in the distal gut [32]. Therefore, intestinal bacteria can synthetize/import and possibly cross-feed different B-group vitamins (vitamins B-1, B-2, B-3, B-5, B-6, B-7, B-9, and B-12) [32,33]. Figure 1 displays the sources of B-group vitamins that might influence the stability of the gut microbiome.

An *in silico* study showed that >20% (by relative abundance) of microbial gut communities are represented by auxotrophic

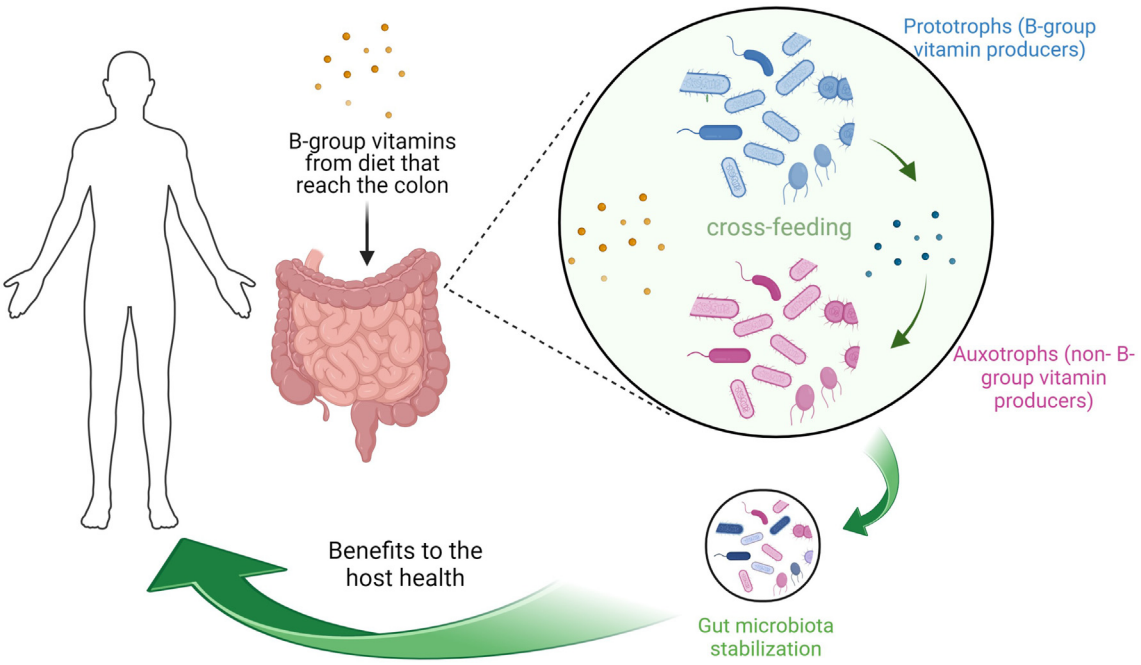

FIGURE 1. Sources of B-group vitamins that might influence the stability of the gut microbiome. The human gut microbiome is represented by bacteria able to produce B-group vitamins (prototrophs) and bacteria that cannot synthetize these vitamins (auxotrophs), which need to obtain them from external sources, such as diet and cross-feeding by other microorganisms. B-group vitamins are suitable for inter-microbial cross-feeding in the distal gut. The gut bacteria can produce/import and possibly cross-feed different B-group vitamins (vitamins B-1, B-2, B-3, B-5, B-6, B-7, B-9, and B-12). These microbial interactions are involved in maintaining the stability of gut microbial communities, influencing the host health (created with BioRender.com).

species (non-vitamin producers), and as so, their viabilities dependent upon acquiring 1 or more B-group vitamins from the diet and/or from prototrophic microorganisms (vitamin producers) [34]. Ortiz et al. [35], using a high-throughput genomic reconstruction modeling, suggested that B-group vitamins drive modules of interacting gut microorganisms based on complementary prototrophic/auxotrophic networks.

Along this line, Soto-Martin et al. [36], using genome sequence analysis and results from *in vitro* growth assays, showed that the most abundant butyrate-producing *Bacillota* species are dependent on B-group vitamins provided by diet or through cross-feeding from other members of the intestinal microbiota. The authors showed that among the butyrate-producing gut bacterial species, those with the highest number of B-group vitamin auxotrophies were *Faecalibacterium prausnitzii*, *Subdoligranulum variabile*, *Eubacterium rectale*, and *Roseburia* spp. [36].

In general, the gut microbiome is a significant source of B-group vitamins, and modifications in the intestinal microbiota composition can significantly impact our dietary B-group vitamin requirements [15]. It is noteworthy that the gut microbiome-based production of vitamins can be influenced by the host health status [14]. For example, decreased intrinsic synthesis was verified in individuals with inflammatory bowel disease (IBD), malnutrition, and metabolic disorders [14]. In general, when vitamins are lacking, chronic health conditions can be generated or aggravated, and a supplementation with individual or various vitamins is a common practice [6].

Bacteria as B-Group Vitamin Producers for the Host

Although most lactic acid bacteria (LAB) and bifidobacteria are characterized as auxotroph for vitamins production, several studies have demonstrated the ability of some strains of these bacterial groups to synthesize *de novo* natural forms of thiamine, riboflavin, folate, cobalamin, and other B-group vitamins [17]. In particular, strains of *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactiplantibacillus plantarum*, *Limosilactobacillus reuteri*, and *Bifidobacterium longum* have been reported to synthesize B-group vitamins [17]. In this context, these bacteria can be used as an alternative to enhance the B-group vitamin amount of food products through the fermentative process [25]. The utilization of LAB and bifidobacteria for vitamin production to obtain fermented bioenriched foods has increasingly become a promising approach in the food development area [25]. Additionally, the use of these vitamin-producing bacteria would certainly lead to a more natural and consumer-friendly way than fortification performed by chemically synthesized vitamins [17,37,38].

Vitamins produced by bacteria are usually kept inside the microbial cells and released through direct diffusion, by specific transporters in the cell membrane or via cellular lysis, either in their growth media or inside the host GIT. The vitamin-producing bacteria (for example, certain strains belonging to LAB and bifidobacteria) can therefore be considered as a good alternative for the *in situ* delivery of B-group vitamins and could act as a vitamin bio-supplement [17].

B-group vitamin–producing bacteria can be isolated from different ecologic niches, including mammal GIT, dairy products, plants, and grains, and can produce variable amounts of vitamins B-1, B-2, B-9, or B-12 [17]. It is noteworthy that the vitamin synthesis by these microorganisms is strain dependent and influenced by different environmental conditions, for example, pH, temperature, and nutrient availability [25,39]. For these reasons, the adequate selection of strains and optimization of fermentation conditions must be performed in order to increase vitamin concentrations in fermented foods [40].

The majority of microorganisms already identified as vitamin producers cannot be characterized as probiotic strains ("live microorganisms that, when administered in adequate amounts, confer a health benefit on the host"—Hill et al. [41]) owing to the lack of studies that prove this characteristic (for example, their survival in the GIT, adhesion to mucosa, and indication of their actions in human studies). However, there are promising probiotic strains (such as *Limosilactobacillus fermentum* CECT5716, *Lacticaseibacillus rhamnosus* GG, and *Bifidobacterium animalis* BB-12) with the ability to produce B-group vitamins [17]. Table 1 [17,25,42–44] summarizes some examples of probiotic bacteria producing B-group vitamins.

The use of probiotic strains could present advantages over non-probiotic bacteria because the former, besides having the ability to produce certain B-group vitamins, may have additional beneficial properties for the host, leading to immunologic, neurologic, and endocrinologic benefits or being able to produce bioactive compounds, among other possible health effects [25].

In this context, the probiotic strain *L. fermentum* CECT5716, isolated from the human milk of healthy mothers, produced both vitamins B-2 and B-9 in culture media, but clinical studies did not assess serum vitamin amounts of subjects that ingested this strain [42]. *Lacticaseibacillus rhamnosus* GG, isolated from the GIT of a

TABLE 1
Examples of probiotic bacteria producing B-group vitamins

Microorganisms	B-group vitamin produced	References
Streptococcus thermophilus TH-4	Folate	[25]
Lactobacillus acidophilus LA-5	Folate	[25]
Limosilactobacillus fermentum CECT 5716	Riboflavin and folate	[42]
Limosilactobacillus fermentum PCC; *Limosilactobacillus reuteri* RC-14	Folate	[25]
Lacticaseibacillus rhamnosus GG	Thiamin, riboflavin, and folate	[17]
Lacticaseibacillus rhamnosus GR-1	Folate	[25]
Lacticaseibacillus paracasei subsp. *paracasei*; *Lacticaseibacillus casei* 431; *Lacticaseibacillus paracasei* subsp. *paracasei* F19	Folate	[25]
Latilactobacillus sakei LZ217	Folate	[43]
Bifidobacterium animalis subsp. *lactis* BB-12	Folate	[25]
Bifidobacterium longum subsp. *longum* BB-46; *Bifidobacterium longum* subsp. *infantis* BB-02	Folate	[25]
Bifidobacterium adolescentis DSM 18352	Folate	[44]

healthy volunteer, produced vitamins B-1, B-2, and B-9 in culture media [17]. *Latilactobacillus sakei* LZ217, isolated from raw cow milk, was characterized as a probiotic folate-producing strain [43]. As for probiotic bifidobacteria, *Bifidobacterium lactis* BB-12 revealed the presence of all genes for thiamin biosynthesis but not for riboflavin, pyridoxine, and folate. Nevertheless, studies that confirm this potential for vitamin production by this strain are limited [17].

Albuquerque et al. [25] assessed for the ability of starter (*Streptococcus thermophilus* ST-M6 and *S. thermophilus* TA-40) and probiotic (*S. thermophilus* TH-4, *L. acidophilus* LA-5, *L. fermentum* PCC, *L. reuteri* RC-14, *Lacticaseibacillus paracasei* subsp. *paracasei*, *Lacticaseibacillus casei* 431, *Lacticaseibacillus paracasei* subsp. *paracasei* F19, *L. rhamnosus* GR-1, and *L. rhamnosus* LGG, *B. animalis* subsp. *lactis* BB-12, *B. longum* subsp. *longum* BB-46, and *B. longum* subsp. *infantis* BB-02) cultures to synthesize folate in a modified MRS broth added with fruit by-products, okara soybean by-products, and amaranth flour. The authors found that all strains tested had the capacity to synthesize folate, as shown by increased amounts, which varied depending on the substrates present in the culture media. This study goes in contrast to the work of Magnúsdóttir et al. [15] that stated that not all folate biosynthesis genes were found in the published genomes of *L. acidophilus* LA-5 and *B. animalis* subsp. *lactis* BB-12. Celik and Sullivan [45] showed that *B. longum* DJO10A and *Bifidobacterium breve* ATCC 15701 were able to grow in folate-free media independent from folate and *p*-aminobenzoic acid, suggesting that the lack of some folate pathway genes in their genome sequences may not be used to predict folate dependency in bifidobacteria. These contrasting results indicated that the lack of some folate biosynthesis genes in the genome is not a sufficient indicator to determine folate dependency. Magnúsdóttir et al. [15] previously showed that the strain *L. plantarum* WCFS1 is missing most thiamin biosynthesis genes but has the ability to produce this B-group vitamin using an unknown pathway or bifunctional genes present in other parts of the bacterial genome. Our hypothesis is that novel biosynthetic pathways might be present in the genomes of strains such as *B. animalis* BB-12 that allow them to produce *de novo* folates even though genome analysis clearly shows that the conventional folate biosynthetic pathway is incomplete. Further studies of microbial interactions in the gut must be performed to understand potential novel biosynthetic pathways that can be obtained through symbiotic relations and to determine novel pathways for *de novo* vitamin production.

Other interesting *in vitro* studies evaluated the potential to produce and release de novo vitamins thiamin, riboflavin, and folate by probiotic strains (*L. rhamnosus* GG, *B. longum* SP 07/3, *Bifidobacterium bifidum* MF 20/5, and *Lactobacillus gasseri* PA 16/8) [17]. The authors showed that *L. rhamnosus* GG was a good producer and releaser of vitamins B-2 and B-9 and a low, but significant, producer of intracellular vitamin B-1 without extracellular synthesis [17].

Besides the *in vitro* potential of folate production by different probiotic bacteria strains, the *in situ* potential has also been studied. Engevik et al. [28], through a molecular analysis, studied the *in situ* production of folate by human commensal microorganisms. The authors verified that only 13.3% of 512 bacterial reference genomes from the human gut microbiome contained all genes involved in the 4 metabolic modules from folate *de novo* synthesis. To the contrary, >86% of genomes needed folate or folate intermediates from other bacteria of the human microbiome or the human diet. Thus, the folate production by probiotic bacteria in the microbiota may be important for the species that do not possess the complete folate biosynthesis genome, which might directly influence the microbiota composition [28]. In addition, owing to the considerable number of gut microorganisms with complete sets of folate biosynthetic genes, the intestinal microbiome may be considered as a significant folate-generating "organ" [28].

Strozzi and Mogna [44] conducted a pioneer pilot study with 23 healthy subjects to assess the folate production by probiotic strains (*Bifidobacterium adolescentis* DSM 18350, *B. adolescentis* DSM 18352, and *Bifidobacterium pseudocatenulatum* DSM 18353) in the human intestine. Volunteers were randomly divided into 3 groups for treatment with a probiotic strain (5×10^9 colony-forming units/d) throughout 30 d. The authors verified that the consumption of these strains lead to a significant increase of folate content in human feces in all treated groups. Additionally, the potential of the 3 probiotic strains, particularly *B. adolescentis* DSM 18352, to colonize the gut environment was shown [44]. Previous studies showed that these strains were able to produce folate in growth media and positively affect the folate status of rats, with increased serum and liver folate concentrations [46,47]. According to Pompei et al. [47] the folate produced by folate-producing bacteria can be used by the gut bacteria that are incapable of synthesizing it and can also be absorbed by the colon. The authors also reported that the gut microbiota forms a complex ecosystem in which metabolic and cross-feeding interactions can take place among the microorganisms and between the microbiota and the animal host [47]. To the contrary, Malinowska et al. [48] reported that some taxa of the human native intestinal microbiota can produce folates under culture conditions; however, this bacterial ability to produce folate does not predict human blood folate status. Additional studies are required to clearly understand the impact of vitamin-producing microorganisms of the native gut microbiota on the host vitamin status because information about this impact is scarce.

In general, the appropriate selection of probiotic vitamin-producing strains for the development of novel functional foods or vitamin bio-supplements with the objective of delivering natural vitamins to the host and the *in situ* production of vitamins by these probiotic strains (as part of the human gut microbiota) has become an interesting approach to help in the prevention of vitamins deficiencies or diseases related to this condition [16,49,50].

Effects of B-Group Vitamins on the Human Gut Microbiome

There is a growing interest in the potential role of micronutrients, particularly vitamins, in shaping the composition of the intestinal microbiota and its metabolic activity and, consequently, in the impact of this modulation on the maintenance of the host's health and the prevention of various diseases [19,51,52]. Most of studies are focused on dietary fibers as prebiotics for the intestinal microorganisms; however, dietary compounds other than fermentable dietary fiber, including B-group vitamins, may also affect the composition of the gut microbiome or the physiology of the GIT [14,19,53]. Emerging evidence has

suggested that B-group vitamins are possible candidates as gut microbiome modulators and play important roles in shaping the diversity and richness of the gut microbiome [3].

Nevertheless, studies, particularly clinical trials, showing the impact of B-group vitamin on the gut microbiome are still scarce [14]. In the following sections, we will focus on the effect of thiamine, riboflavin, folate, and cobalamin on the gut microbiome and the effects of some colon-delivered B-group vitamins. Table 2 [11,18,20,54–65] summarizes the studies describing direct effects of B-group vitamins on the human gut microbiome, and Figure 2 presents the main possible mechanisms of action involved in the modulation of the gut microbiome by B-group vitamins administered orally through high doses, colon-targeting formulations, or vitamin-producing probiotic strains.

Thiamine (vitamin B-1)

Thiamine (vitamin B-1) is an essential cofactor for all living organisms, and its availability may affect the gut microbiome and, consequently, the human health [66]. However, little is known about how thiamine influences the stability of gut microbial communities [66].

Thiamine is a biosynthetic precursor of thiamine pyrophosphate (TPP), which is important for the carbohydrate metabolism and the neural function [13]. The thiamin biosynthesis pathway is found in most of the prokaryotes and eukaryotes (for example, yeast and plants). The thiamine biosynthesis is based on 2 branches that produce stable intermediates, moieties of thiazole (THZ) and pyrimidine (HMP), which are joined using the thiamine-phosphate synthase and then phosphorylated to the active cofactor (TPP). Besides, the thiamine itself can be phosphorylated to TPP [67]. Many microorganisms, including intestinal bacteria, can be auxotrophic for the biosynthesis of both THZ and HMP or for the capacity to combine THZ and HMP; however, pathways to transport these compounds into microbial cells have been described [32,68].

Several bacteria, including intestinal bacteria, need thiamine for their metabolism, for example, to generate energy for their growth [15]. In general, diet and gut bacteria are sources of vitamin B-1. It is noteworthy that in conditions where the supply of dietary thiamine is limited, the abundance of certain bacterial species may reduce [36].

In silico and *in vitro* studies have indicated that thiamin can be produced by gut bacteria [13,15,66]. Costliow and Degnan [66], using an *in vitro* model, showed that the biosynthesis of thiamine is crucial for the growth and competition of *Bacteroides thetaiotaomicron*, a beneficial modulation-associated bacterium in intestinal inflammation, in environments with limited thiamine availability. The authors suggested that changing the concentrations of thiamine may be an alternative to modulate the composition and function of the gut microbiome and concluded that targeted thiamine delivery might be an interesting therapeutic approach to control intestinal dysbiosis linked to diseases [66].

Riboflavin (vitamin B-2)

Riboflavin (vitamin B-2) plays a significant role in cellular metabolism [16]. The riboflavin biosynthesis has been reported in both Gram-positive and Gram-negative bacteria, being well described in *Bacillus subtilis* and *Escherichia coli* [69,70]. The microbial biosynthesis starts from 2 main precursors, guanosine triphosphate and D-ribulose 5-phosphate, derived from purine biosynthesis and/or the pentose phosphate pathway, through 7 enzymatic steps [69,70].

Vitamin B-2 is the precursor of flavin mononucleotide and flavin adenine dinucleotide, coenzymes needed by glutathione reductase, which protects cells against the damaging action of reactive oxygen species [14,71]. Riboflavin may therefore change the luminal microbiome conditions by decreasing luminal reactive oxygen species concentrations, acting as an indirect antioxidant [14]. According to Steinert et al. [18], riboflavin may have a positive effect on the composition of the intestinal microbiota as this vitamin can be metabolized and modify the redox state of the gut environment. For example, the growth of *F. prausnitzii* may be increased by supplementation with riboflavin [18]. This strict anaerobic bacterium has aroused clinical interest because it may directly produce butyrate, have anti-inflammatory properties, and improve the intestinal barrier function by producing butyrate and specific anti-inflammatory peptides [18,72,73].

It is important to highlight that oxidative stress is one of the main stressors for strict anaerobic bacteria, for example, *F. prausnitzii* or *Roseburia* spp. [18,74]. Evidence suggests that riboflavin might improve gut redox conditions and stimulate the growth of these extremely oxygen-sensitive bacteria [18]. Therefore, it can be hypothesized that vitamins or other antioxidant compounds that have redox-mediating functions might have significant prebiotic properties [18]. In the presence of redox mediators, anaerobic bacteria may diminish the oxygenated environment using their metabolism and, thus, decrease oxidative stress [18,75]. Along this line, the effect of riboflavin on the growth of *F. prausnitzii* as agents of electron transfer has been suggested [13,18,75].

Studies have indicated that riboflavin can reach the colon when supplied in quantities >30 mg [18,76]. A pilot study was performed to verify the effects of riboflavin on the fecal microbiome of 11 healthy adults supplemented with a high dose of riboflavin (100 mg/d) during 14 d. The researchers showed that the amount of *F. prausnitzii* per gram of feces improved during supplementation, and the number dropped after a 1-wk washout period [18]. It is important to emphasize that *F. prausnitzii* does not encode genes involved in riboflavin biosynthesis [13,77]. Additionally, an increase in *Roseburia* species and a decrease in *E. coli* were also verified, suggesting that the anaerobic conditions and redox state in the gut were improved [18]. Patients with IBD, particularly Crohn's disease, have low amounts of *F. prausnitzii* and augmented amounts of *E. coli* and other *Enterobacteriaceae*. It is suggested that the *F. prausnitzii*-to-*E. coli* ratio is related to oxidative stress during intestinal inflammation [18,78]. According to the authors, this improved ratio in favor of *F. prausnitzii* might represent an improvement in the redox status because it helps to control dysbiosis during an IBD remission period. To the contrary, Liu et al. [54], in a randomized, placebo-controlled trial with healthy volunteers, showed that the oral riboflavin supplementation in 2 dosages (50 and 100 mg/d for 2 wk) lead to an increased butyrate production in the fecal samples without major changes in the gut microbiota composition, particularly in the abundance of *F. prausnitzii*. In a clinical study with 70 patients, it was shown that riboflavin supplementation resulted in a reduction of systemic oxidative stress, inflammation, and Crohn's diseases symptoms, and this was

TABLE 2
Publications showing direct effects of B-group vitamins on the human gut microbiome

B-group vitamin	Subjects	Study design	Dose/consumption period	Microbiome analysis	Bacteria changes	References
Riboflavin	Healthy adults ($n = 105$)	Randomized, placebo-controlled, double-blind, parallel-group trial	50 or 100 mg/d for 2 wk	FISH	No change	[54]
Riboflavin	Healthy adults ($n = 12$)	Double-blind, randomized placebo-controlled/pilot study	75 mg/d for 4 wk	Shotgun metagenomic sequencing	↑*Clostridium* spp. ↓*Faecalibacterim* spp. ↓*Faecalibacterium prausnitzii* ↓*Eubacterium hallii* ↑*Alistipes shahii*	[11]
Riboflavin	Adults with Crohn's disease ($n = 70$)	Prospective clinical intervention study	100 mg/d for 3 wk	FISH and MGS	↓*Enterobacteriaceae* (FISH) No significant modifications in the fecal microbiome (MGS)	[55]
Riboflavin	Adults with cystic fibrosis ($n = 16$)	Observational study	Riboflavin intakes through 3-d food diary	16 ss rDNA sequencing	↓*Bacteroidota*	[56]
Riboflavin	Healthy adults ($n = 11$)	Single-arm pilot study, pretest compared with posttest	100 mg/d for 14 d	FISH	↑*Faecalibacterium prausnitzii* ↑*Roseburia* spp. ↓*Escherichia coli*	[18]
Riboflavin, pantothenic acid, pyridoxine, cobalamin	Healthy lactating females ($n = 20$)	Prospective longitudinal investigation	24-h dietary recall	High-throughput sequencing	↑*Prevotella* spp. ↓*Bacteroides* spp.	[57]
Nicotinic acid	Healthy subjects ($n = 10$)	Intervention study	Delayed-release nicotinic acid with a weekly increase in the dosage (30 mg up to 300 mg)	16S rDNA amplicon sequencing	↑*Bacteroidota*	[20]
Cobalamin	Healthy infants (4–6 mo old) ($n = 88$)	Cross-sectional study	Cobalamin intake through breastfed	16S rRNA gene sequencing	No change	[58]
	Healthy infants (4–6 mo old) with vitamin B-12 deficiency ($n = 11$)	Intervention study (without control group)	Intramuscular injections [250–500 μg 2× weekly (1 wk) and 500 μg (3 wk)]	16S rRNA gene sequencing	No change	
Cobalamin	Healthy females their infants born at term ($n = 22$, mother–infant pairs)	Cohort study	Maternal vitamin B-12 intake using FFQ3 (months of pregnancy and 3 mo postpartum)	16S rRNA gene sequencing	No change (infant gut microbiome)	[59]
Cobalamin	Mother–infant dyads ($n = 73$)	Nested cross-sectional study	Vitamin B-12 intake using FFQ during pregnancy	16S rRNA gene sequencing	↑*Klebsiella* spp., *Bifidobacterium* spp., *Streptococcus* spp., *Enterococcus* spp., *Dorea* spp., *Faecalibacterium* spp., *Agathabacter* spp. (infant gut microbiome)	[60]
Riboflavin, pyrodixine, folate, and cobalamin	Males with endoscopically normal colon after an elective colonoscopy procedure	Cross-sectional study	Vitamin B-2, B-6, B-9, and B-12 intake using FFQ	16S rRNA gene sequencing	↑Verrucomicrobiota ↑*Faecalibacterium* spp., *Roseburia* spp., *Alistipes* spp., *Odoribacterium* spp., *Dialister* spp., *Akkermansia* spp., *Haemophilus* spp. ↓*Erysipelatoclostridium* spp., *Bacteroides* spp., and *Lachnospiraceae* (UncO8895) (colonic mucosa–associated microbiome)	[61]
Cobalamin	Healthy children ($n = 75$)	Cross-sectional study	Vitamin B-12 intake, 24-h dietary recall	16S rRNA gene sequencing	No change	[62]
Folate and cobalamin	Healthy adults ($n = 69$)	Open-label, randomized, multicenter study	Serum vitamin B-9 and B-12 concentrations	16S rDNA gene-targeted qPCR for	↑Bifidobacteria	[63]

(*continued on next page*)

TABLE 2 (*continued*)

B-group vitamin	Subjects	Study design	Dose/consumption period	Microbiome analysis	Bacteria changes	References
				Clostridium cluster IV and bifidobacteria		
Cobalamin	Healthy adults (n = 56)	Cross-sectional study	Vitamin B-12 intake using FFQ	16S rRNA gene sequencing	↓*Enterobacteriaceae*	[64]
Cobalamin	Females who were not pregnant or lactating (n = 102)	Cross-sectional study	Vitamin B-12 intake using 2 24-h dietary recalls (above compared with below median)	16S rRNA gene sequencing	Differentially abundant microorganisms: Pseudomonadota, Archaea, *Odoribacteriaceae, Clostridiaceae*; differentially abundant with vitamin B-12 below median: *Ruminococcaceae*	[65]

Abbreviations: FFQ, food frequency questionnaire; FISH, fluorescent in situ hybridization; MGS, metagenomic shotgun sequencing.

associated with a decrease in *Enterobacteriaceae* [55]. Nevertheless, the potential therapeutic effect of riboflavin on the gut microbiome needs to be further investigated, particularly through clinical studies.

Folate (vitamin B-9)

Folate (vitamin B-9) plays important roles for the cell metabolism, including DNA replication, repair, and methylation and synthesis of nucleotides [40,79]. The *de novo* biosynthesis pathway of folates is a distinctive feature of certain prokaryotes and plants [80,81]. This pathway involves the conversion of guanosine triphosphate into the biologically active cofactor tetrahydrofolate, through 7 consecutive steps [80].

Folate biosynthesized by bacteria can be absorbed by folate transporters in the human colon [13]. Although the absorption rate of folate in the colon is lower than that in the small intestine, specific transporters and carriers are expressed in colonic epithelial cells that may be involved with the folate absorption there [48,82]. Nevertheless, studies showing that folate or folate-producing bacteria can modulate the gut microbiome are limited. Zhang et al. [83], using a folate-deficient rat model to assess the impact of folate-producing strains and biofortified yogurt on intestinal dysbiosis, verified that the administration of *L. plantarum* GSLP-7V or its fermented yogurt during 10 d restored the disrupted intestinal microbiota and recovered the serum folate and homocysteine to normal amounts. In addition, the authors suggested the potential of the folate-producing LAB for the treatment of folate deficiency–associated diseases. Moreover, an *in vitro* model using fecal slurry cultures evaluated the effect of *L. sakei* LZ217 (a potential probiotic strain) on the human gut microbiota. Fermented samples containing the strain significantly increased the abundance of the phylum *Bacillota* and the genera *Lactobacillus*, *Faecalibacterium*, *Ruminococcus*, and *Butyricicoccus*, besides increasing butyrate production by fermentation [43].

Cobalamin (vitamin B-12)

Cobalamin (vitamin B-12) is the only vitamin synthesized exclusively by bacteria and archaea and is obtained from the diet through the consumption of foods of animal origin [32,40,84,85]. The consequences of vitamin B-12 deficiency are mainly verified in the blood and the nervous system [86]. In addition to other health problems (hematologic, neurologic, and obstetric), recent studies suggest that vitamin B-12 may be related to modulating the composition and function of the gut microbiome [4]. Nevertheless, the effect of this vitamin on the gut microbiome is still not well known [4]. Vitamin B-12 may be considered as a signaling molecule for the spatial and functional organization of the gut microbiome [84].

Cobalamin belongs to a group of compounds recognized as corrinoids and can be considered as the most widely studied example of vitamin cross-feeding in microbial communities [32]. The corrinoids present in the distal colon may be of dietary and microbial origin, and dietary cobalamin that reaches the colon is probably converted to other corrinoids by the intestinal microbiome [87]. The microbial biosynthesis of vitamin B-12 is a highly coordinated and complex process involving ~30 enzymatic steps [88]. In diets where vitamin B-12 is limited (for example, diets low in animal-source foods), evidence suggest

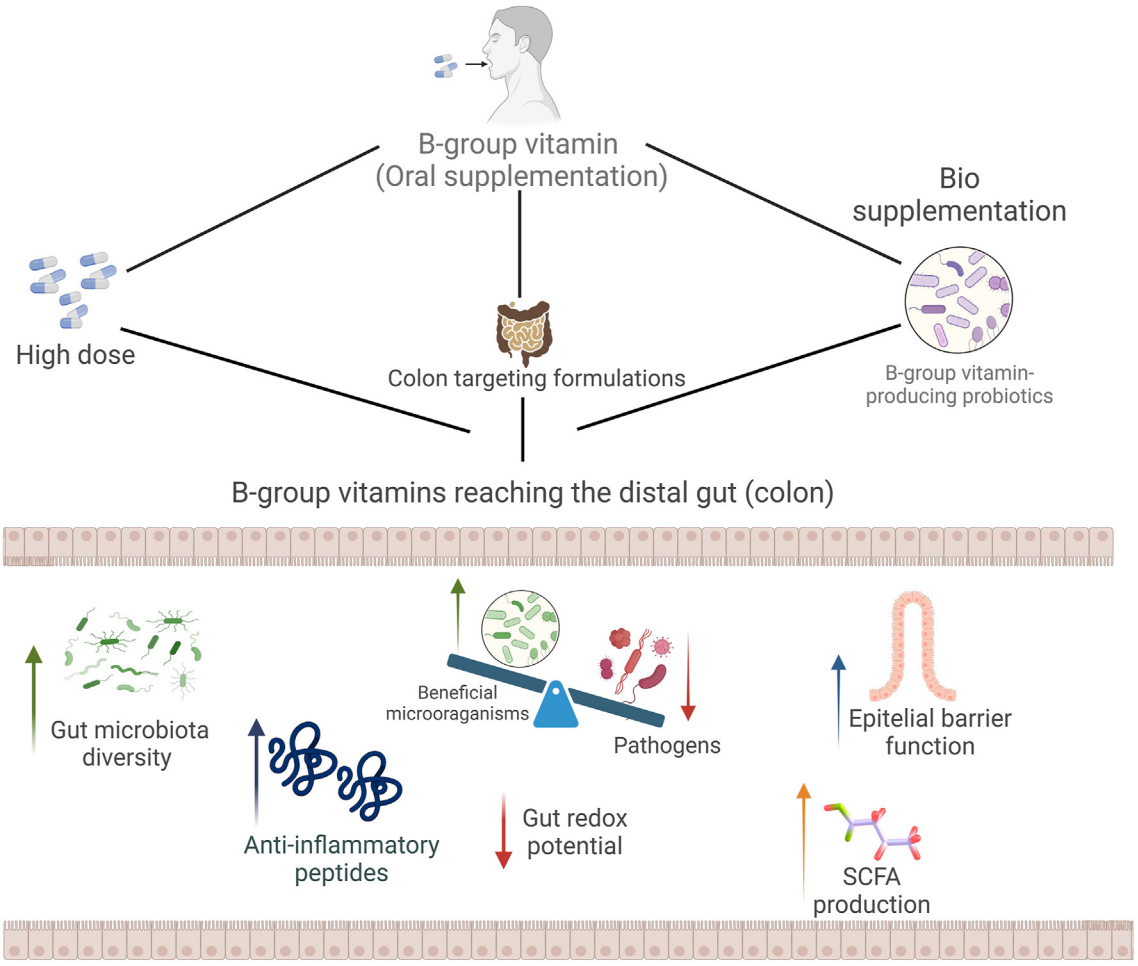

FIGURE 2. The main possible mechanisms of action involved in the modulation of the gut microbiome by B-group vitamins administered orally through high doses, colon-targeting formulations, or vitamin bio-supplement (vitamin-producing probiotics). The B-group vitamins can reach the distal intestine or even the colon, where these vitamins may lead to potential health benefits for the host. Some vitamins, when supplied in high doses or when delivered on the distal gut, may cause a beneficial modulation of the gut microbiome through increasing the microbial diversity, the proportion of beneficial microorganisms (for example, *Bacteroides thetaiotaomicron*, *Faecalibacterium prausnitzii*, and *Roseburia* spp.), the production of short-chain fatty acids and of anti-inflammatory peptides, and improving the epithelial barrier function and reducing the gut redox potential and the proportion of pathogenic microorganisms (created with BioRender.com).

that composition of the gut microbiome may be stabilized by microbial corrinoid production and cross-feeding [32].

According to Allen et al. [89], individuals can absorb ~50% of vitamin B-12 from a 1-μg oral dose in the ileum, with absorption decreasing with increasing doses. In general, cobalamin is normally absorbed into the distal part of the small intestine, and the excessive cobalamin may reach the colon and modify the gut microbiome. In the large intestine, the gut bacteria may metabolize and convert ~80% of vitamin B-12 into its analogs (for example, cobamides) through modification of the benzimidazole base of vitamin B-12 [87,90]. The capacity to use vitamin B-12 and its analogs might be considered as a competitive advantage for certain bacteria in the gut [91]. In this context, the composition and/or metabolic activity of the intestinal microbiota might change under conditions of adequate or insufficient vitamin B-12 [4]. Thus, a few years ago, it has been speculated that this vitamin might play a role in modulating the intestinal microbial ecology [51].

Wang et al. [84], using an *in vitro* colonic model, verified that supplementation of cobalamin and whey was able to increase the phyla *Bacillota* and *Bacteroidota* and decrease the phylum *Pseudomonadota*, which might represent a better and healthier colonic environment.

A recent systematic review including 22 studies (3 *in vitro*, 8 animal, and 11 human observational studies) was performed to evaluate the relationship between vitamin B-12 and the gut microbiome [4]. The authors verified that 19 studies reported that vitamin B-12 intake, status, or supplementation was related to gut microbiome outcomes, such as β-diversity and α-diversity, bacterial relative abundance, functional capacity, or short-chain fatty acid production. Importantly, the results of the *in vitro* studies indicated that vitamin B-12 can increase α-diversity and change the composition of the gut microbiome (β-diversity). To the contrary, findings from animal and human studies were more heterogeneous [4].

In this context, some observational studies have attempted to assess the link between vitamin B-12 and the human gut microbiome [58–65]. Boran et al. [58] verified that there was no evidence of differences in the gut microbial composition between vitamin B-12–deficient and B-12–sufficient infants. In the

same study, these authors also administered intramuscular vitamin B-12 in a subgroup of infants with vitamin B-12 deficiency (intervention without a control group) during 4 wk and showed that there was no difference between the pre and post-treatment composition of gut microbiota. In a cross-sectional study with healthy children aged 2–9 y, Herman et al. [62] did not find any significant association between vitamin B-12 dietary intake and relative abundance of several bacterial taxa. To the contrary, Valentini et al. [63] observed that increased serum folate and vitamin B-12 concentrations were associated with increases of *Bifidobacterium* spp. in stool samples of subjects with low-grade inflammation. In another cross-sectional study, the abundance of *Enterobacteriaceae* in the fecal microbiota of elderly (aged 65–84 y) was negatively correlated with cobalamin amounts [64].

A cross-sectional study conducted by Mörkl et al. [65] in lactating females, using the median vitamin B-12 intake, reported differential abundance of *Pseudomonadota*, Archaea, *Odoribacteriaceae*, and *Clostridium* spp. However, the direction of this association was not stated.

Gurwara et al. [61] verified that the community composition and structure of the colonic mucosa–associated gut microbiota differed significantly by dietary consumption of riboflavin, pyridoxine, folate, and cobalamin. In general, the higher consumption of these B-group vitamins was related with more relative abundance of *Faecalibacterium*, *Alistipes*, and *Odoribacter* and less abundance of *Bacteroides*, *Erysipelatoclostridium*, and *Lachnospiraceae* (Unc8895) species [61].

Other studies have evaluated the relationship between maternal B-group vitamin intake during pregnancy and neonatal gut microbiota. In this line, Selma-Royo et al. [60], in a nested cross-sectional study, showed that higher maternal vitamin B-12 intake was associated with higher relative abundance of *Klebsiella* spp., *Bifidobacterium* spp., *Streptococcus* spp., *Enterococcus* spp., *Dorea* spp., *Faecalibacterium* spp., and *Agathabacter* spp. in infants. Conversely, a cohort study in mother–infant dyads with duration of 3 mo did not reveal any significant association between maternal vitamin B-12 consumption (along the 9 mo of pregnancy and $\leq$3 mo after delivery) and the gut bacterial abundance in infants [59].

In this sense, the idea of evaluating the influence of vitamin B-12 on the human gut microbiome becomes an attractive target of investigation in a future perspective because prospective observational studies and randomized trials are limited and controversial [4].

Colon-targeted B-group vitamins

One approach to assess whether vitamins can have a direct effect on the intestinal microbiome is through the use of high doses of vitamins or colon-targeting formulations [14]. The use of this colon-targeted delivery systems is advantageous because, under physiologic conditions, B-group vitamins do not reach the large intestine but are absorbed in the proximal small intestine [14]. In this sense, microencapsulation/nanoencapsulation of vitamins can be a promising approach for targeted delivery of vitamins, protecting these active agents against harmful conditions during processing and delivery and maintaining their functions in the colon [92].

A human intervention study showed that the microencapsulated delayed release of niacin (vitamin B-3) significantly increased the relative abundance of phylum *Bacteroidota* over a 6-wk period of supplementation, and these results were related to improved biomarkers for systemic insulin sensitivity and metabolic inflammation. It is important to note that the healthy volunteers in this study received a weekly increase in the dosage of niacin (30 up to 300 mg) [20]. Niacin may have antioxidant and anti-inflammatory properties and act as a modulator of the gut barrier function and bacterial endotoxin production, which may directly impact the gut microbiome [13]. Hashimoto et al. [93], using a model of murine angiotensin I converting enzyme (peptidyl-dipeptidase A 2), suggested that both tryptophan and its metabolite nicotinamide are important regulators of the intestinal microbiota and the inflammatory process.

Following this line, Pham et al. [11] evaluated the effect of riboflavin (75 mg/d) formulated as a colon-release form on the composition and metabolic activity of the human gut microbiome over a period of 4 wk, using a double-blind, randomized, placebo-controlled, parallel arm study. The authors reported that the fecal content of riboflavin increased compared with that at baseline (419 compared with 169 μg/100 g); but there was no significant influence on plasma vitamin B-2 amounts, indicating that riboflavin was mainly released into the large intestine. In addition, the authors did not verify any increase in the ratio of *F. prausnitzii* in the fecal microbiome; however, riboflavin stimulated *Clostridium* spp. and *Alistipes* spp. [11]. According to the researchers, these results support a direct action of vitamins on the intestinal microbiota. Additionally, they also mentioned that these findings are related to high doses of riboflavin that are directly provided to the colon and may not be applicable to the consumption of foods or dietary supplements that are absorbed into the upper portions of GIT [11].

In conclusion, advances in biotechnology and bioinformatics will certainly provide more detailed mechanisms about B-group vitamins as new prebiotic candidates that can confirm their direct association with the prevention and treatment of various diseases. Based on the results of several studies, what is known to date is that B-group vitamins may beneficially modulate the gut microbiome, despite not being direct substrates for intestinal microbial fermentation. In general, vitamins, including B-group vitamins, might act directly and/or indirectly on the gut microbiome. However, clinical studies supporting the effects of B-group vitamins as modulators of the gut microbiome are still limited because there is no consensus on their role based on available studies. Some studies suggest that when B-group vitamins are provided in large doses or when they are delivered to the colon, they can beneficially modulate the gut microbiome. So far, few randomized studies have been performed to assess the impact of different B-group vitamins on the human intestinal microbiome, which makes their evaluation as prebiotic compounds a challenge. Therefore, more in-depth and well-designed studies, particularly randomized clinical trials, are required to unambiguously verify whether B-group vitamins might be considered as potential prebiotic compounds or only as modulators of the human gut microbiome.

Author contributions

The authors' responsibilities were as follows—RB, SMIS: designed the research; RB, ACCC: carried out the scientific literature search and wrote the paper; ACCC, MACA: prepared

the figures; RB: had the primary responsibility for the final content; JGL, SMIS: critically reviewed and edited the paper; and all authors: read and approved the final version of the manuscript.

Conflict of interest

The authors report no conflicts of interests.

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