Vitamin biosynthesis in the gut: interplay between mammalian host and its resident microbiota

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Abstract

In recent years exhaustive efforts have been made to dissect the composition of gut-associated microbial communities and associated interactions with their human host, which are thought to play a crucial role in host development, physiology and metabolic functions. While such studies were initially focused on the description of the compositional shifts in the microbiota that occur between different health conditions, more recently they have provided key insights into the functional and metabolic contribution of the gut microbiota to overall host physiology. In this context, an important metabolic activity of the human gut microbiota is believed to be represented by the synthesis of various vitamins which may elicit considerable benefits to human health. A growing body of scientific literature is now available relating to (predicted) bacterial vitamin biosynthetic abilities, with ever-growing information concerning the prevalence of these biosynthetic abilities among members of the human microbiota. This review is aimed at disentangling if and how cooperative trophic interactions of human microbiota members contribute to vitamin production, and if such gut microbiota-mediated vitamin production varies according to different life stages. Moreover, it offers a brief exploration on how different diets may influence vitamin production by shaping the overall composition and metabolic activity of the human gut microbiota, while also providing preliminary insights into potential correlations between human microbiota-associated vitamin production and occurrence of human diseases and/or metabolic disorders.

General introduction

Vitamins are essential, non-caloric micronutrients involved in a plethora of metabolic and regulatory processes in living micro- and macro-organisms, ranging from bacteria to mammals [1,2]. Typically, most vitamins exist as groups of chemically related, nutritionally active compounds, commonly referred to as vitamers [3]. Vitamins can broadly be classified into two categories based on their solubility properties, which influence their functions and sites of action. Specifically, fat-soluble vitamins, namely, vitamins A, D, E, and K, dissolve in fat or other hydrophobic solvents and are for example important to protect cell membranes against free radical damage and to exert effects within the cell nucleus to regulate gene expression [4]. In contrast, vitamin C and all B group vitamins are water-soluble [5] and typically act as cofactors in a wide variety of biochemical reactions within the cell cytosol [6]. In humans, vitamin solubility also influences their mode of absorption. Indeed, while fat-soluble vitamins require dietary fats and bile acids for absorption, being transported through the lymphatic system before entering the bloodstream, water-soluble, diet-derived vitamins are typically absorbed directly into the bloodstream through the intestinal wall of the small intestine [7,8]. Notably, when intraluminal vitamin availability is low, vitamin absorption processes are facilitated by substrate-specific transport systems, while passive diffusion occurs at higher concentrations [8–10].

Except for vitamin D, which humans can produce endogenously following exposure to ultraviolet light [11], most vitamins must be obtained from external sources. Due to their solubility characteristics, water-soluble vitamins cannot be efficiently stored in the human body, leaving individuals susceptible to deficiencies and necessitating a continuous dietary intake to meet requirements [5]. An exception to this is vitamin B12, which humans can store in substantial amounts in the liver for several years, thereby reducing the risk of vitamin B12 deficiency [12].

Although the diet represents the primary exogenous source of vitamins, the human gut microbiota, which is comprised of trillions of microorganisms, has been recognized as a potential production platform for vitamins, including vitamin K2 (menaquinone) and various B vitamins, such as thiamine (B1), riboflavin (B2), niacin or nicotinic acid (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate (B9 or B11), and cobalamin (B12) [13]. In fact, while gut bacteria produce vitamins to fulfill their own metabolic needs, any excess or release into the surrounding environment due to spontaneous microbial cell lysis has the potential to become accessible to their human host [14,15]. This concept aligns with evidence from germ-free animal studies, which are more susceptible to vitamin deficiencies, likely because of the absence of vitamin K- and vitamin B-producing bacterial elements of the gut microbiota [16,17]. Unlike conventionally raised animals, germ-free animals require dietary supplementation of these vitamins to prevent deficiency [18]. For instance, vitamin K deficiency was rapidly induced in male germ-free rats maintained on a vitamin K-deficient diet, whereas conventionally bred animals on the same diet did not exhibit signs of deficiency [19]. Remarkably, mono-colonization of germ-free rats with *Escherichia coli*, a known producer of vitamin K2, restored normal levels of this vitamin within 24-48 hours [19]. Similar observations have been reported in human studies, where individuals maintained on a low-vitamin K diet for 3-4 weeks did not develop vitamin K deficiency. However, when these individuals were treated with broad-spectrum antibiotics to suppress the gut microbiota, a significant reduction in plasma prothrombin levels was observed [20], further highlighting the contribution of gut microbiota to the vitamin K status of their host.

Interestingly, while dietary vitamins are generally absorbed in the human small intestine, specialized transport systems localized in the colonic epithelium will provide efficient

supplementary uptake capacity for vitamins produced by the microbial community residing in the colon [21,22], suggesting that gut microbiota-derived vitamins are of nutritional value to the host and especially to the local colonocytes [7].

The extent to which gut microbiome-derived vitamins contribute to host requirements and systemic status remains somewhat unclear. To the best of our knowledge, just a single study has so far addressed this issue across all eight B-group vitamins [23], estimating that 86 %, 37 %, 31 %, and 27 % of the daily recommended intake of vitamin B6, B9, B12, and B3, respectively, can be provided by human gut commensals [23]. However, this study did not account for vitamin-utilizing bacteria, and other research issues about the actual contribution of microbially derived vitamins to the host, particularly vitamin B12. Notably, these latter studies suggest that this vitamin is unlikely to be supplied to the host in significant quantities, as the predominant corrinoids produced by gut microbiota are cobalamin analogues that are inactive in mammalian cells [24,25]. Instead, vitamin B12 appears to play a crucial role in shaping the composition and functionality of human gut microbial communities [17,24,26,27].

In the following sections of this review, we will provide a comprehensive overview of the current body of knowledge on vitamin production by human-gut associated bacteria, focusing on B-group vitamins and vitamin K, which are the most relevant vitamins synthesized by human-gut associated bacteria among the essential (micro)nutrients [13,28]. Notably, the most recent findings in this area are predominantly derived from metagenome- and genome-based studies, offering insights into the genetic and metabolic potential of these microorganisms.

1. Methodological approaches to measure and predict bacterial vitamin biosynthesis

Due to their impact on human health, understanding vitamin biosynthetic abilities of bacteria inhabiting the diverse (micro)ecosystems of the human body has attracted significant interest from

153 the scientific community [29]. Specifically, the human gut microbiota has emerged as a rich source
154 of microbial taxa capable of producing a wide array of B-group vitamins as well as vitamin K in
155 the form of (mena)quinones [13].

156 In recent decades, the study of bacterial vitamin production primarily relied on *in vitro* cultivation-
157 based techniques. These methods involve cultivating bacteria under controlled laboratory
158 conditions followed by quantification of microbially synthesized vitamins from either cell extracts
159 or culture supernatants (Figure 1). These approaches are still used today and exploit the strict
160 requirement of certain bacteria for a particular B-group vitamin, with measurements based on the
161 correlation between growth of a vitamin-dependent test microorganism and the physiologically
162 available amount of that vitamin in the medium [30,31] (Figure 1).

163 In addition to these microbiological assays, there are several analytical approaches available to
164 detect and quantify B vitamins, including immunoassays, including vitamin-specific ELISA tests,
165 spectrophotometry, electrophoresis, fluorimetry, and high-performance liquid chromatography
166 (HPLC) coupled with ultraviolet or fluorescence detection [32] (Figure 1). While enabling rapid,
167 cost-effective, and efficient analysis, most of these methodologies are restricted to assessing
168 samples with unsophisticated background matrices or abundant B vitamin content, such as
169 pharmaceutical formulations and dietary supplements [33,34]. Additionally, despite their high
170 sensitivity and specificity, these approaches are set up to measure levels of individual B vitamins
171 [32,35,36], and rarely provide a comprehensive B vitamin profile. More recently, methods based
172 on liquid chromatography (LC) coupled with tandem mass spectrometry (MS/MS) have emerged
173 as the most frequently used technique for accurate determination of B vitamins, with the advantage
174 of simultaneously detecting multiple structurally diverse, water-soluble vitamins from various
175 food and biological matrices, such as human milk, plasma, whole blood, and feces, as well as

bacterial culture supernatants [37–45]. In general, liquid chromatography-tandem mass spectrometry (LC-MS/MS) relies on measuring mass-to-charge (m/z) ratios of ionized molecules, involving a two-stage approach. Firstly, chromatographic separation of target compounds is performed using HPLC. In particular, for the separation of water-soluble vitamins, reversed-phase HPLC (RP-HPLC) employing a non-polar stationary phase and a polar mobile phase [46] is a highly suitable technique due to its ability to yield superior peak shape and robustness of chromatographic columns [47–49]. Among various types of stationary phases (SP) used in RP-HPLC [46], C18-based SP has been widely applied to separate water-soluble vitamins, employing a combination of water and organic solvents as the mobile phase for elution [46]. For example, C18-based SPs have been effectively employed to concurrently distinguish active forms of various B-group vitamins from complex matrices, including pyridoxal, pyridoxamine, pyridoxine, four cobalamins, and folate vitamers [48,50–55].

Following chromatographic separation based on increasing hydrophilicity, the fractionated compounds are introduced into a tandem mass spectrometry analyzer for further analysis. Commonly, this analyzer consists of a triple quadrupole mass spectrometer [33], where the compounds are ionized and fragmented, typically by an ionization source such as electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) [56–59]. It is currently recognized that water-soluble vitamins exhibit enhanced responsiveness in positive ionization mode, with the notable exception of folic acid and ascorbic acid, which demonstrate higher responsiveness in negative ionization mode [60–62].

While these approaches have been utilized to directly assess, quantify, and empirically validate vitamin production in bacteria with high sensitivity [35,63], they can only be applied to gut bacteria cultivated under *in vitro* conditions. Notably, many bacterial species and strains, especially those

199 microbes referred to as microbial dark matter [64], remain currently uncultured under *in vitro*
200 conditions. This challenge underscores the need for techniques and approaches that do not rely on
201 cultivation of microorganisms under laboratory conditions.

202 In recent decades, advancements in genome sequencing, the concomitant reduction in DNA
203 sequencing costs and the development of associated bioinformatics tools for sequence analysis
204 platforms have provided valuable insights into the encoded potential of bacterial genomes through
205 comprehensive functional annotation and metabolic reconstruction [65] (Figure 1). These efforts
206 have included the identification of microbial genes associated with vitamin biosynthesis, with a
207 growing body of research correlating genomic data with experimental findings that elucidate
208 genetic pathways and regulatory mechanisms involved in bacterial vitamin biosynthesis [66–72].
209 Over time, comparative and functional annotation of bacterial genomes has become much more
210 productive due to the development of sophisticated annotation platforms, functional analysis
211 software, and manually curated databases containing publicly accessible genomic, proteomic,
212 transcriptomic, metabolomic and protein structure information. Among these, the most renowned
213 resources are MetaCyc (https://metacyc.org/), SEED (http://www.theseed.org/), PATRIC
214 (https://www.patricbrc.org), the Kyoto Encyclopedia of Genes and Genomes (KEGG,
215 (https://www.genome.jp/kegg/), and Protein Data Bank (PDB, https://www.wwpdb.org/), which
216 allow researchers to browse and obtain a wide variety of data, including genomes, genomic
217 features, protein families and 3D structures, and reconstructed pathways [73–78]. Although none
218 of these metabolic pathway catalogs are exclusively dedicated to the genes involved in microbial
219 vitamin synthesis, they cover a wide range of microbial genomes and annotated gene sequences
220 that can be searched to identify specific genes implicated in vitamin biosynthesis pathways across
221 diverse microbial taxa. Consequently, by applying microbial genomics to the identification of

vitamin-related genes and pathways, scientists can now access not only many cost-effective, high-throughput sequencing services but also an extensive pool of publicly available bioinformatic resources. These resources readily aid in identifying vitamin biosynthesis-associated genes through sequence homology with well-characterized sequences (Figure 1). This approach has proven effective in predicting vitamin-producing potential of both currently culturable and yet unculturable bacterial taxa of the human gut microbiota [70,79–82] (Figure 1). In this regard, recent comparative genomic analyses have significantly contributed to elucidating the occurrence of B-vitamin biosynthetic pathways in bacterial genomes, identifying potential gut commensal producers, and revealing intriguing vitamin-dependent inter-species cross-feeding relationships [70,81,83,84]. The genetic basis underlying the biosynthetic potential of gut microbes is discussed in detail in the following section of this review. To provide a few examples, the riboflavin and niacin biosynthetic pathways have emerged as the most prevalent vitamin production capabilities among members of the human gut microbiome [81]. The reason for the widespread biosynthetic potential of these vitamins has been attributed to their involvement in crucial microbial metabolic functions, ranging from maintaining cellular homeostasis to facilitating critical biochemical processes such as energy production, redox reactions, and DNA repair [85,86].

In contrast, complete biosynthetic pathways for cobalamin appear to be much less common among human gut commensals, most likely because this vitamin is not essential for growth of many bacteria, as they have cobalamin-independent enzymes [82,87]. However, multiple genomic investigations have shown that only a minority of the cobalamin-utilizing microorganisms possess the full biosynthetic pathway for this cofactor [87,88], thus relying, where relevant, on its environmental availability as well as on intricate cross-feeding networks [24,89]. These findings

have led to the hypothesis that certain B-complex vitamins play a crucial role in shaping and driving ecological microbe-microbe relationships within the human gut [80,90,91].

Expanding from the hypothesis which poses that B vitamins influence microbial interactions, genomic data have been used to construct microbial genome-scale models that offer a mechanistic understanding of metabolic traits within microbial communities [76,92–95] (Figure 1). Intriguingly, such validated *in silico* modelling, by integrating data from distinct components such as cells, molecules, and pathways [96], allows for a broadening of perspective from individual microbes to community outcomes, thereby aiding in capturing overall metabolism of entire ecosystems. A compelling example in the context of vitamin production by human-associated microorganisms is illustrated by a recent study, which systematically infers vitamin-associated metabolic abilities of nearly one thousand genomes of common human gut commensals, revealing which vitamins constitute essential or optional nutrients under specific growth conditions [92]. Notably, based on this study, roughly 60 % of the tested enteric bacteria depend on external sources of vitamin B1, followed by vitamins B2 and K2, which were predicted to be essential for more than 40 % of gut microbes. Moreover, integrating requirements and biosynthetic abilities across various gut commensals has shown the presence of complementary profiles of vitamin biosynthesis within microbial communities. Interestingly, these findings demonstrate that vitamin biosynthetic capabilities may explain the recurrent association of specific microbial species, including those underlying the so-called Community State Type (CST) [97], as described in the following section.

However, despite the progress and promising outlook of these model-based approaches, they remain challenging to implement for complex microbial communities and are, therefore, mainly limited to rather simple microbial model systems. Indeed, microbial communities exhibit intricate

networks of interactions where individual species rely on and influence reciprocal activities [84,98,99]. In these highly interactive communities, such as the symbiotic consortia of the human gut microbiota, behavior of individual members is tightly coordinated, often resembling a single functional unit rather than a gathering of independent (micro)organisms. This complexity presents challenges for traditional reductionist approaches and necessitates holistic strategies to fully understand ecological and functional community dynamics.

In this context, the advent and common use of whole-metagenome shotgun sequencing (WMGS) has significantly improved our ability to dissect the intricate dynamics of microbial communities. Indeed, while early sequencing technologies were limited in their output by their ability to generate several million bases of DNA sequence information per run, the current gold standard platforms, such as the Illumina NovaSeq, can generate up to 6 terabases of high-quality nucleotide sequence data per sequencing run [100], vastly expanding our depth of understanding and precision in studying microbial communities. Notably, by employing a technique that entails the untargeted sequencing of all microbial DNA extracted from a given (bio)sample, WMGS sequencing facilitates the cataloging of genes occurring within complex microbial ecosystems. While these technologies are undeniably powerful, they are not entirely unbiased, and incorrect functional annotations may occur due to limitations in reference databases. Ideally, these approaches should be complemented, wherever possible, by cultivation-based methods to experimentally validate and refine *in silico* predictions (Figure 1). When used to analyze sequences related to vitamin biosynthesis in the fecal metagenome, commonly employed as a proxy for the distal colon microbiota [101,102], this powerful tool represents a cornerstone for readily delving into the vitaminogenic potential encoded by the human gut microbiota [103] (Figure 1). Despite the current lack of specific resources to identify vitamin biosynthetic genes within complex

microbial communities, the functional annotation, as well as the estimation of prevalence and relative abundance of microbial genes associated with vitamin biosynthesis, can be achieved by inferring homology between decoded metagenomic data and the extensive range of comprehensive reference databases of bacterial sequences (Figure 1). In this regard, well-annotated sequence resources commonly used to functionally annotate metagenomes in terms of vitamin biosynthesis are fundamentally the same as mentioned above as used in genome-level investigations, e.g., KEGG, Gene Ontology (GO), and Metacyc databases. Specifically, within these huge catalogs, functional information is curated to enable the assignment of genes to biological processes or pathways. Accordingly, in metagenomic analyses of vitamin biosynthesis, query read sequences can be matched with reference genes in the database, enabling precise mapping of these sequences to their corresponding metabolic pathways.

A common procedure to functionally characterize metagenomic samples involves *de novo* assembly of reads into contigs, followed by gene prediction and annotation, usually through comparisons with reference catalogs containing genes of known function (Figure 1). Notably, when these databases include sequence information related to vitamin-related genes, the presence of these structures can be rapidly identified in the newly assembled genome. However, compared to individual genomes, gene characterization from metagenome-assembled sequences provides additional challenges, mainly due to the possible vast numbers of genomic fragments involved, which increases the probability of incomplete annotation. In this context, well-established tools for metagenome assembly and annotation, such as MetaProdigal [104], MEGAHIT [105], MetaGeneMark [106], and metaSPAdes [107], try to address this issue. Notwithstanding, they may limit the discovery and characterization of vitamin-related genes from low-abundant

313 microorganisms, as attempts to reconstruct these genomes often result in incomplete or fragmented
314 assemblies due to insufficient read coverage [64,108].
315 Metagenomic assembly may not always be feasible or reliable, as it is significantly impacted by
316 factors such as the number of sequence reads (depth of sequencing), as well as the richness and
317 evenness of the microbial species comprising the metagenome [109,110]. Consequently, likely due
318 to these considerations, some researchers frequently opt to perform metagenome functional
319 annotation by directly comparing individual short reads to annotated gene sequence repositories,
320 thus bypassing the assembly step [111] (Figure 1). In fact, by mapping decoded metagenomic data
321 to a reference database of known vitamin biosynthesis sequences, it is possible to estimate the
322 prevalence and relative abundance of gut microbiota-derived genes, including the identification of
323 vitamin metabolic pathways, as well as the assessment of the contribution of each bacterial species
324 to the vitamin biosynthetic capacity of the whole microbial consortium [112–114].
325 Consistently, publicly available workflows for read mapping-based annotation have been
326 developed, including HUMAnN3 [115], METAnnotatorX2 [116], and MG-RAST [117]. These
327 bioinformatic pipelines generally rely on BLAST-like tools such as DIAMOND [118], as well as
328 the read aligners Bowtie2 and BWA [119,120], to associate short reads directly with a reference
329 catalog of microbial sequences, enabling the estimation of comprehensive functional profiles.
330 Although the relative abundance of individual functionally annotated genes can sometimes be
331 informative [100], microbial vitamin-related functional abilities are likely better described as
332 pathways, implying the need to simultaneously consider multiple, intertwined genes [121]. This
333 task is particularly challenging in functional explorations of the human gut microbiome due to the
334 inherent variability of microbial genomes typically found in fecal metagenomic samples [122,123].
335 Indeed, individual genes can participate in multiple pathways, complicating the attribution of

specific functions to distinct metabolic processes. Additionally, genes associated with certain vitamin biosynthesis pathways may be conserved across different microbial species, while others may be absent or replaced by functional analogs [81,124,125]. This heterogeneity necessitates a complete awareness of the presence of homologous and non-homologous but functionally analogous gene counterparts in the reference collection, upon which the accuracy of identification and quantification of vitamin-related genes within metagenomes depends. In this context, some of the read-mapping annotation tools, such as HUMAnN3, offer the ability to estimate a single abundance measure of microbial pathways from metagenomic data by exploiting associations between genes and biological processes documented in the MetaCyc database [115].

Alternatively, with prior metabolic pathway knowledge, the abundance of a given enzymatic pathway can be estimated by summing the number of metagenomic sequences mapped to all participating genes of that pathway, provided that the length of the individually mapped genes is taken into account. Moreover, by calculating the coverage of each pathway as the number of steps for which the associated enzyme-encoding gene was detected within the metagenome, divided by the total number of steps constituting the pathway, this procedure allows coverage-based evaluation of pathway completeness [126]. Notably, an enzyme-mediated, multi-step reaction can be reasonably considered present and complete if it meets a predetermined global coverage threshold [126], or, alternatively, if a subset of well-established essential and conserved enzymes is identified. Indeed, as B-group vitamin biosynthetic pathways may encompass alternative biochemical routes with enzyme variants, a subgroup of vitamin-related genes, previously identified as strictly necessary for the *de novo* biosynthesis [70], can be effectively evaluated in order to assess the completeness and variability of such biosynthetic routes within metagenomic samples from the human gut (for detailed information on B-vitamin biosynthetic pathways and

genes, please refer to the following section of this review). For example, although the initial steps of cobalamin biosynthesis can proceed via either aerobic or anaerobic pathways, thus involving different enzyme variants, the subsequent downstream steps are universally conserved across various cobalamin-producing commensal species of the human gut [70]. Similarly, based on the amino acid precursors, alternative routes have been identified for the *de novo* generation of the intermediate quinolinate as part of the biosynthetic pathway to produce the active form of vitamin B3, while the final biochemical steps to synthesize this vitamin involve conserved enzymes/genes [70]. Moreover, likely due to its fundamental role in cells, this latter cofactor can be obtained by various salvage routes, which deserve consideration as they enable intracellular production of this vitamin without the requirement for a complete *de novo* biosynthetic pathway [70].

Such extensive genetic diversity can be effectively scrutinized and managed through metagenomic approaches supported by comprehensively designed databases, addressing crucial questions regarding the prevalence, abundance, and variation of B-group vitamin-producing species across various human populations, as well as the influence of external factors, such as diet, age, and lifestyle, on B vitamin biosynthetic potential (Figure 1). For instance, by comparing metagenomic functional profiles across different populations, recent research has unveiled country-specific potential for gut microbiota-mediated B vitamin biosynthesis, with Chinese individuals showing a significantly higher relative abundance of genes for B-group and K2 vitamins when compared to subjects from other countries, including the USA, Spain, Denmark, and India [112,127].

Similarly, by using DIAMOND to map metagenomic read sequences to the KEGG database, the relative abundance of vitamin biosynthetic pathways has also been evaluated across different human disease cohorts, highlighting, for instance, disparities between healthy individuals and

those with type 2 diabetes, with the latter group showing a higher relative abundance of metabolic pathways involved in vitamin K2 biosynthesis [112,114].

Besides uncovering functional characteristics of human-associated microbial communities in relation to host factors, metagenomics offers the ability to gain insight into microbe-microbe interactions governing the microbial consortium ecology. Indeed, abundance and taxonomic data derived from metagenomic sequencing can be used to predict correlation-based networks, identifying co-occurring or mutually exclusive relationships among different organisms in ecosystems [128–131]. These relationships can then be represented as network nodes, corresponding to individual microbial species, with edges connecting taxa exhibiting significant correlation patterns. Focusing specifically on vitamin biosynthesis, such correlation-based networks have demonstrated significant predictive ability in identifying microorganisms pivotal for B vitamin provision within a complex microbial community. Indeed, in recent studies, the construction of metagenome-informed networks enabled the estimation of the significance of predicted vitamin-producing bacteria in shaping the microbial interactions within their local environment [113,132], revealing, for example, cobalamin and folate producers as central hubs in the microbial networks of adult and infant gut microbiomes, respectively [133].

Despite its numerous advantages, metagenomics still faces certain limitations. One of its primary shortfalls is the inability to elucidate what genes are actively expressed to produce functional proteins [134]. To bridge this gap, metagenomic information can be complemented and enhanced by metatranscriptomics [135–137] and metaproteomics [137–139], which enable assessment of gene expression or protein abundance, respectively. In this way, patterns of vitamin-related genes can be identified across various physiological conditions or, for example, in response to dietary

changes, providing a real-time depiction of the microbial vitamin biosynthesis status rather than the genetic potential offered by metagenomics.

Nevertheless, despite the potential of these technologies, the application of omics-based methodologies to discover microbial vitamin-related genes in the human gut microbiota remains largely underrepresented, underscoring the need for more extensive and integrated omics-based research efforts in this area. Continued efforts to integrate omics data, computational modeling, and experimental validation are required to enhance our understanding of human-associated microbial vitamin biosynthetic activities.

2. Genetics of vitamin biosynthesis and transport mechanisms in key members of the human gut microbiota

As previously mentioned, certain bacteria can produce B-group and K2 vitamins through dedicated *de novo* biosynthetic pathways, which are summarized below. In this context, referring to one or more B-vitamins, virtually individual microorganisms can be categorized as either a B-vitamin-producer, reflecting its prototrophic capabilities, or a B-vitamin-acquirer, i.e., being auxotrophic and thereby needing to obtaining B-vitamins from the surrounding environment [129,140]. Additionally, in the absence of key genetic features, microorganisms can scavenge essential vitamers *via* salvage pathways, which enable them to recover and recycle vitamins and/or their precursors from the environment [92]. However, salvage mechanisms have also been frequently identified in prototrophic bacteria. In these microorganisms, such pathways represent a chance to adopt an opportunistic lifestyle, switching from the energetically costly *de novo* synthesis to a more economical salvage route, depending on the availability of vitamins in the environment [70].

Historically, identification and understanding of metabolic pathways involved in the biosynthesis of ubiquitous cofactors and their precursors (vitamins) were largely confined to a few model organisms, such as the Gram-negative *Escherichia coli* and the Gram-positive *Bacillus subtilis*. Knowledge of the genetic requirements for vitamin production by these model organisms can be used to interrogate the currently available extensive genomic data in order to determine the presence or absence of vitamin biosynthetic pathways across a multitude of species.

Consistently, recent comparative analyses within reference collections of human-associated bacterial genomes [70,81,92] have revealed a notable variability in the structure of vitamin biosynthetic pathways, even among different prototrophic species, reflecting diverse metabolic capabilities and environmental adaptations. For instance, some bacteria may employ alternative enzymes to catalyze identical biochemical reactions, or certain (accessory) enzymes may be present or absent without affecting the overall biosynthetic capability for a specific vitamin [70]. However, core gene sets involved in the biosynthesis of each active cofactor have been identified as conserved across several prototrophic species [70].

In this section, we discuss available data regarding the conservation level of the genetic background necessary for *de novo* vitamin synthesis across common human-associated bacteria, including members of the gut [141], skin [142,143], and oral microbiomes [144] (Figure 2).

2.1 Thiamine (Vitamin B1)

Vitamin B1, also referred to as thiamine monochloride, thiamine chloride, or aneurine, plays an essential role in carbohydrate and branched-chain amino acid metabolism by acting as a cofactor for both pyruvate dehydrogenase and α-ketoglutarate dehydrogenase in glycolysis and the tricarboxylic acid (TCA) cycle [145–147].

449 The human colonic microbiota can synthesize *de novo* both free B1 vitamin and its active
450 phosphorylated form (thiamine pyrophosphate, TPP) [97]. Specifically, in bacteria, thiamine
451 synthesis utilizes a branched pathway leading to the separate synthesis of two precursors: thiazole
452 phosphate (THZ-P moiety) and pyrimidine pyrophosphate (HMP-PP moiety) [148]. The thiazole
453 moiety can be derived from an oxidative condensation of 1-deoxy-D-xylulose 5-phosphate (DXP),
454 cysteine, and glycine or tyrosine [148], and two alternative routes were identified in bacteria for
455 its synthesis (Figure 2). The THZ-P and HMP-PP moieties are then condensed and phosphorylated
456 by thiamine phosphate synthase and thiamine monophosphate kinase, respectively, to generate the
457 biologically active form of thiamine (Figure 2) [148].
458 Notable key commensals of the human gut, including members of the *Bacteroides* and
459 *Bifidobacterium* genera, *Prevotella copri*, *Agathobacter rectalis* (formerly *Eubacterium rectale*),
460 and some members of the *Ruminococcus* genus, have been predicted to synthesize this vitamin, as
461 revealed by *in silico* analyses of their genomes [149,150]. Additionally, certain opportunistic
462 pathogenic species from the Pseudomonadota phylum (formerly Proteobacteria), such as those
463 belonging to the *Pseudomonas* and *Klebsiella* genera, as well as *E. coli*, are also capable of
464 producing thiamine. In contrast, despite the requirement of vitamin B1 for its metabolism,
465 including the conversion of pyruvate to acetyl-CoA in the butyrate production pathway,
466 *Faecalibacterium prausnitzii* lacks an intact thiamin biosynthetic pathway, indicating its
467 dependence on environmental sources of thiamin or by establishing trophic interaction (e.g., cross-
468 feeding activities) with other members of the human gut microbiota [83,149]. Moreover, among
469 various bacterial species isolated from the human nasopharynx and oral cavity [142,143] only a
470 minority of the species from the *Streptococcus*, *Veillonella*, and *Actinomyces* genera are capable
471 of synthesizing vitamin B1 [81]. Similarly, only a few members of the human skin microbiota

[151] possess the thiamin biosynthetic genes. These include *Cutibacterium acnes* (formerly classified as *Propionibacterium acnes*), and certain species belonging to the *Staphylococcus*, *Corynebacterium* genera [81].

TPP synthesized by the microbiota within the large intestine was historically regarded as nutritionally insignificant to the host because of the prevailing notion that the intestinal absorptive epithelia lacked the ability to transport such a large, hydrophilic, and charged molecule across their phospholipid bilayer, prior to its enzymatic hydrolysis into free thiamine [152]. However, subsequent scientific data has suggested that human colonocytes can acquire microbiota-derived thiamine either *via* a process similar to that functioning in the small intestine for free thiamine or through specific and high affinity TPP transporters, such as TPPT-1 (encoded by the SLC44A4 gene [153–155]. Intriguingly, the finding of competent uptake mechanisms in human colonocytes for both free thiamine and its phosphorylated TPP form clearly indicates that microbially produced thiamine has the potential to contribute meaningfully to thiamine nutrition of the host, particularly enhancing the cellular (micro)nutrition and health of the colonocytes.

2.2 Riboflavin (Vitamin B2)

Riboflavin, also known as vitamin B2, plays a pivotal role in diverse biochemical reactions within living cells, serving as a precursor for two essential coenzymes, i.e., flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN). These coenzymes are crucial electron carriers in flavoprotein-mediated redox reactions and are involved in a variety of metabolic processes, including the electron transport chain, the TCA cycle, fatty acid oxidization (β-oxidization), and redox homeostasis [156]. Moreover, in bacteria, riboflavin, its biochemical precursors and

derivates are involved in several extracellular processes, including quorum sensing signaling and host-microbe cross-talk [157,158].

Bacteria can *de novo* synthesize free riboflavin through five enzymatic steps utilizing guanosine-5'-triphosphate (GTP) derived from the purine biosynthesis pathway, and ribulose-5-phosphate (R5P), an intermediate from the pentose phosphate pathway [159,160] (Figure 2). However, when riboflavin is environmentally available, bacteria usually repress their endogenous biosynthesis *via* an FMN-sensing mRNA riboswitch, which also transcriptionally controls the genes responsible for riboflavin transport from the extracellular environment [161–164].

Although the pathway for riboflavin biosynthesis, when present, is well conserved across bacteria, variations exist among different evolutionary lineages regarding the structure and organization of the riboflavin biosynthesis proteins (Rib) and corresponding *rib* genes. For instance, *E. coli* utilizes two distinct monofunctional enzymes, RibA and RibB, to process the precursors GTP and R5P separately [165,166] (Figure 2). In contrast, *Bacillus subtilis* employs a bifunctional enzyme named RibA, encompassing both GTP cyclohydrolase II and dihydroxybutanone phosphate synthase activities for the same biosynthetic reactions [167] (Figure 2). By exploiting sequence homology with these well-characterized genes in model microorganisms, genome comparative analyses showed that all assessed genomes of the Fusobacteria and Bacteroidota (formerly Bacteroidetes), essentially all Pseudomonadota, and a large portion of the currently known Bacillota (formerly Firmicutes) possess the genetic capacity to produce riboflavin [81], making riboflavin the most prevalent B vitamin produced across these phyla. Specifically, among the bacterial elements of the human gut microbiota, all currently known species from the *Bacteroides* genus (including species reclassified into the genus *Phocaeicola*), *Anaerobutyricum hallii* (formerly *Eubacterium hallii*), *P. copri*, and some members of the *Ruminococcus* genus are

equipped with complete pathways for vitamin B2 synthesis [70,81]. In contrast, the ability to produce *de novo* riboflavin is less prevalent among gut-associated Actinomycetota (formerly Actinobacteria), being absent in the *Collinsella* and *Bifidobacterium* genera, with the exception of the *Bifidobacterium longum* subsp. *infantis* species [35]. Nevertheless, although prominent gut commensals appear able to produce riboflavin, only 3% of the daily reference intake (DRI) of this vitamin was estimated to be derived from the gut microbiota [81].

Endogenous riboflavin biosynthesis was also found conserved in *C. acnes*, as well as members of the *Corynebacterium* and *Staphylococcus* genera of the human skin microbiome [70,81,142]. Additionally, riboflavin genes are present in examined *Prevotella* and *Veillonella* species typical of the human oral microbiome, but notably absent in members of the *Streptococcus* genus [168].

2.3 Niacin (vitamin B3)

Niacin, also known as vitamin B3, is the generic name for nicotinamide (NAM), nicotinic acid (NA), and related derivatives, such as nicotinamide riboside. Metabolically active forms of this vitamin are nicotinamide adenine dinucleotide (NAD^+), nicotinamide adenine dinucleotide phosphate ($NADP^+$), and their respective reduced forms [NAD(P)H)], which provide reducing equivalents for cellular biochemistry and energy metabolism [169,170]

Several gut microbial species can synthesize vitamin B3 from tryptophan (Figure 2) [171]. However, based on recent reconstructions of vitamin biosynthetic pathways among human gut commensals, the amino acid aspartate is most commonly used to synthesize the quinolinate precursor of NAD^+ (Figure 2) [70,172]. In contrast, downstream of this intermediate, the genes involved in NAD^+ synthesis, namely *nad*C, *nad*D, and *nad*E (Figure 2), are highly conserved in bacterial prototrophs for niacin [70,81].

It has been estimated that the human gut microbiota can provide 27% of the RDI of niacin through corresponding *de novo* biosynthesis pathways, which are present in the majority of the genomes associated with the human gut microbiota [81]. Generally, the phyla Actinomycetota and Bacillota contain lower ratios of *de novo* producers when compared to assessed members of the phyla Pseudomonadota, Fusobacteria, and Bacteroidota [81]. However, niacin can be produced in the human gut by *P. copri* and species from the *Bacteroides*, *Bifidobacterium*, *Ruminococcus*, *Clostridium*, and various recently reclassified genera which had previously been assigned to the genus *Eubacterium* [29,92]. Additionally, this essential micronutrient is produced by *Neisseria* and *Prevotella* species in the oral microbiome, as well as *Corynebacterium* and *Acinetobacter* species from the skin microbial community. In contrast, the *de novo* niacin biosynthesis pathway is predicted to be absent in most species belonging to *Faecalibacterium*, *Veillonella*, *Enterococcus*, *Streptococcus*, and *Staphylococcus* genera [172].

2.4 Pantothenic acid (vitamin B5)

Pantothenate, also known as vitamin B5, is a crucial precursor for the biosynthesis of coenzyme A (CoA) which represents a universal and essential cofactor involved in numerous cellular metabolic processes, including the synthesis and degradation of fatty acids, the synthesis of phospholipids, and the functioning of the tricarboxylic acid (TCA) cycle [173].

In bacteria, *de novo* synthesis of pantothenate requires the intermediate pantoate, obtained from the valine biosynthetic pathway via the enzyme encoded by the *pan*B gene, and the amino acid aspartate, which is converted into β-alanine by the product of the *pan*D gene (Figure 2) [173]. Pantoate and β-alanine precursors are ultimately condensed by the pantothenate synthetase (the *pan*C gene product) to yield pantothenate, which is released from the cell or subjected to the downstream enzymatic steps leading to the CoA synthesis (Figure 2) [173]. Interestingly, while

565 *pan*B and *pan*C are contained within a relatively conserved operon, comparative analyses have
566 shown that some bacterial prototrophs lack the *pan*D gene [70]. This suggests that β-alanine could
567 be acquired exogenously through a salvage pathway or synthesized through an as yet
568 uncharacterized, alternative pathway.
569 Assessments of reference collections of human-associated bacteria have predicted pantothenate
570 biosynthetic abilities in approximately all genomes from Bacteroidota and Pseudomonadota, as
571 well as half of Bacillota and only a minority of Actinomycetota. Specifically, key human gut
572 commensals such as *Enterococcus faecalis, P. copri*, *E. coli*, as well as members of the *Bacteroides*
573 and (species previously assigned to the) *Eubacterium* genera, possess the complete pathway for *de*
574 *novo* vitamin B5 synthesis [81,92]. However, the lack of direct evidence supporting the absorption
575 of pantothenic acid in the colon leaves open the question of whether or not bacterially synthesized
576 pantothenic acid is nutritionally relevant to the host.
577 Similarly, among bacteria associated with the human oral cavity, the *Porphyromonas*, *Prevotella*,
578 and *Actinomyces* genera are identified as primary producers of pantothenate, whereas in the skin
579 microbiota, bacteria predicted to autonomously produce vitamin B5 include those belonging to the
580 genera *Acinetobacter*, *Staphylococcus*, and *Corynebacterium* [81].
581
582 **2.5 Pyridoxine and its derivates (Vitamin B6)**
583 Vitamin B6 exists in several forms, including pyridoxine (PN), pyridoxal (PL), and pyridoxamine
584 (PM), all of which can be phosphorylated at the 5' position to generate three additional vitamers:
585 pyridoxine phosphate (PNP), pyridoxal phosphate (PLP), and pyridoxamine phosphate (PMP).
586 Among these, pyridoxal 5'-phosphate (PLP) is the most biologically active form, serving as a
587 cofactor in many important enzymatic reactions of living organisms [174]. PLP-dependent
588 enzymes exist within five of the seven enzymes classes defined by the International Union of

589 Biochemistry (https://iubmb.qmul.ac.uk/enzyme/), i.e., oxidoreductases EC 1; transferases EC 2;
590 hydrolases EC 3; lyases EC 4; isomerases EC 5, underlining the wide variety of biochemical
591 reactions which PLP supports in cells [175,176].
592 In the human gut, vitamin B6 is synthesized as PLP using two alternative routes, identified as
593 deoxyxylulose 5-phosphate (DXP)-dependent pathway and DXP-independent pathway [177]. The
594 first route condenses DXP with 4-phosphohydroxy-l-threonine to produce PNP, which is then
595 oxidized to PLP by the enzyme encoded by the *pdx*H gene (Figure 2). In the DXP-independent
596 pathway, the PLP synthase complex (encoded by the *pdx*S gene) uses D-ribose 5-phosphate (R5P),
597 glutamine (Gln), and glyceraldehyde 3-phosphate (G3P) as precursors to directly generate PLP
598 (Figure 2). Members of the Bacteroidota and Pseudomonadota phyla predominantly utilize the
599 DXP-dependent pathway for vitamin B6 biosynthesis, while Actinomycetota are more likely to
600 use the DXP-independent route [81], underscoring lineage-dependent metabolic strategies.
601 Regardless of the pathway employed, members of the *Bifidobacterium*, *Bacteroides*, and
602 *Prevotella* genera, as well as many Pseudomonadota and several Bacillota, are predicted to
603 synthesize vitamin B6 in the colon [70,81]. However, other key human gut bacteria, such as
604 members of the *Veillonella* genus members, *E. faecalis*, as well as the butyrate-producing *F.*
605 *prausnitzii*, and *Roseburia inulinivorans*, are auxotrophic for B6 vitamers and rely on salvage
606 enzymes, primarily represented by the PL/PN/PM kinase (*PdxK*) or PL kinase (*PdxY*) depending
607 on their substrate specificities (Figure 2), to recover environmental vitamin B6 [178,179].
608 Dietary and bacterially synthesized PLP is hydrolyzed to free vitamin B6 in the intestine, where it
609 is absorbed by specialized and regulated transporters expressed by human colonocytes [180,181].
610 Interestingly, while hydrolysis of vitamin B6 is necessary for its intestinal absorption, this process
611 may be favored by an acidic intestinal pH [181,182]. Accordingly, it is reasonable to suggest that

612 the presence of lactic acid-producing bacteria, such as enteric lactobacilli residing in the small
613 intestine may enhance dietary vitamin B6 bioavailability in this area of by lowering luminal pH
614 [183]. However, scientific literature on this topic is still scarce, and further investigations are
615 needed to confirm the potential role of these bacteria in facilitating vitamin B6 absorption.
616
617 **2.6 Biotin (vitamin B7)**
618 Biotin, also referred to as vitamin B7 or vitamin H, is a crucial cofactor for six biotin-dependent
619 carboxylases: acetyl-CoA carboxylase, methylcrotonyl-CoA carboxylase, pyruvate carboxylase,
620 urea carboxylase, geranyl-CoA carboxylase, and propionyl-CoA carboxylase [184]. These
621 enzymes are vital for the metabolism of fatty acids, carbohydrates, and amino acids, and are widely
622 distributed across nature [184].
623 In addition to dietary sources, humans are also exposed to bacterial sources of vitamin B7. Indeed,
624 intestinal bacteria can synthesize this micronutrient *de novo* as free biotin through a biochemical
625 pathway that can be divided into two stages. The first stage involves the generation of the pimelate
626 moiety, which contributes to seven of the ten carbon atoms in biotin, followed by the assembly of
627 the biotin rings (Figure 2). While the genes involved in the latter step are conserved across various
628 biotin-producing bacterial species, the synthesis of the pimelate intermediate can proceed via two
629 alternative routes. Among these, the first well-characterized pathway, found in *E. coli*, is a
630 modified fatty acid synthetic route that requires the action of the *bio*C and *bio*H genes, encoding a
631 malonyl-ACP methyltransferase and a pimeloyl-ACP methyl esterase, respectively [185,186]
632 (Figure 2). Based on current genomic data, this pathway appears to be predominant among
633 bacteria. However, several evolutionary distinct *bio*H functional equivalents, including *bio*G, *bio*J,
634 *bio*K, and *bio*V [187,188] (Figure 2), have been identified in diverse bacterial species, increasing
635 the diversity and complexity of genetic features in biotin synthesis.

636 Another well-studied route for pimelic acid synthesis, being quite distinct from the BioC-BioH
637 mechanism in *E. coli*, has been identified in *Bacillus subtilis* and involves the enzyme bioW, a
638 pimeloyl-CoA synthetase, which directly generates pimeloyl-CoA [185,189,190] (Figure 2).
639 Biotin has biological activity only when it is covalently linked to a biotin-accepting enzyme via a
640 specific lysine residue [7,191]. Therefore, once synthesized, the newly formed biotin molecule is
641 covalently attached to its cognate polypeptide by an enzyme known as biotin protein ligase, in a
642 process analogous to reactions catalyzed by aminoacyl-tRNA synthetases [192].
643 Comparative genomic analyses predict that only a minority of representative organisms within the
644 human gut microbiota can synthesize vitamin B7 *de novo*, with members of the *Bacteroides* and
645 many Pseudomonadota being the primary contributors. Consistently, the human gut microbiota is
646 estimated to provide just 4.5% of the DRI for biotin [81]. However, some gut-associated
647 microorganisms, such as *Akkermansia muciniphila*, are expected to produce biotin when provided
648 with exogenous supply of pimeloyl, as they possess the downstream biotin biosynthesis genes [70].
649 Interestingly, *Bifidobacterium longum* has been shown to produce pimelate *in vivo* [193], thereby
650 potentially supplying biotin precursors to other microbial community members. Although *B.*
651 *longum*, like most Actinomycetota, apparently lacks a (complete) genetic pathway to produce
652 biotin, they have compensated for this functional deficiency with the presence of the BioY
653 transporter, found in approximately 80% of Actinomycetota genomes [70]. This enables
654 bifidobacteria to internalize vitamin B7 from the environment, likely produced by co-occurring
655 microorganisms, thus facilitating complex trophic interactions based on the sharing of precursors
656 and final products of the vitamin B7 biosynthetic pathway.
657 Utilizing the knowledge of bacterial species that can produce vitamin B7 and the genetic pathways
658 involved, it is also possible to predict biotin biosynthesis capability in certain oral species from the

659 *Veillonella* and *Porphyromonas* genera, as well as in *Staphylococcus epidermidis* and *C. acnes* as
660 members of the human skin microbiome [81].
661
662 **2.7 Folate (vitamin B9)**
663 Naturally occurring folate, or its synthetic counterpart folic acid, is essential for one-carbon
664 metabolism, which includes transferring carbon units during RNA and DNA biosynthesis and
665 repair, DNA methylation, as well as amino acid metabolism [194]. The active form of vitamin B9
666 is known as tetrahydrofolate (THF), although other naturally occurring folates include the
667 polyglutamate forms of 5-methyl THF, and 10-formyl THF [195].
668 Intestinal bacteria synthesize THF *de novo* as either mono- or polyglutamates by condensing the
669 6-hydroxymethyl-7,8-dihydropterin pyrophosphate (DHPPP) and the para-aminobenzoic acid
670 (pABA) intermediates (Figure 2), which therefore are both required for folate production [196].
671 However, as detailed previously [70,196], some microorganisms lack the ability to independently
672 synthesize pABA. Although such microorganisms should, therefore, be considered auxotrophs for
673 folate, they can still produce this vitamin when pABA is available in the environment. This is the
674 case for various species within the *Lactobacillus* and *Bifidobacterium* genera, which can produce
675 folate by scavenging pABA from host dietary metabolites or other community members [72,197].
676 Interestingly, *in vitro* assays have demonstrated that bifidobacteria isolated from the human gut are
677 generally capable of producing folate, unlike non-human-associated strains [197,198]. High-
678 folate, pABA-dependent producers have been identified in certain infant gut-specialized species,
679 including *Bifidobacterium bifidum* and *B. longum* subsp. *infantis* [196,199], reinforcing the notion
680 of host-microbe coevolution and the importance of such symbiotic relationships from early
681 infancy. Indeed, microbe-derived folate is easily processed by mammalian cells, and there is direct
682 evidence that microbial folates are absorbed by the host through a proton-coupled folate transporter

683 in the colon, which functions optimally at an acidic-pH [22,200]. Beyond bifidobacteria, other
684 bacteria such as *Veillonella*, *E. faecalis,* and *R. inulinivorans* have been predicted to produce folate
685 in the presence of pABA, while the complete pathway for vitamin B9 biosynthesis has been
686 identified in members of the *Bacteroides*, and *Ruminococcus* genera, most of Pseudomonadota, as
687 well as *P. copri* and *A. muciniphila* [70]. Within the human oral cavity and skin microbiomes,
688 bacteria of the *Prevotella* genus, along with *Staphylococcus* and *Acinetobacter* species, are known
689 to possess the complete capability to autonomously produce folate [81].
690
691 **2.8 Cobalamin (Vitamin B12)**
692 Vitamin B12, commonly referred to as cobalamin, encompasses a family of chemically complex
693 vitamers, including hydroxy-, methyl-, deoxyadenosyl-, and cyano-cobalamin, all of which
694 contain the mineral cobalt [201]. The cyano form, being the most stable, is widely used in
695 supplements and fortified foods, while the natural forms, methyl-, and deoxyadenosyl-cobalamin
696 (AdoCbl), are synthesized exclusively by prokaryotes [68]. Similar to folate, cobalamin functions
697 as a cofactor in biochemical reactions involving methyl group transfer, which are vital for nucleic
698 acid synthesis as well as protein and lipid metabolism, including the production of short-chain
699 fatty acids (SCFAs) [82,202,203]. As anticipated, bacteria inhabiting the human gut can produce
700 cobalamin and various corrinoid analogs in the colon [204]. Bacterial *de novo* vitamin B12
701 biosynthesis can proceed through either an aerobic or an anaerobic pathway, both starting from the
702 precursor uroporphyrinogen III (Figure 2). In the aerobic pathway, molecular oxygen is utilized in
703 several steps, including cobalt insertion, whereas in the anaerobic route, cobalt insertion occurs
704 earlier and is oxygen-independent (Figure 2). Despite the possible presence of lineage-specific
705 non-homologous alternatives that have as yet to be identified, comprehensive comparative
706 analyses of experimentally validated cobalamin-producing bacteria have identified three

conserved genes essential for corrin ring synthesis, namely *cbi*L, *cbi*F, and *cbi*C in the anaerobic pathway, which are orthologous to *cob*I, *cob*M, and *cob*H, respectively, in the aerobic pathway [82] (Figure 2).

Bacterial cobalamin synthesis is a highly complex and energy-intensive process, requiring approximately 30 enzymatic steps [205]. This complexity likely explains why relatively few metabolic pathways depend on cobalamin, and why some bacteria do not require it for growth, while others exhibit auxotrophy for this micronutrient. Recent metabolic reconstructions of vitamin biosynthesis abilities in over 2,000 representative genomes of the human gut microbiota have shown that up to 60-80% of these genomes lack the cobalamin biosynthetic pathway [70,92]. Certain bacteria, such as members of the *Bacteroides Veillonella*, *Clostridium*, *Klebsiella*, *Ruminococcus* genera, as well as the butyrate-producing *Roseburia intestinalis, Ag. rectale*, and *F. prausnitizii*, have been predicted to produce cobalamin. However, members of the *Bifidobacterium* and *Prevotella* genera, and *Bacteroides thetaiotaomicron* appear to lack this capability [70,82], while *E. coli* synthesizes cobalamin only when provided with the intermediate cobinamide [206]. Within the phylum Actinomycetota, the capability to produce vitamin B12 appears nearly exclusive to species of human skin microbiota, including those of the *Corynebacterium* genera and *C. acnes* [68,70]

Given the considerable metabolic and energy cost required for *de novo* vitamin B12 synthesis, some cobalamin-dependent species have evolved the ability to salvage intermediates or the final cobalamin product from other species, generating intricate networks of microbial interactions centered around the acquisition of this micronutrient [24,82]. In this context, the BtuBFCD transporter is recognized as the primary mechanism for vitamin B12 transport in bacteria [87,207]. However, recent research efforts have identified multiple functionally distinct cobamide

transporters in bacteria, with up to three distinct systems in *Bacteroides thetaiotaomicron* [87]. While all these transport mechanisms can bind cobalamin, each exhibits additional specialization for other corrinoids, reflecting the diverse array of cobamides that can be environmentally available [87].

2.9 Menaquinones (vitamin K2)

Vitamin K2, also known as menaquinone, is a lipid-soluble vitamin playing several critical roles in human health, primarily by activating specific proteins involved in calcium metabolism and blood coagulation. Structurally, menaquinones are a group of 2-methyl-1,4-napthoquinone structures that differ in the length of their polyisoprenyl side chain (MK-n, with "n" indicating the number of polyprenyl units, ranging from 4 to 13). While the naphthoquinone ring allows for electron-transfer, the polyisoprenoid side chain imparts the lipophilic properties of the quinones [208]. The most recognized forms of menaquinone are menaquinone-4 (MK-4) and menaquinone-7 (MK-7). However, while long-chain menaquinones (MK-7, MK-8, and MK-9) are primarily produced by microbial metabolism, MK-4 is predominantly sourced from animal-based foods [209].

In bacteria, MK-n are integral components of the electron transfer chain within the cytoplasmic membrane. In particular, most Gram-positive and anaerobic Gram-negative bacteria rely exclusively on MK-n as their electron carriers [210]. In addition, MK-n also contribute to sporulation, as seen in Gram-positive bacteria, such as *Bacillus subtilis*, and contribute to the pathogenicity of certain bacteria, including *Staphylococcus aureus* and *Mycobacterium tuberculosis* [211].

Various bacterial species involved in food fermentation generate MK-n as an integral part of their energy metabolism. The naphthoquinone ring of MK-n is synthesized *via* the o-succinylbenzoate (OSB) or futalosine pathway [208], which shares the precursor chorismate (Figure 2), supplied by the shikimate pathway. The polyisoprenyl side chain of menaquinones can be synthesized by either the 2-C-methyl-D-erythritol-4-phosphate (MEP) or mevalonate (MVA) pathway (Figure 2). Regardless the specific pathway utilized for MK-n synthesis, the naphthoquinone ring precursor and the isoprenyl side chain are synthesized separately and subsequently condensed by the prenyltransferase enzyme (MenG/UbiE) to form the functional menaquinone molecule (Figure 2). This newly synthesized molecule may then undergo further modifications, producing different MK-n variants depending on the length of the isoprenoid side chain [212]

The ability to synthesize menaquinones *de novo* appears to be relatively rare among bacteria, with only a minority of Bacillota and Actinomycetota, and slightly more than half of Bacteroidota and Pseudomonadota predicted to possess this capability [70,92]. Long-chain MKs, such as MK-6, MK-7, MK-8, MK-10, MK-11, and MK-13 are expected to be produced by different bacteria resident in the human large intestine, such as members of the *Bacteroides*, *Prevotella*, *Enterococcus*, and *Veillonella* genera [81,92,212,213]. Conversely, species from the *Bifidobacterium*, *Collinsella aerofaciens* and most of the butyrogenic bacteria, including *R. intestinalis*, as well as some strains from the species *F. prausnitzii*, and *Ag. rectale*, lack the genetic capability to endogenously produce MKs [92]. Although the potential production of vitamin K2 has been largely focused on enteric microbes due to the intriguing possibility that bacterial-derived menaquinones may contribute to the host's vitamin K status, other bacteria also possess this capability. This includes *C. acnes* and members of the *Staphylococcus* genus within the human

774 skin microbiota [212], as well as in *Streptococcus mitis*, *Streptococcus oralis*, and *Streptococcus*
775 *mutans* associated with the human oral cavity [70,81].
776
777 **2.10 Vitamin production by bacterial communities**
778 While virtually all microbial communities inhabiting different parts of the human body can
779 produce vitamins, a substantial body of research has focused on uncovering the functional potential
780 of the human gut microbiota, owing to its significant impact on human physiology [214–216]. A
781 relatively recent attempt to address the vast interindividual variability of the human gut microbiota
782 has introduced the concept of "enterotypes", which proposes the existence of recurrent bacterial
783 patterns among gut microbial communities [97]. These patterns, initially defined as three discrete
784 clusters based on the dominance of key bacterial taxa, such as *Bacteroides*, *Prevotella*, or
785 *Ruminococcaceae*, provide a framework to stratify microbiota data and to simplify its inherent
786 complexity [97]. The classification of gut microbiota into three distinct enterotypes has been met
787 with both enthusiasm and criticism, with much of the debate arising from alternative perspectives
788 suggesting the existence of smooth abundance gradients among key genera rather than sharply
789 defined clusters [217–219]. Additionally, the prevalence and composition of enterotypes have been
790 shown to vary based on cohort characteristics, geographical regions, methodological approaches,
791 and taxonomic resolution, raising doubts about the analytical foundation of enterotypes.
792 Accordingly, since the publication of the original work, numerous independent studies have
793 followed, employing clustering methods and alternative approaches to replicate enterotypes in new
794 datasets and even extending the concept to other ecosystems, such as the vaginal microbiota [220–
795 222], and host organisms [223–226]. While some research has highlighted different numbers of
796 microbial clusters or the absence of discernible structures [227,228], others identified enterotype-
797 like patterns similar to the original definition, with *Bacteroides* and *Prevotella* consistently

798 emerging as central drivers of variation in the human gut microbiota [228–231]. These taxa exhibit
799 significant variability in relative abundance and are mutually negatively correlated, suggesting
800 distinct ecological niches and competitive interactions [131,219,232,233]. Despite limitations, and
801 the fact that the resulting clustering only partially reflects the more complex structure within the
802 population, the three-enterotypes concept remains the most widely used and referenced model,
803 providing a conceptual framework which we used below in our discussion of the heterogeneity in
804 human gut microbiome functional capacities related to vitamin biosynthesis.
805 Accordingly, under the widely accepted assumption that certain configurations of relative
806 microbial abundance occur more frequently than others [131,228], the aggregation of specific
807 bacterial species has been shown to uniquely shape the functional potential of the microbial
808 community, including those related to the synthesis of essential vitamins. When functional
809 variations were explored among the first-defined enterotypes, it was shown that enterotype 1,
810 dominated by *Bacteroides* genus in co-occurrence with *Parabacteroides*, *Roseburia*, and
811 *Faecalibacterium* genera, is enriched in genes essential for the synthesis of vitamins B7, B2, and
812 B5 [97] (Figure 3). In contrast, genes for vitamin B1 and B9 biosynthesis are more abundant in
813 enterotype 2, which is overrepresented by the *Prevotella* genus, along with members of the
814 *Enterococcus*, *Streptococcus*, and *Desulfovibrio* genera [97] (Figure 3). Moreover, no specific
815 vitamin synthesis was significantly associated with enterotype 3. This is in agreement with the
816 observation that the composition of this microbial cluster varies across studies, resulting in a less
817 well-defined community but generally distinguished by an overrepresentation of Firmicutes and,
818 in some cases, a high abundance of the *Ruminococcus* genus [97]. However, the greater diversity
819 of species enriched within this cluster, according to the original enterotype definition, suggests
820 diverse vitamin production capabilities (Figure 3).

Recently, *in silico* metabolic modeling has examined vitamin requirements and biosynthetic capabilities across a comprehensive collection of human-associated bacterial genomes [92]. When applied to the enterotype framework, these findings reveal the intriguing presence of complementary vitamin production capabilities among members of the same microbial community [92]. For example, members of the *Streptococcus* and *Enterococcus* genera, which are associated with the *Prevotella*-dominated enterotype [97], exhibit vitamin synthesis profiles that have been observed to complement the metabolic limitations of the *Prevotella* genus. Specifically, *Streptococcus thermophilus* and *Enterococcus faecalis* may compensate for the absence of biosynthetic pathways for vitamins B1, B5, and K2, which are essential for growth of *P. copri*, as predicted by *in-silico* analyses [92]. In turn, these microbial groups may benefit from the biosynthetic potential for vitamins B2, B3, B5, and B6, provided by *P. copri* [92]. In contrast, no complementary abilities were observed between genomes from the *Prevotella* genus and members of the *Bacteroides*, *Anaerostipes*, or *Parabacteroides* genera, all of which have been linked with the *Bacteroides*-dominated enterotype [92]. While the limitations associated with the use of discrete enterotypes and the potential biases of *in-silico* prediction must be acknowledged, as also discussed above, this compelling evidence nonetheless raises the possibility that B vitamins act as essential mediators of microbe-microbe cross-feeding, thereby contributing to the assembly of gut microbial communities [24,80,89,129]. This interplay is particularly evident in the case of vitamin B12. Indeed, this vitamin and its derivatives have been proposed to be involved in extensive cross-feeding activities among co-inhabiting bacterial species due to the high energy expenditure required for its *de novo* synthesis and the resulting significant proportion of auxotrophies [87]. Consistently, a relatively high abundance of vitamin B12 prototrophs has been identified in all three established enterotypes (Figure 3), including members of the *Blautia*, *Faecalibacterium*,

844 *Anaerostipes*, and *Bacteroides* genera, which potentially supply B12 to auxotrophic species,
845 allowing fecal communities to function without the need for exogenous B12 sources [89].
846
847 In parallel with metagenomic studies, recent comparative genome analyses have contributed to
848 understanding the vitamin biosynthetic potential of various human-associated microbes, as
849 summarized in Figures 3 and 4. These studies, utilizing a reference catalogue of over 2,000
850 bacterial chromosomes, have highlighted that the distribution of vitamin biosynthetic pathways is
851 not homogeneous across bacterial phyla. Specifically, while the Bacteroidota and Pseudomonadota
852 phyla encompass the majority of prototrophs, biosynthetic capabilities for B vitamin production
853 are generally less prevalent among members of the Bacillota and Actinomycetota (Figure 3).
854 More in detail, all studies concur in identifying human gut commensals of the *Bacteroides* genus
855 as prototrophic for all required B-group vitamins, except for cobalamin (vitamin B12) and
856 menaquinones (vitamin K2) in a small number of strains [81,92] (Figure 3). For this reason,
857 members of the *Bacteroides* genus are proposed to serve as key vitamin suppliers within the human
858 gut microbiota, supporting survival and growth of numerous auxotrophic microbial taxa [70]
859 (Figure 3). Similarly, various genera from the Pseudomonadota phylum, including well-known
860 human gut commensals such as members of the *Enterobacter*, *Pseudomonas*, and *Klebsiella*
861 genera, as well as *E. coli*, have been identified *in silico* as multi-prototrophs. Specifically,
862 according to separate studies using a reference collection of human gut commensals [81,92] these
863 taxa may produce menaquinones and B-group vitamins, except for thiamin, whose predicted
864 biosynthetic pathway appears to be operational in only a minority of Pseudomonadota (Figure 3).
865 In contrast, a multi-auxotrophy was detected *in silico* and confirmed *in vitro* for the human
866 butyrate-producing *F. prausnitzii* [70,80,81] which, therefore, was designated as a prominent B-

867 vitamin consumer in microbial gut communities (Figure 3). Among the genomes of other butyrate
868 producers commonly found in the human gut, such as members of the *Eubacterium*, *Roseburia*,
869 *Anaerostipes*, and *Coprococcus* genera, the most prevalent B-vitamin biosynthetic pathways were
870 those for vitamin B2, B3, and B12, followed by vitamin B1, B5, and B6 (Figure 3). These *in silico*-
871 predicted vitamin-related biosynthetic abilities were validated by growth on *in vitro* culture
872 conditions, demonstrating, for instance, the need for vitamin B1 to support growth of *R.*
873 *inulinivorans* or vitamin B9 to allow growth of *F. prausnitzii* and *Ag. rectale* [83]. In contrast, most
874 investigated butyrate-producing strains are able to grow in the absence of cobalamin, niacin,
875 pantothenate, pyridoxine, and riboflavin [83], reflecting prototrophies for these micronutrients or
876 the lack of such vitamin requirement.
877 Interestingly, growth of butyrate-producing bacteria that are auxotrophic for a specific vitamin has
878 been demonstrated to be sustained *in vitro* by the concomitant presence of a prototrophic species
879 [83]. This illustrates that complementary vitamin biosynthetic potential can indeed lead to the
880 effective sharing of essential micronutrients, thereby sustaining co-occurring strains and
881 expanding the array of B-vitamins available to the host.
882
883 Alongside butyrogenic gut commensals, certain strains of bifidobacteria have garnered significant
884 interest for their beneficial functions in the human gut, particularly in promoting gastrointestinal
885 roles by enhancing nutrient absorption, mitigating digestive and systemic disorders, supporting
886 immune functions, and producing B vitamins [234–242].
887 Members of the *Bifidobacterium* genus, such as *B. longum* subsp. *longum, B. longum* subsp.
888 *infantis, B. bifidum*, *B. breve*, are recognized as key constituents of the infant gut microbiome
889 [243,244]. However, some bifidobacterial species, including *B. longum,* persist throughout the

890 entire host lifespan in the human gut microbiota, although at a lower abundance [245,246]. In this
891 context, elucidating vitamin biosynthesis capabilities of this bacterial group has been a research
892 goal.
893 The *Bifidobacterium* genus has generally been recognized for their ability to synthesize several B-
894 group vitamins, including thiamine, riboflavin, nicotinic acid, pyridoxine, and folate [29] (Figure
895 4), though differences and specificities among various species are evident, as detailed in the
896 following section. While bifidobacteria have not been reported to produce vitamin K, some species
897 such as *B. longum* subsp. *longum,* require menaquinone-4 for *in vitro* growth [247]. Regarding
898 vitamin B2 biosynthesis, it should be noted that the complete gene set needed for *de novo*
899 riboflavin production has been found primarily in bifidobacterial strains isolated from primates
900 [35]. The only exception to this is the human-associated *B. longum* subsp. *infantis* (sub)species,
901 whose genomes incorporate a complete *rib* operon for riboflavin biosynthesis [35]. In contrast, all
902 human-origin bifidobacteria possess the ability to synthesize folate under *in vitro* conditions
903 (Figure 4), with *B. adolescentis*, *B. catenulatum*, and *B. pseudocatenulatum* producing particularly
904 high levels of folate. In contrast, *in vitro* folate production by non-human bifidobacterial species
905 was generally lower [198]. Interestingly, the administration of high folate-producing
906 bifidobacterial strains has been shown to increase fecal and serum folate levels in both rats and
907 humans [248,249], providing evidence of how beneficial compounds produced by members of this
908 taxa can contribute to host physiology.
909
910 Vitamin production capabilities have also been extensively explored in lactobacilli, as they are
911 present in fermented foods and thus ingested by humans through diet, subsequently colonizing the
912 gastrointestinal tract, at least transiently. This phenomenon has recently been investigated in the

bacterial component of raw milk cheeses, demonstrating that such bacteria can effectively be transferred from food to the gut microbiota of consumers [250], potentially exerting a functional impact on the gut microbiome, including vitamin production [251]. Moreover, the widely accepted and long-standing assumption that lactobacilli establish stable and numerically significant populations in the upper intestinal tract, where they are thought to associate with the epithelium and where most vitamin absorption occurs [7,252,253], underscores their potential role in host vitamin metabolism within this critical gut region. Numerous studies indicate that lactobacilli are capable of synthesizing various vitamins (Figure 4) [67]. Among these, the most prevalent are cobalamin and menaquinone, with their biosynthetic pathways identified in approximately 60% of lactobacilli, based on recent genome investigations [92]. Moreover, while certain lactobacilli potentially synthesize vitamin B9 given exogenous supplies of the essential intermediate pABA [70,196,254], other species of lactobacilli lack the genetic repertoire for *de novo* synthesis of DHPPP precursors and are therefore expected to remain incapable of folate production even in the presence of pABA [196]. In contrast, the biosynthetic pathways for niacin and pyridoxal are less widespread in lactobacilli genomes.

In addition to their presence in fermented foods intended for human consumption, members of the *Lactobacillus* genus are a fundamental component of the normal microbiota of the human vaginal tract. Similar to the microbial community inhabiting the human gut, also the vaginal microbiota of healthy non-pregnant women has been investigated through the concept of community state types, or clusters of recurrent microbial profiles. Originally, based on 16S rRNA gene profiling, this bacterial community has been classified into five compositional patterns [220], known as vaginotypes. These classifications have been revisited in subsequent publications [221,255,256], and, more recently, re-evaluated using whole-metagenome shotgun sequencing [222].

These studies consistently highlight that three vaginotypes tendentially reflect mixtures of lactobacilli, with a marked dominance of a single *Lactobacillus* species, i.e., *Lactobacillus crispatus*, *Lactobacillus iners*, or *Lactobacillus jensenii*, respectively. Moreover, the majority of works identified a fourth CST, with high abundance of *Lactobacillus gasseri* [257]. In contrast, the fifth vaginotype, is characterized by a more heterogeneous bacterial population, with low abundance of the *Lactobacillus* genus [221,255,256]. However, its composition lacks consistency across studies. While the original work characterizes this vaginotype by high proportions of *Prevotella*, *Dialister*, *Atopobium*, *Gardnerella* and other strictly anaerobic bacteria [220], other reports have further subdivided this non-*Lactobacillus* community into diverse sub-structures that capture variations and describe less common compositions, including those containing genera such as *Streptococcus*, *Anaerococcus*, and *Corynebacterium* genera [221,255,258].

So far, microbial vitamin production has not been extensively investigated within the vaginal microbiome, nor has sufficient evidence been provided regarding the potential role that bacterially-produced vitamins may play from a host perspective in the vaginal environment. [259,260]. However, considering the key microbial constituents identified through vaginal microbiome clustering, it is plausible to hypothesize distinct vitamin biosynthetic potentials, while acknowledging the limitations imposed by dimensionality reduction and the inherent temporal variability of the vaginal microbiome [221,261,262]. These predictions should not be regarded as absolute but rather as indicative trends based on a few dominant microbial species within each community. As illustrated in Figure 4, the four *Lactobacillus*-dominated vaginotypes display specific vitamin biosynthetic capabilities. For instance, the genomes of *L. crispatus* and *L. jensenii* have been shown to encode genes for vitamin B2 biosynthesis, whereas *L. iners* is predicted to produce folate, and *L. gasseri* harbors genes enabling *de novo* biosynthesis of vitamin B1. In

contrast, the non-*Lactobacillus*-dominated vaginotype is expected to exhibit a broader range of vitamin synthesis potential, encompassing thiamine, pantothenic acid, and folate, reflecting the presence of multiple co-inhabiting species within this microbial community, as opposed to the more homogenous *Lactobacillus*-dominated vaginotypes. Nevertheless, based on currently available scientific literature, no clinical relevance has yet been attributed to the production of vitamins by different microbial communities within the vaginal microbiome. Accordingly, further research is needed to elucidate whether or not metabolic abilities encoded by these communities, particularly pertaining to vitamin biosynthesis, play a role in vaginal or systemic health.

3. Microbe-derived vitamins throughout human lifespan: focus on early life

The early life gut microbiota plays a significant role in shaping health status and immune system development [263]. Many factors are known to influence the composition of this microbial community, including gestational age (full-term or pre-term), birth mode (vaginal or Caesarean section), feeding practice (breastfed or formula-fed), early environment exposure (hospital or home birth), and geographical location [264–267]. Human milk is the primary nutrient source for breast-fed infants, providing the developing neonate with a rich supply of carbohydrates in the form of lactose and the more complex human milk oligosaccharides (HMOs), which reach the large intestine structurally intact [268–270]. In addition, breast milk is a source of micronutrients, such as minerals, proteins, growth factors, and vitamins [271]. The vitamins included in this rich compendium include vitamins A and D, and various B vitamins, e.g., B1, B2, B6, and B12 [272,273]. Moreover, breast milk contains its own microbial community, whose taxonomic composition has been shown to vary based on host factors, such as maternal diet and gestational age [272,274]. Commonly detected human milk microorganisms belong to genera such as *Bifidobacterium*, *Streptococcus*, *Veillonella*, members of the genus formerly known as

983 *Lactobacillus*, and *Staphylococcus* [272,274]. Although mother-to-infant vertical transmission of
984 microbes predominantly involves intestinal bacteria, there is also evidence suggesting that
985 microbial strains can be transferred from the mother's milk to the infant [275,276], contributing to
986 the establishment and development of the microbial gut community in the offspring. Specifically,
987 strains from the genera *Bifidobacterium* and *Bacteroides* (including species recently reassigned to
988 the *Phocaeicola* genus) have been shown to exhibit the highest transmission rates from mother to
989 infant [277–280]. These strains have also been shown to effectively colonize and adapt to the
990 infant's intestinal environment, primarily due to their ability to metabolize human milk
991 oligosaccharides (HMOs) [281,282], which represent an essential nutrient source for bacteria
992 nutrition during the milk-based diet phase [283,284].
993
994 Given the well-documented significant changes and evolution of the microbiota from birth through
995 old age [285], it is reasonable to consider that the production of vitamins by this microbial
996 community may also undergo analogous fluctuations [133,141]. Indeed, following the first three
997 years after birth and throughout adulthood, the microbiota achieves and maintains a relatively
998 stable state characterized by high biodiversity, although it remains subject to changes influenced
999 by diet, lifestyle, and medical interventions [286–289]. In contrast, the elderly often experience a
1000 decline in microbial diversity and a shift towards a more imbalanced microbial state, which can
1001 impact/affect the community's ability to produce essential vitamins and potentially contribute to
1002 deficiencies commonly observed in older populations [133,290]. Consistent with this assumption,
1003 metagenomic-based functional analysis of the human gut microbiome throughout the human
1004 lifespan shows an initially limited capacity for vitamin production during infancy, which expands
1005 and peaks in adulthood, followed by a marked decline in the elderly population (Figure 5a) [133].

As discussed below, host age not only influences the overall microbial capacity to produce vitamins but also alters their profiles, with certain vitamins being associated with specific life stages rather than others (Figure 5a) [133,291].

Focusing on early-life, during which the foundation for subsequent gut microbiome structure and functional potential is formed, it has been elucidated that many early gut microbes can *de novo* synthesize certain vitamins, thus perhaps contributing to the host's vitamin requirements and supporting growth of other auxotrophic gut residents (Figure 5b). In particular, *Bifidobacterium* members and LAB possess metabolic capacities to produce certain B vitamins, although strain-level variations are evident [198], while high levels of vitamin K2 synthesis genes have been correlated with high abundances of the *Bacteroides/Phocaeicola* and *Escherichia/Shigella* genera [292] (Figure 5b). Interestingly, a recent study has highlighted differences in the biosynthetic potential of vitamin K2 and cobalamin based on geographical origin. Specifically, an increased abundance of genes for the production of these two cofactors was found in the gut microbiomes of infants from the US, which correlated with higher levels of *Bacteroides/Phocaeicola* and *E. coli* [133].

Variation in biosynthetic abilities was also observed as a result of the infant diet. Specifically, the gut microbiota of infants exclusively breastfed until the age of six months was shown to exhibit an enhanced capacity for adenosyl-cobalamin (vitamin B12) biosynthesis when compared to that of infants who had not been breastfed [293]. Consistently, LAB, some of which can produce vitamin B12 [294], were found in higher relative abundance in breastfed infants, indicating that the presence of lactic acid bacteria (LAB) may contribute to vitamin B12 availability in these

1028 infants [293]. Moreover, vitamin B12 production in the infant gut has been linked to the presence
1029 of *Blautia* species [295].
1030 It has been reported that *Bifidobacterium* members, many of which are among the first bacteria to
1031 colonize the infant gut, possess the biosynthetic ability to produce vitamins B2, B6, B9, and B12
1032 [35,198] (Figure 5b). In this regard, Rodionov *et al.* [70] determined through metabolic genotype
1033 reconstruction that 62 *Bifidobacterium* strains possess an incomplete B1 biosynthetic pathway, in
1034 which an iminoglycine synthase-encoding gene appears to be lacking (the product of the *thi*O or
1035 *thi*H genes, Figure 2), while the genes of all other B1 synthesizing enzymes were identified.
1036 Therefore, the authors proposed that alternative enzymes or additional uncharacterized factors may
1037 still need to be identified for vitamin biosynthesis pathways employed by certain bacteria [70].
1038 Within the *Bifidobacterium* genus, strains of *B. longum* subsp. *infantis* have been identified as
1039 capable of synthesizing riboflavin [35,296]. This biosynthesis is achieved by the products of the
1040 *rib* cluster as has been described for the *B. longum* subsp. *infantis* ATCC 15697 genome, although
1041 this ability does not appear to be widespread across the genus [35]. As *B. longum* subsp. *infantis*
1042 is a typical infant gut colonizer and a fervent HMO degrader, an additional riboflavin supply may
1043 be required when dominant in this environment as this vitamin is a precursor of flavin
1044 mononucleotide (FMN) and flavin adenine dinucleotide (FAD), essential co-factors in redox
1045 reactions of cell metabolism [294]. Additionally, *B. bifidum*, a species typically associated with the
1046 early-life gut microbiota and breastfeeding [297] has been shown to convert dietary A vitamin to
1047 the metabolite retinoic acid via an aldehyde dehydrogenase activity [298].
1048
1049 Folate is an important co-factor especially during embryogenesis and in early life, which are
1050 characterized by rapid cell divisions. For this reason, folic acid supplementation is regularly

advised by health authorities to pregnant women or women trying to conceive to ensure a healthy pregnancy. Specifically, the World Health Organization recommends that women of childbearing age consume 400 µg/day of folate, with an increase to 600 µg/day during the periconceptional period [299]. Although human breast milk, with an average folate concentration of 85 µg/l, is generally sufficient to meet the daily folate requirements of a newborn, certain situations, such as premature birth, can increase the need for this micronutrient [300,301].

Several elements of the infant gut microbiota possess the intrinsic ability to generate folate, suggesting the importance of folate prototrophs among early life microbiota members (Figure 5b). Among these, members of the *Bifidobacterium* genus, e.g., *B. adolescentis* [199], *B. longum* subsp. *infantis* [198], *B. longum* subsp. *longum* [198], *B. breve* [198], and *Bifidobacterium catenulatum* [302], have folate production capabilities. However, the ability of *Bifidobacterium* strains to produce folate has previously been reported to be strain-specific [198,199,302]. Moreover, non-*Bifidobacterium* species associated with the infant gut microbiome, including those belonging to the *Collinsella*, *Veillonella*, and *Prevotella* genera may have the potential to contribute to intestinal folate levels in infants within the first 2-4 months after birth [303] (Figure 5b).

Consistently, high levels of *de novo* folate biosynthesis genes have been significantly associated with infants, whereas adults showed a higher proportion of genes assigned to metabolizing dietary folate [304].

For certain microbes, vitamin production may be important for cross-feeding purposes, including the exchange of B vitamins and their precursors [70], thereby aiding the development and enhancing the stability of the gut microbial community. Moreover, B vitamins are vital co-factors in metabolic processes directly involved in immune system development of the host. In this

context, vitamin production by early life gut bacteria may assist in the maturation of the intestinal (micro)environment and the associated microbiota by providing metabolites for other microorganisms typically detected in older infants and adults. For example, *F. prausnitzii*, a prominent butyrate producer in the adult gut and an early colonizer of the infant gut following the introduction of solid foods [265,305], depends on thiamine as a co-enzyme for butyrate production, and potentially requires riboflavin as part of the electron transfer flavoprotein complex of butyryl-CoA dehydrogenase [83,149,306]. Consistently, *F. prausnitzii*, is predicted to be auxotroph for thiamine and appears to encode a thiamine transporter (ThiT) [70,307] for the environmental acquisition of this micronutrient. Interestingly, as previously mentioned, bifidobacteria associated with the infant gut are generally capable of producing thiamin, which can be released extracellularly during cell lysis as part of normal cellular turnover (Figure 4, Figure 5b) [308]. Meanwhile, *Bacteroides* species and *E. coli* have been shown to provide riboflavin (Figure 5b), possibly promoting *F. prausnitzii* growth, which in turn supports the overall health and development of the infant gut microbiome [309]. Although the specific amount of riboflavin produced by *E. coli* or *Bacteroides* has not been directly demonstrated to be sufficient for *F. prausnitzii* growth, recent studies have provided *in vitro* evidence for the existence of cross-feeding interactions between B vitamin auxotrophs and prototrophs in synthetic microbial communities [83,89,310]. Specifically, *F. prausnitzii*, whose growth was shown to be reduced in the absence of thiamine, is able to maintain its relative abundance in a thiamine-free medium when co-cultured with a verified thiamine-prototrophic strain [83]. Moreover, *B. bifidum*, and various species from the *Bacteroides* and *Blautia* genera, have been revealed as potential folate cross-feeders of other auxotroph species, such as *Roseburia intestinalis*, and *Roseburia faecis* [83,310]. While these findings are based on small-scale experiments involving a limited number of strains, they do not

preclude the possibility that similar cross-feeding interactions occur for other vitamins and among additional co-occurring partners within the gut microbiome.

Differences in the infant gut microbiota composition before and after the introduction of solid food and cessation of breastfeeding, i.e., weaning, have been noted [293,311,312]. Solid food promotes growth of a more diverse collection of microbes, which translates to an increased functional repertoire of the gut microbiota [312]. For example, in infant samples where *B. longum* subsp. *longum* was present, there was a noticeable shift in HMO-utilizing genes before and after weaning, with fewer genes detected after weaning [313]. Mancabelli *et al.* [141] observed variations in the enzymes associated with B vitamin synthesis and the age group of the participants in their study. They observed a positive correlation with enzymes required for niacin and thiamine biosynthesis and the group aged 1-4 years old, in contrast to the other three groups: 5-17 years, 18-64 years, and 65+ [141]. The defining microbes present in the microbiota of the 1-4-year-old group were shown to be *Bifidobacterium* species, specifically *B. breve*, *B. longum* subsp. *longum*, and *B. bifidum* as well as *Veillonella parvula* and *E. coli* [141]. This suggests the existence of a connection between the species present and generated vitamins, which are required for host development and changes across the lifespan. Similar age-related differences in relation to gut microbial vitamin production and early life have been noted, such as genes for the synthesis of vitamin B5, B7, and B9 being significantly enriched in newborns compared to older infants [292,304]. In contrast, increasing levels of genes related to the biosynthesis of vitamin B1, B6, and B12, have been observed with age [292,304] (Figure 5). Among these, cobalamin has been proposed to play a crucial role in maintaining the balance and stability of the gut microbial community in healthy adults [133] (Figure 5). Indeed, vitamin B12, which escapes host absorption or is derived from prototrophic gut commensals, appears to trigger a complex web of interactions within the gut

microbiota [314]. On the one hand, competition for cobalamin can occur among gut bacteria, influencing the relative abundance and community structure of the microbiota [87]. On the other hand, collaborative interactions also arise from this dependency. Bacteria capable of producing cobalamin can support growth of cobalamin-dependent species through mutualistic relationships, thereby enhancing the stability and functionality of the microbial community [80].

These observations prompt reflection on how certain microbial species and their metabolic products influence the host at particular life stages, underscoring the dynamic nature of the gut microbiome and its adaptive capacity to meet the host's nutritional needs.

4. Production of vitamins by microbiomes from different human body sites

Although the human gut attracts significant interest from the scientific community due to its high bacterial density and complex microbial interactions implicated in various human diseases [315–317] other human body anatomical compartments, including the skin, oral cavity, airways, and vaginal tract, also provide habitats for organized microbial communities. Similar to intestinal microbial communities, these bacterial consortia are implicated in various aspects of host health, as their dysbiosis, or compositional imbalance, has been associated with a range of diseases. For example, dysbiosis of skin microbiota has been linked to dermatological conditions like eczema and psoriasis, while imbalances in the oral microbiota are associated with periodontal disease and systemic conditions, including cardiovascular disease [318,319]. Similarly, disturbances in the lung microbiota are connected to respiratory issues such as asthma, chronic obstructive pulmonary disease (COPD), and SARS-CoV-2 infections [320,321]. Alterations in the vaginal microbiota can also lead to infections and reproductive health problems, including infertility and pre-term birth [322].

For this reason, in recent decades, extensive metagenomic efforts have been directed to elucidate the composition and functional roles of commensal consortia across various anatomical sites, extending beyond those associated with the gut.

As described above, the occurrence of vitamin biosynthetic genes in prominent individual members of the oral, skin, and vaginal microbiota has been revealed through recent genome investigations using public genome reference collections [70,81,83]. Nevertheless, comprehensive data on the vitamin production potential of entire microbial communities across the human body remain scarce or even lacking. To address this gap, we integrated data from recent shotgun metagenomic sequencing efforts of various human-associated microbial communities, including those of the oral cavity, skin, vaginal tract, and lung, to extrapolate information on the capacity for vitamin biosynthesis within various microbiomes, providing a more complete view of the functional roles that microbiota may play in this regard beyond the gut. As depicted in Figure 6, the concerted vitamin biosynthetic potential within the human skin commensals reveals a high prevalence of genes for riboflavin production, which has been proposed to play an important role in skin barrier integrity [323]. Indeed, extracellular bacteria-derived intermediates of riboflavin biosynthesis have been shown to be recognized by specific host immune cells, known as mucosal-associated invariant T (MAIT) cells, which play a crucial role in protecting against cutaneous pathogens and promoting tissue repair [324]. Consistently, a recent study performed in mice have demonstrated that skin-resident MAIT cells are activated in response to exposure to [325]. In contrast, a mutant strain of this microorganism, lacking the crucial gene *rib*D involved in riboflavin biosynthesis (Figure 2), failed to induce a MAIT cell response [325], supporting the idea that microbially synthesized riboflavin is required to elicit a local MAIT-cells immunosurveillance activation in the human skin.

A similar mechanism has been proposed for various microbial B-vitamin metabolic products within the pulmonary microbiome [326]. Specifically, microbial derivatives of riboflavin and folic acid degradation are taken up by antigen presenting cells (APCs) via MR1, a highly conserved major histocompatibility complex (MHC) class I-related protein [323]. These metabolites are subsequently presented to MAIT cells, which express T-cell receptors (TCRs) that recognize bacterial antigens presented by MR1 [327]. Although the bacterial load in this human (sub)niche is notoriously low, it is typically inhabited by members of the *Streptococcus*, *Veillonella*, and *Prevotella* genera [328,329], which are capable of producing riboflavin and folate, leading to a relatively high proportion of genes involved in the synthesis of these B vitamins (Figure 6). Notably, pulmonary bacterial infection models have highlighted that microbial riboflavin and folate metabolites are important in the early MAIT-cell control of *Streptococcus pneumoniae*, and *Klebsiella pneumoniae* infection [326]. In this context, these vitamin-derived metabolites represent a potential mechanism through which MAIT cells sense microbial activity across mucosal membranes, thereby potentially modulating local immune responses and mucosal barrier functions.

As demonstrated by the presence of microbial genes for B vitamin production in metagenomic studies, the vaginal and oral microbiomes are also able to produce various B vitamins (Figure 6), potentially contributing to host health. However, despite these insights, significant gaps remain in our understanding of the role and effect of bacteria-derived vitamins in these body districts. This underscores a critical need for future research in this area, as gaining such insights could significantly advance our knowledge of host-microbiome interactions and their implications for human health.

5. Impact of diet on the vitamin-producing or -consuming gut microbiota

The bioavailability of vitamins for the host depends on the dietary supply and how this supply is modified by the microbes in the gut that can produce, consume and/or cross-feed vitamins (Figure 7). It is well established that dairy, meat, and plants provide a good source of vitamins for the host [330–334]. Beyond the role of food as carriers of vitamins to the host, the dietary macronutrients, micronutrients, fibers, and their associated bioactive compounds can affect the composition of the gut microbiota, and their activity linked to the production or consumption of vitamins [335,336]. These effects are further influenced by lifestyle, gender, and age [335,337,338]. For example, it has been recently highlighted in a (male) mouse model that dietary fibers, such as inulin, can boost microbiota-derived B vitamin availability in the host [339].

Given the limited genetic capacity for *de novo* vitamin biosynthesis among members of the Actinomycetota and Bacillota phyla, as discussed above, one would then expect that bacteria within these phyla may rely on exogenous sources of various vitamins, represented by amount of vitamins that escapes from host absorption. Consistently, a substantial body of literature demonstrates that dietary vitamins serve as powerful modulators of the gut microbiome [340]. The intake of individual vitamins has been linked to distinct alterations in gut microbiota composition, highlighting the nuanced interplay between specific micronutrients and microbial communities [341–345].

Vitamins available in the gut environment can also originate from co-occurring bacterial producers. This phenomenon has been demonstrated *in vitro*, where Bacillota bacteria were shown to survive in environments deficient in vitamins B1 and B12 when co-cultured with vitamin-producing members of the same phylum [83,89].

Consistent with these reports, various studies have in recent decades revealed membrane transport systems in these bacteria, which are required for the uptake of exogenous sources of various vitamins (Figure 7). However, despite the critical importance of vitamin-related molecules in prokaryotes, our understanding of the mechanisms underlying the uptake of B vitamins and their precursors remains limited. Comparative genomic approaches have significantly advanced the (tentative) identification of vitamin transporters in both prototrophic and auxotrophic bacteria, suggesting their broad distribution across diverse taxa and reinforcing the concept of B vitamin-mediated cross-feeding within the microbiota [70,87,125,161,163,346–361] (Figure 7).

One of the most well-studied cases involves the genetic arsenal of *Bacteroides thetaiotaomicron* for the uptake of cobalamin and other corrinoids. This species is equipped with three distinct genetic loci dedicated to vitamin B12 uptake, in contrast to the Gram-negative model organism *E. coli*, which harbors just a single locus for this function [87,362,363]. The presence of multiple outer membrane vitamin B12 transporters is a common feature in the *Bacteroides* genus, highlighting the critical role of B12 uptake for this taxon [364].

More recently, it has been observed that bacterial extracellular vesicles produced by *B. thetaiotaomicron* contain multiple high-affinity vitamin B12 binding proteins [27], suggesting that vesicle-mediated mechanisms play a critical role in scavenging vitamins from the environment and further highlighting the sophisticated strategies employed by gut bacteria to acquire essential nutrients.

Thus, ultimately, the interactions between bacterial vitamin producers, consumers, and cross-feeders orchestrates the supply of vitamins to the gut microbiota shaping the overall availability of these crucial molecules to the host beyond dietary intake.

In the following sections, the effects of dietary vitamins (including supplements) and other dietary components on gut microbiota members are discussed in detail for each vitamin.

5.1 Thiamine (Vitamin B1)

Beyond *de novo* synthesis from amino acids (Cys, and Tyr, or Gly), bacteria can also produce TPP following uptake of this vitamin or pathway-associated precursors, such as the THZ and HMP moiety, by 26 known transporters which differ based on substrate specificity [70].

Consistent with the role of amino acids in vitamin B1 production, the type of diet and associated food matrix significantly influence the gut microbiota's ability to produce, consume, or cross-feed on this vitamin. Interestingly, compared to children (mean age of 9.8 years), adults with a mean age of 56.8 years were shown to possess a higher microbial pathway presence related to vitamin B1 biosynthesis [365]. Additionally, healthy individuals who consumed a vegetarian diet were shown to exhibit significantly higher abundances of certain B-vitamin-producing bacteria compared to those on an omnivorous diet [127]. These bacteria were primarily from the phylum Bacillota, which relies on vitamin B1 for its metabolic processes and are considered consumers and cross-feeders (producers-consumers) (Figure 7). The Bacillota identified include various members of the *Ruminococcus* genus, along with *Clostridium leptum*, *Eubacterium ventriosum*, *Clostridium symbiosum*, *Anaerostipes hadrus*, and *Blautia glucerasea*. In addition, a higher abundance of multi-prototrophs Bacteroidota (*Parabacteroides goldsteinii* and *Bacteroides intestinalis*), and *Pseudomonadota* (*Parasutterella excrementihominis)* were observed in the vegetarian group. Although an omnivorous diet can provide vitamin B1, with pork meat as the highest source, vegetarian diets offer a higher thiamine content, primarily from sources such as whole grains (including oats, wheat, brown rice, millet, sorghum, and soybeans), enriched or

fortified foods, nuts, whole-grain products, baker's yeast and bread [366,367]. To investigate the potential association between vitamin B1 intake and gut microbiota composition, a correlative analysis between thiamine intake and bacterial species was performed in healthy individuals, which showed effects primarily on Bacillota. Specific correlations were observed with *Roseburia* spp.*, Veillonella rogosae*, *V. parvula*, *F. prausnitzii*, and *Veillonella infantium*. Extending this line of investigation, the consumption of thiamine correlated with an increased abundance of *Ruminococcaceae* in the gut of healthy individuals, as well as with higher fecal butyrate production, whereas total dietary fiber intake from the diet did not show this correlation [149]. Indeed, vitamin B1 plays a crucial role in butyrate synthesis by acting as a cofactor in the conversion of pyruvate to acetyl-CoA [83], where this SCFA provides many health benefits such as causing satiety and improved gut integrity [368,369]. By using a vitamin B1-deficient diet, which reduced the abundance *Ruminococcaceae* in mice [149], the necessity of exogenous thiamine for growth and stability of these bacteria and for maintaining butyrate production in the gut was established.

The effect of diet on other phyla has also been observed regarding the potential of the gut microbiota to produce vitamin B1. Of note, intake of guar gum, an indigestible soluble polysaccharide (galactomannan family), activated microbial B-vitamin metabolic pathways [370], including thiamine phosphate formation from pyrithiamine and oxythiamine (degradation pathway) and thiamine diphosphate salvage II, which involves the phosphorylation, conversion, and recycling of thiamine derivatives to maintain self-regulation and nutrient homeostasis, confirming thiamine prototrophy of bacteria. These changes were accompanied by alterations in the composition of the gut microbial community, with an increase in Bacteroidota (*Parabacteroides distasonis*, *Barnesiella intestinihominis*, *Bacteroides ovatus*, *Bacteroides*

caccae, *Parabacteroides merdae*, *Bacteroides finegoldii*), Bacillota (*Ruminococcus bicirculans*, *Lachnospira pectinoschiza*, and *Ruminococcus torques*), Verrucomicrobia (*A. muciniphila*) and Actinomycetota (*Collinsella aerofaciens*) [370]. Whilst vitamin B1 intake has been shown to correlate with Pseudomonadota (*Haemophilus parainfluenzae*), Actinomycetota (*B. pseudocatenulatum*), and Bacterioidetes (*Bacteroides xylanisolvens*) [371], further studies are needed to ascertain the functional role of these microbes for production and consumption of thiamine, and how any changes in the dietary supply can influence the host, as has been demonstrated for Bacillota.

5.2 Riboflavin (Vitamin B2)

Vitamin B2 plays a crucial role in many biochemical reactions, exerting antioxidant and anti-inflammatory functions in the host [372]. This micronutrient is abundantly found in eggs, fruits, dairy products, meat, and green vegetables in the form of FMN and FAD [373]. Whilst the only known riboflavin biosynthetic pathway was shown to be absent in most Actinomycetota and half of Bacillota, as we described above, the associated microorganisms were shown to be able to internalize vitamin B2 from the environment using the RibU riboflavin transporter or carry other genes with predicted roles in riboflavin uptake or salvage, which indicates their reliance on riboflavin-derived cofactors for growth [70,81].

In assessing the impact of diet, including vitamin intake, on microbial communities, it has been shown that a four-week colon-targeted vitamin B2 supplementation improved the α-diversity of gut microbiota, significantly increased the abundance of *Alistipes* and *Clostridium*, and decreased the abundance of *Faecalibacterium* in healthy individuals [374]. Notably, in this study, faecal and plasma levels of riboflavin were measured. There was an increase in fecal vitamin B2 content

compared with the baseline, while the vitamin level in the plasma did not change. A negative correlation has been reported between the abundance of *Streptococcus* and riboflavin intake [375]. Reducing vitamin B2 supplementation to two weeks in healthy individuals increased the abundance of *F. prausnitzii* per gram of feces as compared to the extended supplementation [343]. *F. prausnitzii* is a major butyrate producer in the human gut, known for its anti-inflammatory and gut barrier-enhancing properties [376,377]. In addition to the findings for *F. prausnitzii*, an increase in *Roseburia* species and a decrease in *E. coli* were observed, perhaps reflecting enhanced anaerobic conditions and redox status in the gut [343]. Active forms of vitamin B2 are required by glutathione reductase, which protects cells from reactive oxygen species (ROS). Consequently, vitamin B2 may indirectly act as an antioxidant, reducing luminal ROS, and creating conditions that favor growth of *F. prausnitzii* and other strict anaerobes, perhaps at the expense of *E. coli* [343]. The role of this vitamin in electron transfer flavoprotein complex with butyryl-CoA dehydrogenase is established, which directly affects butyrate production [83,378], and in turn, host health [379]. Indeed, several studies have shown that vitamin B2 supplementation significantly increases butyrate production in humans [343,375,380,381]. In contrast to these findings, Chinese individuals with natural long-life spans have more SCFA- and lactic acid-producing bacteria but show reduced activity of genetic pathways associated with vitamin B2 biosynthesis [382], whereas the gut microbiotas of Italian centenarians have an enrichment of microbial vitamin B2 biosynthesis pathways and SCFA production [382]. Additionally, it has been shown that the Western diet is linked to vitamin biosynthesis [383,384]. These findings suggest that dietary differences amongst individuals living in different parts of the world, as well as their age and associated health, influence the interaction between dietary and microbial supply of riboflavin.

Utilizing the knowledge on bacterial species that can produce vitamin B2, and the genetic pathways involved, several studies have attempted to isolate and identify strains that over-produce this vitamin. Of note, strain *Lactiplantibacillus plantarum* M5MA1-B2, originally derived from maize-based fermented alcohol beverage, was shown to over-produce riboflavin and to survive an *in vitro* gastro-intestinal environment [385,386]. Similarly, the human isolate *Limosilactobacillus reuteri* AMBV339, a natural riboflavin overproducer capable of synthesizing and excreting surplus amounts of this vitamin beyond its own metabolic requirements, was shown to act as a strong food biofortification candidate, especially in coconut beverages and buttermilk fermentations. The strain demonstrated remarkable resilience to survive in gastric juice as well as inhibiting growth of an enteric bacterial pathogen under *in vitro* conditions [387]. The data highlights the importance of modulating microbial riboflavin production through genetic manipulation or diet to improve human health outcomes beyond SCFA production. Notably, the biologically active forms of vitamin B2, FMN and FAD, are considered important co-factors in energy production reactions associated with carbohydrate, fat, and protein metabolism, as well as in the synthesis and activation of other essential vitamins such as pyridoxine and folate [159,294,388].

5.3 Niacin (Vitamin B3)

In accordance with their low ratio of *de novo* producers, the phyla Actinomycetota and Bacillota, were predicted to convert exogenous vitamin B3 into NAD through niacin salvage pathways, which are absent in the Bacteroidota genomes [334]. Consistently, systems for the uptake of nicotinamide and nicotinic acid are highly prevalent in Bacillota, but also in bacteria belonging to Pseudomonadota and Fusobacterium, suggesting that they consume this vitamin [81].

In a study assessing the effect of vitamin B3 on the fecal microbiome, 10 metabolically healthy volunteers received daily delayed-release microcapsules, delivering nicotinic acid and nicotinamide to the ileocolonic region to directly target the gut microbiome in this region for six weeks, with weekly increasing dose. A significant increase in the abundance of Bacteroidota was observed in the nicotinic acid supplementation group, whereas no significant changes were observed in the nicotinamide group [345]. Since nicotinamide metabolism requires two functional enzymes, namely nicotinamidase (PncA) and nicotinamide phosphoribosyltransferase (NadV), and since assessed Bacteroidota members lack these two genes, these findings may explain the observed difference in the microbiome-modulating ability of nicotinic acid and nicotinamide [389].

5.4 Pantothenate (Vitamin B5)

It is estimated that just 0.078% of colonic pantothenate is produced by the human gut microbiota, contributing to 4.5% of the DRI of this vitamin [81], while the remaining pantothenate is presumed to be derived from dietary sources. Despite its crucial role in the host and the gut microbiota, studies investigating its effects on healthy humans remain limited. A study found that fiber guar gum consumption modulated phosphopantothenate biosynthesis in healthy individuals [370]. This metabolic pathway is related to the synthesis of phosphopantothenate, which requires the activity of 14 genes, with an additional three genes involved in the uptake of pantothenate and coenzyme A (CoA) precursors [70]. Notably, similar to vitamin B1, the activity of microbial vitamin B5 biosynthetic pathways increased in adults (with a mean age of 56.8 years) compared to children (with a mean age of 9.8 years) [365]. These effects were shown to be accompanied by lower microbial diversity in children, and an overrepresentation of glycan degradation, in contrast to adult microbiomes which showed higher abundances of carbohydrate metabolism pathways [365].

However, at the genus level, the relative abundance of *Bacteroides* increased in the gut microbiota of children, while a higher relative abundance of Bacillota was noted in adults [365]. The difference in relative abundance of species in the Bacteroidota and Bacillota phyla may be related to the type of polysaccharides consumed in the two age groups. Indeed, *Bacteroides* can utilize both plant and host-derived polysaccharides, as well as metabolize various glycans [390,391]. Consistent with these effects, the provision of a sulfated polysaccharide from *Sargassum fusiforme* to cultures grown in a simulated digestion tract environment, led to an increase in the relative abundance of Bacteroidota and decrease the relative abundance of Bacillota [392]. Notably, the relative abundance of *Bacteroides* increased, accompanied by enhanced production of SCFAs and pantothenic acid, suggesting a functional relationship between the type of polysaccharide environmentally available and microbial production of pantothenate [392].

5.5 Biotin (Vitamin B7)

The contribution of the human gut microbiota to the host biotin status is influenced by diet and host health. The impact of fiber, specifically guar gum (8g/day for 18 days), on healthy individuals demonstrated an increase in microbial activity related to vitamin B7 biosynthesis in the gut [370]. This pathway involves several enzymatic steps to convert biotin to its final form, suggesting that this fiber can stimulate vitamin B7 production by the gut microbiota. Additionally, another study found that biotin and fiber intake from the diet correlated with Operational Taxonomic Units (OTUs) and reduced visceral fat mass in older female twins (age 68.33 ± 9.76; BMI 25.87 ± 4.37) [393]. Interestingly, the OTUs were strongly correlated with reduced visceral fat compared to nutrient intake alone. Overall, these findings suggest that fiber consumption affects vitamin B7 metabolism and its production by the gut microbiota and that a clear synergistic relationship between dietary biotin and fiber exists, which emphasizes the importance of nourishing the gut

microbiota with these combined nutrients to enhance microbial biotin production, with potential benefits for host health.

5.6 Folate (Vitamin B9)

The interplay between diet, folate intake, nutrient metabolism and gut microbiota is highly complex, intricate, and interdependent. Vitamin B9 levels are influenced by diet, gut microbiota composition and microbiome activity, which all contribute to production and/or availability of this vitamin.

Specific dietary folate patterns, categorized into healthy and Western, influenced the gut microbiota composition in adult men and women. Higher folate intake (406 ± 190 vs. 297 ± 112 μg/d), and the potential for vitamin B9 production by fecal microbiota were shown to be associated with the healthy diet group [394]. In this study, bacterial genera with high potential for folate production included *Bacteroides* (*Ba. coprocola*), *Sutterella* (*S. wadsworthensis*), *Parasutterella*, members of the *Prevotellaceae* family and Proteobacteria (*E. coli* Nissle) [66]. Conversely, bacterial taxa whose members were associated with low vitamin B9 production potential include the *Christensenellaceae* group, *Akkermansia* (*A. muciniphila*), *Alistipes*, and the *Ruminococcus* genus [199]. At the species level, *P. copri* showed a positive association with folate production potential, while *F. prausnitzii* had a negative correlation [66]. In addition, while in this study the overall diet quality did not prove to be associated with the folate production potential of gut microbiota, the intake of specific macronutrients, such as fat and simple carbohydrate intake, were negatively associated with folate synthesis potential [66]. Therefore, these outcomes confirm that specific dietary habits influence folate synthesis by the gut microbiota [394]. However, bacterial vitamin B9 production does not appear to significantly influence circulating folate levels in humans [394]. This suggests that endogenous microbial synthesis may have a limited impact on

overall folate bioavailability, with dietary intake likely playing a more dominant role in maintaining systemic levels of vitamin B9. Nevertheless, it is worth noting that dietary probiotic supplementation, particularly with bifidobacteria and lactobacilli, has been associated with increased serum and plasma folate levels in both rats and humans, highlighting a potential role for specific bacteria in modulating host folate status [199,395].

As part of a healthy diet, fiber intake has been linked with vitamin B9 metabolism. Specifically, guar gum (8g/day for 18 days) has been shown to influence the metabolism of this vitamin in healthy individuals by enhancing key bacterial pathways, such as folate transformations II and III [370], which play a crucial role in increasing cellular retention of vitamin B9, improving its function as a coenzyme, and facilitating its reduction to tetrahydrofolate by bacterial enzymes, followed by methylation to form active folate derivatives like 5-methyl-THF [396]. This enhancement is associated with guar gum fermentation in the colon, which may alter the composition and activity of gut microbiota, promoting growth of folate-producing bacteria. Therefore, these findings demonstrate that a healthy diet including vegetables, whole grains, and fiber or fermented food using starter cultures with LAB strains such as *La. plantarum*, *Latilactobacillus sakei*, and *S. thermophilus* [69], may modulate the gut microbiota and maintain folate metabolism, promoting beneficial effects on the host's overall metabolism.

5.7 Cobalamin (Vitamin B12)

Beyond *de novo* production, the microbial contribution of vitamin B12 to the host is indirectly influenced by the microbial consumption involving 22 genes associated with the uptake of this vitamin [81] as well as the impact of food matrix associated with diet, and its interaction with other nutrients (e.g. folate). Notably, vitamin B12 intake from the diet is positively correlated with the

gut microbial genus *Clostridium* which also shows a positive correlation with meat consumption by healthy individuals [371]. Similarly, *S. thermophilus* was positively correlated with vitamin B12 intake and showed positive associations with lactose, calcium, vitamin B2, and a strong positive association with galactose [371]. These findings suggest that an increased consumption of meat and dairy products (such as milk) is a primary source of vitamin B12 [367]. On the other hand, *Lachnospira eligens* (formerly *Eubacterium eligens*) is associated with vitamin B12 intake and correlated with the consumption of food groups containing eggs, vegetables, nuts, and fruits. Notably, the species mentioned belong to the phylum Bacillota (and some Bacteroidota), and their adaptability to survive in the absence of cobalamin was also demonstrated. This finding stems from *in vitro* culturing of the gut microbiota from healthy adult-donors, which survived in media lacking vitamin B12 [89]. Whilst the α- and β-diversities were not affected by the culture medium, the availability of vitamin B12 in the media had subtle effects on bacterial growth. Notably, *Lactobacillus* and *Barnesiella intestinihominis* grew in media lacking cobalamin [89]. Conversely, adding excess vitamin B12 to the medium increased the abundance of *P. distasonis*. Furthermore, metabolic effects were observed under these conditions, particularly with regards to propionate production, where vitamin B12 is known to act as a cofactor in the conversion of succinate to propionate [89]. These observations suggest potential health benefits of vitamin B12 supplementation in the diet as a way to increase the host bioavailability and enhance propionate-mediated health effects [368,369,397].

5.8 Vitamin K2

Elucidating the impact of diet on the bioavailability of vitamin K has been hampered by the fact that the bacterial-derived form (menaquinone or vitamin K2) differs from that derived from plants (phylloquinone or vitamin K1). Moreover, vitamin K2 exists in 15 isoforms (MKs) [332,398]

which differ in the structure of their side chains. While much of the MKs produced are thought to be absorbed in the lower part of the intestine, host tissues are also able to produce these isoforms from the conversion of vitamin K1 [332,398]. Given the diverse MKs that exist in the gut and in tissues, it is no surprise that the effects of vitamin K extend beyond coagulation to include roles in cognition and fat metabolism [332,399]. Among dietary factors influencing the bioavailability of vitamin K1, intake of green leafy vegetables has been shown to increase circulatory levels of vitamin K1 in adult obese humans, with the effect observed in both sexes [400]. Interestingly, the vitamin level did not correlate with the microbial communities. Removing the confounding effects of obesity, Karl *et al*. explored the relationship between diet, gut microbiota, and K2 vitamin forms (MK5-13) derived from bacteria in healthy humans [401]. The study showed decreased fecal level of vitamin K2 with intake of whole-grain rich diets compared to refined grain rich diets, where the differences can be attributed to the changes in the gut microbiota. Further analysis showed contributions by *Bacteroides* and *Prevotella* for this variability [401]. Additionally, in healthy adult females, dietary supply of vitamin K was significantly correlated with an increase in fecal relative abundance of *Bifidobacterium* and negatively correlated with the relative abundance of *Bacteroides* [341]. The increased relative abundance of *Bifidobacterium*, known to promote gut health, may be due to vitamin K2 and certain derivatives being recognized as growth factors of these bacteria under *in vitro* conditions [402]. Collectively, these studies in healthy humans suggest contrasting effects of dietary factors and vitamin K supplementation on the bioavailability of vitamin K for the host, either through direct supply to circulation or indirectly via changes in the gut microbiota, including those of different phyla. Extending this line of investigation to include the impact of aging and associated decline in diet and health, it has been shown that the microbial potential to produce MKs is associated with differences in cognitive performance in this age

1489 category [403]. Notably, positive associations were obtained for MKs 6, 12 and 13 with cognitive
1490 functions, whereas negative associations were obtained for MKs 4, 8, 9 and 10 with health
1491 outcomes. The study further showed that a greater abundance of *Prevotella* (producing MK-11, -
1492 12 and -13), *Paraprevotella* (producing MK-10, -11, -12 and -13), and *Barnesilla* (producing MK-
1493 11 and -12), all being members of the phylum Bacteroidota, were associated with highest cognitive
1494 performance [403]. While this study does not provide sufficient evidence to confirm cause and
1495 effect relationships, the data nonetheless indicate that changes in diet and age can affect the
1496 bioavailability of vitamin K through microbial effects.
1497
1498 **6. Therapeutic and probiotic interventions to modulate vitamin production**
1499 The role of microbiota on human health has been extensively reviewed and new studies continue
1500 to demonstrate that dysbiosis of microbiota may not only be a consequence of a particular disease
1501 but may also be a contributing factor [214,404]. In this sense, alterations in composition of the gut
1502 microbial community have been associated with obesity, type 2 diabetes, non-alcoholic liver
1503 disease, cardio-metabolic diseases, and inflammatory bowel diseases (IBD), [214,405], as well as
1504 other diseases like bladder, colorectal and breast cancer, arthritis, autism, depression, anxiety, sleep
1505 disorder, and hypertension [406–408] and very recently with neurodegenerative diseases (such as
1506 Alzheimer's and Parkinson's) through the gut-brain axis [315,409].
1507 The severity of these diseases has also been shown to be related to vitamin concentrations in the
1508 bloodstream, thereby supporting the inclusion of vitamin supplementation in certain treatment
1509 protocols.

1510 The effects of vitamin B2 have been studied in various pathologies such as age-related cataracts,
1511 diabetes, sepsis and septic shock, kidney, liver and lung injuries, and cardiovascular diseases [410–

417]. For example, a colonic inflammation model using female rats has shown that the antioxidant and anti-inflammatory activities of this vitamin help restore the antioxidant status of the colonic tissue and mitigate oxidative damage associated with colonic injury [418]. Similarly, another study found that riboflavin effectively reversed chemically induced hepatic lesions in male rats in a dose dependent manner [419]. Regarding vitamin B9, recent investigations have revealed that folate fortification, while primarily aimed at preventing neural tube defects in newborns when administered to pregnant women, also provides additional unintended benefits, including improved hemoglobin concentrations, decreased risk of cardiovascular diseases, and improved cognitive function [420]. Moreover, various studies have demonstrated the anti-inflammatory effect of supplementation with this vitamin. In this regard, experimental evidence includes findings from animal models, such as female mice with allergic dermatitis [421] and alcoholic fatty liver disease [422] as well as humans studies conducted in small cohorts of both female and male individuals with hypertension [423], and children suffering from obesity [424]. A synergic antioxidant effect of this vitamin and vitamin B12 was also demonstrated in a model of nicotine-induced pancreatic damage in male rats [425]. Regarding IBD, some studies have shown that this condition may be associated with folate deficiency and that folic acid supplementation may reduce the risk of developing colorectal cancer in these patients [426]. Specifically, a recent meta-analysis involving nearly 40,000 male and female IBD patients found that high folate intake may reduce colorectal cancer risk, particularly in US and European individuals with high alcohol consumption, although no similar effect was observed for rectal cancer [427].

Vitamin B9 has also been shown to influence the composition of the gut microbiota, promoting species known for their beneficial effects on host health. A recent study using an *in vitro* intestinal mimicking media demonstrated that high doses of folic acid reduced the proportion of *Bacteroides*

while increasing the proportion of butyrate-producing members of the *Faecalibacterium* genus [428]. Another study categorized healthy male participants into high- versus low-intake of B vitamins, including vitamin B9, based on their daily consumption of certain nutrients [428]. Bacterial taxonomic analysis of colonic biopsies revealed an increased abundance of the *Akkermansia* genus in individuals with high folate intake [428]. Notably, this taxon has been associated in other studies with seizure prevention in epilepsy, improved intestinal barrier integrity, and mitigation of experimental alcoholic liver disease [429].

In Parkinson's Disease (PD) patients, B-group vitamins are often described as dietary factors that would be involved in the etiology of this disease [430]. A benefit of the intestinal microbiota for the human host is the production of vitamins and it was seen that microorganisms involved in the biosynthesis of certain B vitamins, such as B7, B2, B1, and B9, are decreased in patients with PD [97]. Consistently, vitamin B2 is decreased in many patients with PD, and it was shown that the administration of high doses of this vitamin could reverse some of the symptoms of the disease by acting against oxidative stress, mitochondrial dysfunction and neuroinflammation that are associated with the pathogenesis of PD [431,432]. On the other hand, PD treatments, such as the use of levodopa can cause deficiencies of vitamin B12, vitamin B6 and folates [433,434], which are crucially involved in harmful homocysteine (Hcy) concentrations, thus highlighting the potential benefit of nutritional interventions to prevent side effects related to this treatment.

Thus, modulating the intestinal microbiota is being evaluated as a means to increase vitamin intake and not only treat certain diseases, but also to prevent them or to decrease their severity. In this respect, the intestinal microbiota can be modulated using prebiotics, probiotics, synbiotics and even postbiotics [435]. While the concepts of probiotics, defined as beneficial live microorganisms, and prebiotics, which are non-digestible food components that promote the

growth of beneficial bacteria, as well as their combination into a single product known as symbiotics, are well-established, the concept of postbiotics is a more recent development. Specifically, the term “postbiotic” refers to bioactive compounds produced by probiotic bacteria during fermentation. These metabolites can include SCFAs, enzymes, peptides, polysaccharides, and cell wall fragments, all of which may exert beneficial effects on host health even in the absence of live microorganisms [436]. Postbiotics are emerging as a promising area of research due to their stability, safety, and potential health benefits. Indeed, unlike probiotics, postbiotics do not need to survive the digestive tract, making them more versatile for incorporation into a wide range of food products and dietary supplements [437].

The use of vitamin-producing probiotics has been shown to be effective in the prevention and treatment of numerous diseases using cell culture and animal models, especially in intestinal inflammatory diseases and colorectal cancer [see reviews [438], [439] [69] and [440]]. In this context, the riboflavin-producing strain *La. plantarum* CRL2130 has been shown to prevent excessive increase of pro-inflammatory cytokines (IL-6, IFN-γ, IL-17, and TNF-α), thereby mitigating the symptoms of ulcerative colitis [441], and intestinal mucositis [442] in chemically induced female mice models. Similarly, folate-producing LAB, such as *S. thermophilus* CRL808 and CRL415, have been shown to inhibit pro-inflammatory cytokines, reducing chemically induced mucositis in female mice [443]. The combination of a riboflavin-producing strain with a folate producer has been described to be effective not only in improving breast cancer therapy in cell cultures and in mice, but also decreasing one of the undesirable side effects (mucositis) that often limits the continuation of chemotherapy [443].

The potential neuroprotective properties of *La. plantarum* CRL2130, a strain that overproduces vitamin B2, were confirmed in an *in vivo* murine model of Parkinson’s disease (PD) [444], in

which the administration of *La. plantarum* CRL2130 attenuated motor deficits and prevented dopaminergic neuronal death in male mice. In the study, these effects were partially attributed to the antioxidant/anti-inflammatory properties riboflavin produced by this strain, as improvements in motor skills were similarly observed in a group of male mice receiving commercial vitamin B2. Likewise, orally administration of *La. plantarum* CRL1905, a high vitamin B1-producing strain, was shown to ameliorate motor deficits in a male mouse PD model, producing effects comparable to those of commercial vitamin B1 [444]. These benefits were linked to a reduction in pro-inflammatory cytokines in serum, along with localized anti-inflammatory effects in the brain [444]. In another work, a combination of *La. plantarum* CRL2130 producing vitamin B2, the folate producer *S. thermophilus* CRL808, and the strain *S. thermophilus* CRL807 with immunomodulatory properties was evaluated in a chronic parkinsonism (male) mouse model [445]. In this study, the neuroprotective effect associated with this mixture of selected Lactic Acid Bacteria (LAB) was related to the modulation of the immune response in male mice, altered by the presence of the neurotoxin. Furthermore, the effect of levodopa-benserazide treatment was maintained and, in some cases, improved in the presence of the LAB mixture [445]. Finally, treatment with this LAB mixture in combination with levodopa-benserazide was able to partially modulate the dysbiosis associated with the model, approaching the conditions observed in healthy controls [445].

Although these results appear to suggest a promising use of LAB to complement strategies for neurodegenerative disease treatments, the application of such vitamin-producing bacteria must be performed in human studies in order to demonstrate their effectiveness. Furthermore, the use of postbiotics, consisting of microbial synthetized substances, including vitamins, also holds a significant therapeutical potential. These microbial-derived substances could be incorporated into

regular diets or used as therapeutic agents to prevent or manage diseases associated with, or exacerbated by, insufficient vitamin intake [446]. Additionally, many existing studies in animal models predominantly use male animals [419,425,444,445], revealing an opportunity to further explore vitamin metabolism and its implications in female populations, which have been comparatively less represented in current research.

Caveats and future perspectives

It is important to acknowledge that many studies referenced in this review have inherent limitations that warrant careful consideration. These include challenges such as low sequencing depth, which may restrict the resolution of microbial taxonomic and functional profiles, and reduced sample sizes, which may limit the generalizability and robustness of some findings. Additionally, the variability in methodologies, including differences in bioinformatic pipelines, reference databases, and experimental conditions, further complicates the interpretation and comparison of results across studies.

Microbiome-based research is rapidly evolving, with new tools and technologies incessantly being developed. Advances such as long-read sequencing, and integrated multi-omics approaches have the potential to dramatically enhance our understanding of the gut microbiome and its functional roles, including vitamin biosynthesis. These innovations may provide deeper insights into microbial interactions, host-microbiota crosstalk, and previously uncharacterized microbial taxa or pathways, potentially revising or refining current conclusions. As we learn more about the complexities of the gut microbiome, it is likely that future research will address many of the current limitations, offering a more comprehensive and detailed understanding of microbial contributions

to vitamin synthesis. This progression emphasizes the need to continuously revise hypotheses as new evidence emerges.

CONCLUSIONS

The human body is home to very complex microbial communities that engage in molecular interactions, both among themselves and with the host, producing significant effects on human health. In this context, it has already been extensively documented how microbes deliver compounds, such as small molecules or metabolic end products, which are crucial for establishing and maintaining the climax of microbial consortia. Among microbe-synthesized molecules, vitamins are increasingly capturing the interest of the scientific community [62,243,337]. However, even though vitamin production has long been demonstrated in single-microorganism cultures, recent attention has shifted towards understanding how concerted metabolic interactions within complex microbial communities might be responsible for the biosynthesis of vitamins that ultimately may be partially utilized by the host or other microorganisms following extracellular diffusion or cell lysis. On the other hand, the presence of vitamins in the gut has been shown to significantly modulate the diversity and composition of the gut microbial communities in both animal models and humans [447]. Notably, compelling evidence shows that vitamin D supplementation increases the abundance of beneficial microbes such as *Bifidobacterium* and *Akkermansia* while reducing populations of *Veillonella* and Pseudomonadota [448,449]. The mechanism behind this modulation involves the nuclear vitamin D receptor (VDR) that binds vitamin D. Upon binding vitamin D and its activation, the VDR functions as a transcriptional regulator, influencing the expression of genes involved in various biological processes, which ultimately can indirectly shape the composition and metabolic functions of the gut microbiome [448].

Among the objectives of this research is to explore how the natural fluctuations and variations in gut microbiota composition, which occur throughout its development from infancy through adulthood to old age, impact its capacity to produce vitamins. For instance, a microbiota dominated by bifidobacteria in the first stages of life until weaning clearly shows a relatively high biosynthetic potential for thiamine, pantothenate, biotin, folate and menaquinone [133]. This potential is then enhanced and complemented by biosynthetic abilities for riboflavin and cobalamin at later stages of life [133]. Notably, in the elderly population, the gut microbiota is largely depleted of vitamin microbial producers, which could impact gut inflammation, which is a typical physiological condition of the elderly [450]. By understanding these variations, researchers aim to gain insights into how age-specific shifts in microbial communities influence overall vitamin production, potentially informing strategies for optimizing nutritional health across different life stages. Additionally, a novel frontier of research could be directed to explore how the onset or progression of certain diseases may be linked to a reduction or loss of microbially synthesized vitamins due to disruptions in the composition of microbial consortia [451–453]. Moreover, since a large part of the human microbiome is still far from being precisely characterized, i.e., the human microbial dark matter, it is very plausible that novel microbial vitamin synthesizers will be discovered as part of this still unknown microbiome. This represents a novel frontier not only in human microbiome science but also in the establishment of novel microbial-based biotechnological applications that are useful for the prevention or treatment of vitamin deficiency conditions.

Another highly interesting hot topic is related to the understanding of the production of vitamins by microbes residing in various human body compartments. In fact, while most of the currently available information on this matter focuses on the human gut, other regions, such as the oral cavity, lung, skin, and vaginal tract, are also densely colonized by microbes with the capacity to

synthesize a range of essential vitamins [454]. For instance, certain bacteria associated with the human skin and airways can produce B vitamins, such as riboflavin and folate, which are crucial for maintaining skin barrier integrity and informing immune responses [81].

The ability of these non-gut microbial communities to produce vitamins underscores their potential impact on overall health and highlights their importance beyond the traditional focus on gut microbiota. Despite these findings, the full extent of vitamin production by microbiota inhabiting other (sub)niches in the human body beyond the gut and how they influence host health remains underexplored. Given the crucial roles these microbial communities play in maintaining physiological balance and their potential implications for health and disease [455], expanding our understanding of their vitamin-related functionalities could reveal novel insights into how skin, oral, vaginal, and pulmonary microbiota contribute to host health and could pave the way for new treatments for microbiota-related disorders and enhance personalized medicine approaches.

Recently, significant advancements in research have highlighted the role of food not only as a source of nutrients and organoleptic features but also as a carrier of functional microbes that provide key metabolites and vitamins to the human gut [250,251,456]. This paradigm shift recognizes foods as vehicles for microbes that can directly impact human health by introducing novel vitamin producers to the gut microbiota, thereby expanding the vitamin biosynthesis capacity of resident microbes, at least transiently. For instance, certain fermented foods are rich in microorganisms capable of producing B-group vitamins, such as folate and riboflavin, which are essential for various physiological functions. By incorporating these microbes into the diet, individuals may temporarily improve their vitamin status and overall health. This field of study represents a promising but largely unexplored frontier. Thus, future research should continue to

explore how different foods, and their associated microbes can influence vitamin biosynthesis and contribute to overall health. This exploration could lead to new dietary strategies and interventions aimed at harnessing the full potential of functional foods to support human well-being.

In the context of developing novel translational outcomes in microbiome science, the vitamin-supplementing activities of the human microbiota represent a promising new area of research. In this regard, the establishment of synthetic microbiota composed of cooperative vitamin-producing microbes could have significant applications in disease prevention and treatment. This approach requires careful evaluation of vitamin metabolic pathways, and the development of bioinformatics tools aimed at modeling metabolic interactions within the whole microbial community rather than focusing on single strains. In this context, although the concept of synthetic microbiotas is still in its infancy, their potential as vitamin suppliers under various conditions, such as unbalanced diets or increased vitamin requirements due to diseases, represents a novel frontier in microbiome-based science.

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BIOGRAPHICAL TEXT

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Beyond the gut, her research extends to microbial communities in other human body districts, such as the vaginal and respiratory tracts.
She is the author or co-author of 50 scientific articles published in peer-reviewed journals.

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Prof. **Jennifer Mahony** is a Principal Investigator in the APC Microbiome Ireland research Centre based in the School of Microbiology at University College Cork. She was recently appointed as affiliated Professor at the University of Copenhagen. Her primary research interests include functional genomics pertaining to lactic acid bacteria and food-associated bacteria. Furthermore, she is interested in bacteriophage-host interactions in the context of food fermentations and the human gastrointestinal niche, among others. Additionally, her team is focused on defining the cell surface structures that are central to the interactions of lactic acid bacteria and how knowledge of these may be exploited to (a) improve the sustainability of food production systems, (b) develop novel phage-based therapeutic products and (c) define the impact of phages and bacterial cell surface polysaccharides on complex microbial communities and human health.

Dr. **Kanishka N. Nilaweera** is a Senior Research Scientist in Teagasc (The Agriculture and Food Development Authority, Ireland), a Funded Investigator in the VistaMilk Research Centre (Ireland) and an Associate Faculty member in the APC Microbiome Institute (Ireland). Prior to his move to Ireland, he previously worked in the industry (Zeneca Pharmaceuticals, UK and Servier Pharmaceuticals, France), and the academia (Rowett Research Institute and the University of Nottingham, UK). In his current role, Dr. Nilaweera undertakes research to understand how diet affects the mechanisms controlling body weight and fat stores, with the view to developing dietary

interventions that will support healthy growth. The related work has been published in Journals covering the areas of nutrition, microbiology, endocrinology, neuroscience and physiology, with broader public reached through different media outputs.

Prof. **Paul Cotter** is the Head of Food Biosciences at Teagasc (the Irish Agriculture and Food Development Authority), is a Principal Investigator with the large Irish Research Centres, APC Microbiome Ireland, VistaMilk and Food for Health Ireland and head of microbiology/co-founder of SeqBiome, a microbiome sequencing and bioinformatics service provider. He is a molecular microbiologist, with a particular focus on the microbiology of foods (especially fermented foods), the food systems and of humans, especially athletes, as well as probiotics and postbiotics. Prof Cotter is the author of >400 peer-reviewed, was included in the Clarivate list of highly cited researchers for 2018-2024, received an honorary doctorate from the University of Antwerp in 2024 and is the Field Chief Editor of Frontiers in Microbiology.

Douwe van Sinderen is Full Professor of Molecular Microbiology at University College Cork, Irelan, and holds a PhD in Molecular Genetics from the University of Groningen, The Netherlands. He is a founding Principal Investigator of APC Microbiome Ireland, a multi-institutional, cross-disciplinary research center aimed at investigating the role of the gut microbiota in health and disease.
Van Sinderen's research endeavors revolve around fundamental and applied aspects of bifidobacteria, in particular their comparative and functional genomics, as well as of the molecular interactions between dairy lactic acid bacteria and their infecting bacteriophages.
He is (co-)author on approximately 600 scientific papers published in peer-reviewed journals, editor of several text books on bifidobacteria and lactic acid bacterial phages, listed as inventor on 24 patents, and was designated as a Clarivate highly cited scientist in the last five consecutive years (2020-2024).

Marco Ventura is Full Professor of Microbiology at the University of Parma, Italy. Marco Ventura holds a PhD in Natural Sciences at the Swiss Federal Institute of Technology (ETH) Zurich, Switzerland. He is the Head of the Microbiome Research hub, representing an Interdepartmental Research Centre of the University of Parma focusing on the characterization of the human microbiome.
Ventura's research is focused on the molecular analysis of bifidobacteria, as well as the diversity and host significance of the gut microbiota.
He is the author or co-author of 334 scientific articles published in journals. Marco Ventura was nominated among the highly cited researchers in 2020, 2021 2022, 2023 and 2024 (Top 1% by citation per field and year by Clarivate Analytics Web of Science Clarivate Web of Science).

FIGURE LEGENDS

Figure 1. Schematic overview of key methodological approaches to evaluate vitamin production in currently culturable and not yet cultured bacteria. Culture-dependent approaches include microbiological assays based on test microorganisms listed in the left-bottom part of the figure, HPLC methods for direct vitamin quantification, and whole-bacteria genome sequencing followed by functional annotation. Culture-independent methods rely on genome sequence collections and metagenomic sequencing data to query reference databases of known functional features to infer the potential biosynthetic abilities of a wide range of readily culturable and not-yet-cultured bacteria.

Figure 2. Biosynthesis pathways and salvage routes of menaquinone and B-group vitamins in bacteria. A thick light-purple border indicates genes that are not essential, as they were not detected in all prototrophs. The blue background denotes genes or entire alternative metabolic pathways. Salvage routes are indicated with red arrows and lines. Universal portion pathways, i.e., sets of biosynthetic genes also present in auxotrophic microorganisms, are highlighted with a yellow background.

Figure 3. Schematic representation of the vitamin biosynthetic potential of key members of human microbiomes. Colored bar plot depicts the occurrence of vitamin biosynthetic genes in the main bacterial phyla associated with the human gut. The prevalence of biosynthetic pathways for vitamin biosynthesis is represented across various bacterial taxa through circles. Filled circles indicate the presence of complete vitamin biosynthetic pathways in all members of the given taxon, while empty circles represent their absence. Circles filled three-quarters or three-quarters empty indicate that the majority (more than 50%) of members of the given taxon possess or lack,

respectively, complete vitamin biosynthetic pathways (based on a genome comparative analysis of more than 2,000 reference bacterial genomes).

Figure 4. Schematic representation of the vitamin biosynthetic potential of human-associated bacterial taxa. The prevalence of biosynthetic pathways for vitamin biosynthesis is represented across various bacterial taxa through circles. Colored filled circles indicate the presence of complete vitamin biosynthetic pathways in all members of the given taxon, while empty circles represent their absence. Filled three-quarters or three-quarters empty indicate that the majority members (more than 50%) of the given taxon possess or lack, respectively, complete vitamin biosynthetic pathways (based on a genome comparative analysis of more than 2,000 reference bacterial genomes).

Figure 5. Overview of variation in microbial vitamin biosynthesis throughout human lifespan. Panel (a) shows the relative abundance of global and individual vitamin biosynthetic pathways in the gut microbiota of infants, adults, and elderly, highlighting marked age-associated differences. The phylogenetic tree on panel (b) depicts the distribution of vitamin biosynthetic potential across key bacterial genera of the infant gut microbiota. Colored filled circles indicate the presence of complete vitamin biosynthetic pathways in all members of the given taxon, while empty circles represent their absence. Circles filled three-quarters or three-quarters empty indicate that the majority of members (more than 50%) of the given taxon possess or lack, respectively, complete vitamin biosynthetic pathways (based on a genome comparative analysis of more than 2,000 reference bacterial genomes).

Figure 6. Atlas of microbial vitamin production across human body sites. The schematic representation illustrates the relative average abundance of microbial biosynthetic pathways

involved in the production of B-group vitamins and vitamin K2 across the microbiomes residing in various human body compartments.

Figure 7. Characterization of bacterial phyla as consumers of vitamins. The schematic representation illustrates the interactions between bacterial producers, consumers or cross-feeders, and host cells centered around sharing vitamins or their precursors. Below, the occurrence of predicted bacterial vitamin consumers is represented for the main phyla constituting the human gut microbiota, based on the genomic absence of *de novo* biosynthesis pathways (auxotrophy), coupled with the presence of known transporters for the uptake of exogenous vitamins and related intermediates. The distribution of currently known B-group vitamin transporter systems is presented across a collection of over 2,000 bacterial genomes from human gut-associated species, alongside the occurrence of these systems in corresponding vitamin auxotrophs and prototrophs. These data are reproduced from reference [70].