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REVIEW

Outlook on next-generation probiotics from the human gut

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Abstract
Probiotics currently available on the market generally belong to a narrow range of microbial species. However, recent studies about the importance of the gut microbial commensals on human health highlighted that the gut microbiome is an unexplored reservoir of potentially beneficial microbes. For this reason, academic and industrial research is focused on identifying and testing novel microbial strains of gut origin for the development of next-generation probiotics. Although several of these are promising for the prevention and treatment of many chronic diseases, studies on human subjects are still scarce and approval from regulatory agencies is, therefore, rare. In addition, some issues need to be overcome before implementing their wide application on the market, such as the best methods for cultivation and storage of these oxygen-sensitive taxa. This review summarizes the most recent evidence related to NGPs and provides an outlook to the main issues that still limit their wide employment.

Keywords Next-generation probiotics · Live biotherapeutics · Gut microbiome · *Faecalibacterium prausnitzii* · *Akkermansiamuciniphila* · *Prevotella copri*

Introduction

The importance of the gut microbiome in influencing human health is widely recognized [1]. Indeed, an alteration in the gut microbiome composition (dysbiosis) has been linked to several intestinal and systemic diseases, such as inflammatory bowel and Crohn's disease, obesity, diabetes and metabolic syndrome, allergies, immune and cardiovascular diseases [2, 3]. Although a causative effect is yet to be demonstrated, independent observational studies highlighted the presence of common microbial signatures, specific for each disease.

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Microbiome-targeted intervention to promote host health

Dietary interventions for the modulation of the gut microbiome

Diet is considered as one of the main factors influencing the gut microbiome. Long-term, habitual diet shapes the gut microbiome composition and activities. Several studies demonstrated that the gut microbiome of non-Westernized populations living in Africa or South-America and habitually consuming a diet richer in undigestible fiber and phytochemicals compared to urbanized, Western subjects, show higher abundance of fiber-degrading microbial taxa in their gut microbiome [4]. These microbes are able to degrade complex polysaccharides and phytochemicals entrapped in the matrix, producing health-promoting metabolites from their catabolism, such as short-chain fatty acids (SCFA) from fiber fermentation, isothiocyanates or urolithins from polyphenols, that are usually enriched in the metabolome of these subjects [5, 6]. Consistently, Western subjects consuming a habitual diet rich in products of vegetable origin (e.g., vegetarian/vegan diet, Mediterranean diet) present features in their gut microbiome similar to non-Western populations, such as higher Bacteroidetes/Firmicutes ratio

and higher levels of fiber-degrading bacteria (e.g., *Prevotella*, *Faecalibacterium, Roseburia, Lachnospira*) [5, 7–10]. In addition, these studies demonstrated that a dietary pattern rich in vegetable-based products is associated with a beneficial metabolome and positive health effects, such as a reduced inflammation, lower cardiometabolic risk and an improved glucose homeostasis [6, 9, 10]. However, it was highlighted that both the type of fibre and its structure may influence the effect of the gut microbiome and metabolome [11, 12]. In recent years, the possibility of manipulating the gut microbiome composition and activities as a therapeutic or preventive approach was explored. Dietary interventions targeting the gut microbiome in healthy and diseased populations were carried out, either evaluating the effect of a supplementation with specific foods (e.g., products rich in fiber or polyphenols) or the influence of a more complex dietary pattern (e.g., Mediterranean or vegan diets). Despite the differences in the study design, target population and methods used, most of these studies highlighted the strong impact of the dietary intervention on the gut microbiome and on the host health. A recent study evaluated the effect of a 2-month intervention with a Mediterranean diet in obese/overweight adults [8]. The intervention promoted the increase of *Faecalibacterium prausnitzii*, a microbial species well known for the ability to degrade complex polysaccharides and produce beneficial SCFA. On the contrary, a decrease in the pro-inflammatory *Ruminococcus gnavus* was observed. These changes were associated with a decrease in plasma cholesterol, inflammatory markers and insulin resistance [8]. Consistently, Ghosh et al. [11] observed a similar effect in a longer intervention (1 year) with the Mediterranean diet on elder subjects. However, these and other studies highlighted that the effect of the dietary intervention cannot be generalized. Indeed, the effects of a dietary treatment differ inter-individually and may be influenced by a combination of host and microbiome features [12, 13]. It was suggested that the baseline composition of the gut microbiome may be responsible for the individualized response to the same meal. In addition, building a complex model integrating the microbiome and host-specific features, it was possible to predict the individual's metabolic response with good accuracy [14, 15], demonstrating that dietary recommendations should not be generalized. Therefore, the individual's microbiome should be considered to inform the design of a personalized diet.

Modulation of the gut microbiome by probiotics

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [16]. Probiotic microorganisms may interact with the host and its microbiome through different mechanisms, directly interplaying with human intestinal cells or producing active metabolites, that can indirectly act on the host microbiome by changing the gastrointestinal environment (e.g., pH lowering). In addition, ingested probiotics may compete with commensal microbes for nutrients and binding sites, or by producing antimicrobial compounds (organic acids, bacteriocins). Metabolites produced by probiotic microbes can act at the interface of human cell, binding to receptors on intestinal epithelial, immune, endocrine, and nervous cells [17, 18]. Probiotic strains may explicate their activity in different ways. Some strains promote the production of β-defensin and immunoglobulin A (IgA), thus suppressing the growth of pathogens or reducing the permeability of the intestinal barrier, inducing mucin production and strengthening tight junctions [17–20]. Other strains have an immunomodulatory activity, stimulating the production of anti-inflammatory cytokine, or can produce neuroactive molecules from dietary precursors, such as γ-aminobutyric acid (GABA), kynurenic acid, serotonin, catecholamines and acetylcholine [19–21].

Most of the probiotic strains available on the market belong to a limited number of genera, mainly Lactic Acid Bacteria (LAB; e.g., *Lactobacillus*, *Lactococcus*) or *Bifidobacterium* spp. and the main isolation sources are fermented foods or the human gut [18, 22]. These taxa have been granted the status of Generally Regarded as Safe (GRAS) in the United States or of Qualified Presumption of Safety by the European Food Safety Authority. Although their activity is strain-specific, the influence on human health and on the human microbiome has been widely studied in animals and humans and was recently and extensively reviewed [22–24]. However, recent advances in the knowledge of the gut microbiome suggested that the range of potentially beneficial microbes is much wider, and the human gut microbiome may be considered as an unexplored reservoir of novel probiotics.

Mining the gut microbiome for next-generation probiotics

Next-generation probiotics (NGPs) are microbial taxa that conform to the traditional definition of probiotics, but do not have an history of use for health promotion. They also fit well in the definition of live biotherapeutic products (LBP) given by the US Food and Drug Administration: "a biological product that: (1) contains live organisms, such as bacteria; (2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and (3) is not a vaccine" [25]. Regulation about NGPs is still lacking and varies across countries. In Europe, all microorganisms that have not been used in foods before 1997, must be carefully evaluated by EFSA before being admitted on the market, either as a novel food or as a drug [26].

Several microbial commensals have been evaluated as NGPs. Of these, *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, *Eubacterium hallii, Prevotella copri*, *Bacteroides* spp. are the most promising. NGPs are phylogenetically distant from LAB, that belong to *Firmicutes* (Bacilli class) or *Actinobacteria* phyla (Fig. 1). Most of these taxa (*Prevotella*, *Bacteroides*, *Akkermansia*) are from different phyla (*Bacteroidetes*, *Verrucomicrobia*), while others (*Faecalibacterium*, *Roseburia* and *Eubacterium*) belong to the *Firmicutes* phylum but are from a different class (*Clostridia*; Fig. 1).

Akkermansia muciniphila

Akkermansia muciniphila is the only cultured member of Verrucomicrobia phylum. It can degrade the intestinal mucus layer to obtain energy [27], which has been suggested as one of the factors giving it a competitive advantage in the

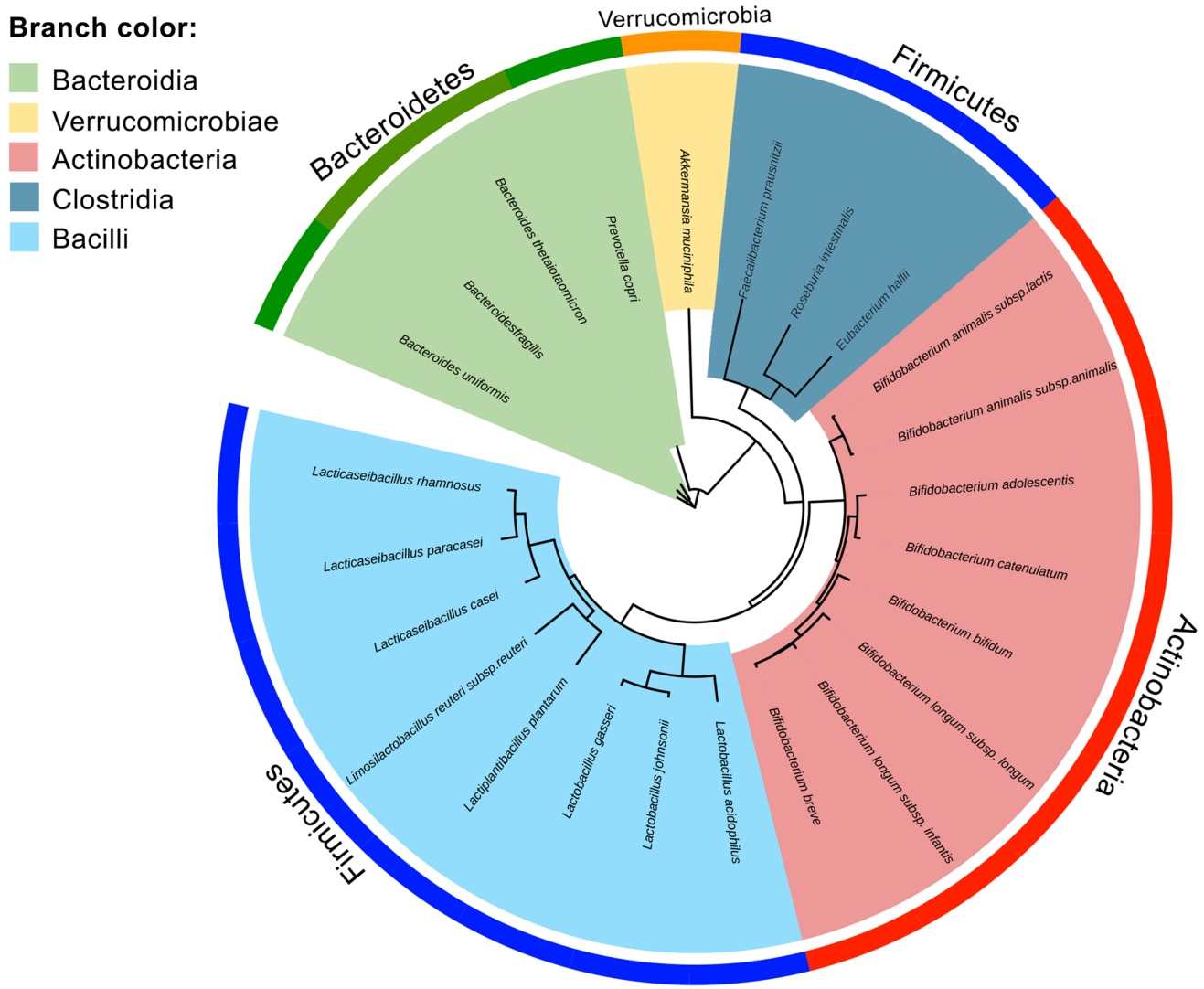

Fig. 1 Phylogenetic tree of species from common probiotics Lactic Acid Bacteria ore recently investigated next-generation probiotics. Outer ring is colored according to the phylum, while branch background is colored according to the class. Phylogenetic tree was based on concatenated marker genes as inferred by PhyloPhlAn 3.0 (https://github.com/biobakery/phylophlan) and visualized using iTOL v6 (https://itol.embl.de). Genomes used are from strains: *Eubacterium hallii* DSM3353; *Akkermansia muciniphila* DSM22959; *Bacteroides fragilis* NCTC9343; B. *thetaiotaomicron* DSM2079; *B. uniformis* ATCC8492; *Faecalibacterium prausnitzii* A2165; *Prevotella copri* DSM18205; *Roseburia intestinalis* R1.82; *Bifidobacterium adolescentis* ATCC15703; *Bif. animalis* subsp. *animalis* ATCC25527; *Bif. animalis* subsp. *lactis* BLC1; Bif. *bifidum* ATCC29521; *Bif. breve* DSM20213; *Bif. catenulatum* DSM16992; *Bif. longum* subsp. *infantis* ATCC15697; *Bif. longum* subsp. *longum* KCTC3128; *Lacticaseibacillus casei* DSM20011; *Lc. paracasei* ATCC25302; *Lc. rhamnosus* DSM20021; *Lactiplantibacillus plantarum* DSM20174; *Lactobacillus acidophilus* DSM20079; *Lb. gasseri* ATCC33323; *Lb. johnsonii* GHZ10a; *Limosilactobacillus reuteri* subsp. *reuteri* DSM20016

animal gut niche [28]. Evidence from several independent studies suggested that it is usually depleted in gut inflammatory conditions (Inflammatory Bowel Diseases, IBD and inflammatory bowel syndrome, IBS), as well as in obesity and diabetes (Fig. 2). Indeed, several studies reported a negative correlation of *A. muciniphila* abundance and obesity [29, 30] and detected an increase in its abundance during weight-loss [31]. However, a recent genome-based study reported the presence of five putative different species, closely related to *A. muciniphila* [32]. Interestingly, only one species was negatively associated with Body Mass Index, highlighting the need of an accurate taxonomic classification within *Akkermansia* genus [32]. The possibility to modulate *A. muciniphila* abundance by diet was also observed: *A. muciniphila* increased upon an intervention with prebiotic fructo-oligosaccharides (FOS) in obese mice and rats [33–35], as well as upon the consumption of a polyphenols-rich pomegranate extract [36]. In addition, the presence of *A. muciniphila* was associated with an improved metabolic response upon a 6-weeks calorie restriction diet: Dao et al. [30] demonstrated that only the group of subjects with higher abundance of A. muciniphila displayed an improvement in insulin sensitivity upon the diet [30], while the group with low A. muciniphila received the same diet, but did not display the same beneficial effects. All these data supported the role of *A. muciniphila* in human health, particularly in glucose homeostasis, and fostered studies on its use as probiotic supplementation (Table 1). Several studies carried out on mice models demonstrated an effect of *A. muciniphila* supplementation on reducing chronic inflammation (endotoxemia) and fat mass gain, improving glucose homeostasis and insulin sensitivity, and increasing energy expenditure, either consuming a normal or a high-fat diet (Table 1). Therefore, most of the existing evidence suggests

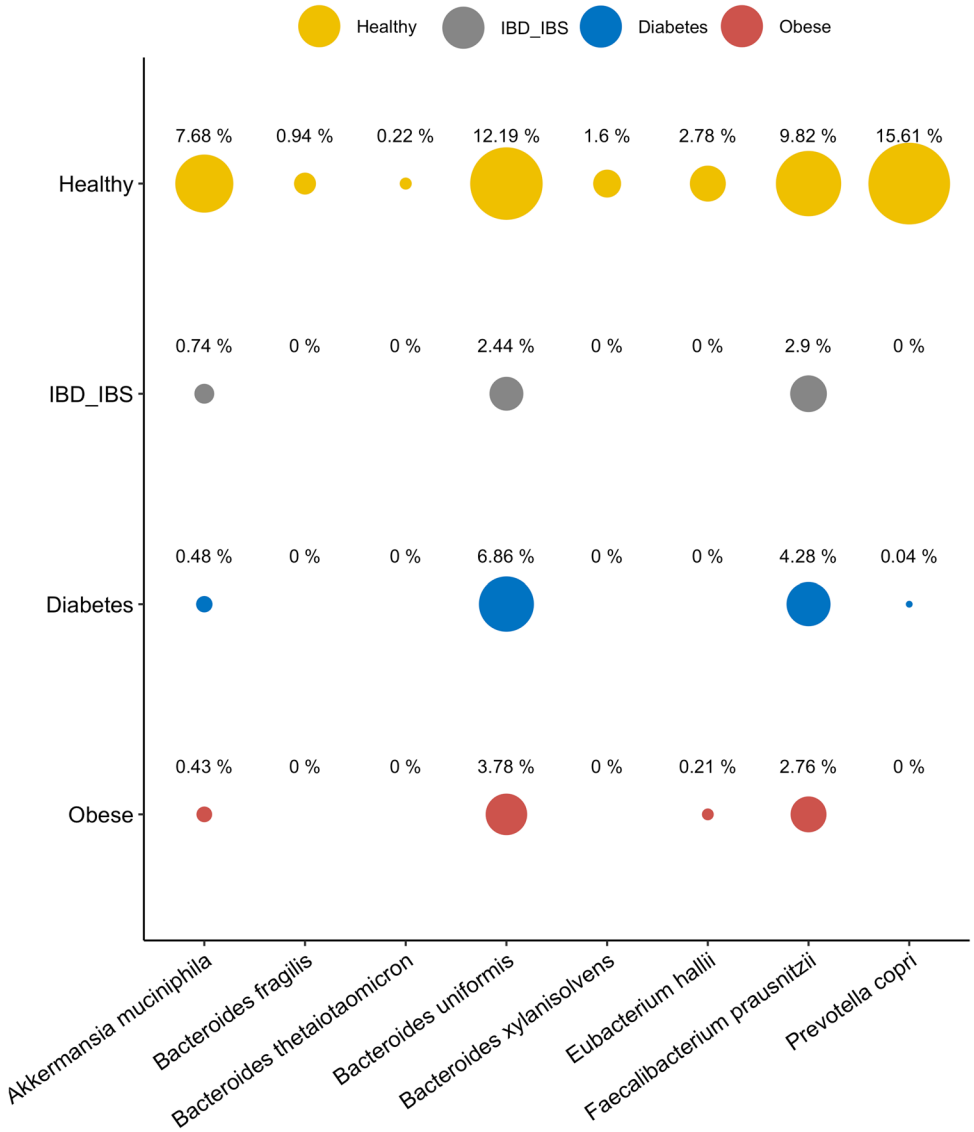

Fig. 2 Average relative abundance in the human gut of species investigated as Next-Generation Probiotics. Data were extracted from *curatedMetagenomicData* Bioconductor package on July 2021 (https://waldronlab.io/curatedMetagenomicData/). IBD, Inflammatory Bowel Disease; IBS, Inflammatory Bowel Syndrome

Table 1 Animal trials using next-generation probiotics

	Number of animals	Age	Study details	Condition of the microorganism	Method of administration	Dose	Frequency	Treatment length	Results	References
A. muciniphila ATTC BAA-835	54	6 weeks	Accelerated aging	N.A	Oral gavage	2×10^8	Three times a week	10 weeks	Improvement of immune system and gut permeability	[41]
A. muciniphila p2261	245	7 weeks	Fecal transplant from cancer patients	Live or pasteurized	Oral gavage	1×10^8–1×10^9	Three times in 2 weeks	14 days	Reduced inflammation; production of anticancer metabolites	[42]
A. muciniphila ATCC BAA-835	N.A	6–8 weeks	Acute colitis	Pasteurized and purified membrane protein	Oral gavage	1.5×10^8 of pasteurised *A. muciniphila*; 3 µg of Amuc_1100 protein	N.A	From 2 weeks before treatment to sacrifice	Pasteurised *A. muciniphila* and Amuc_1100 relieved colon shortening and splenomegaly and attenuated histological injuries in the proximal colon	[43]
A. muciniphila ATTC BAA835	24	6–7 weeks	Colitis	Live	Oral gavage	3×10^9	Daily	14 days	Colon histological damage and mucosal barrier improvement; Reduced inflammation	[44]
A. muciniphila ATTC BAA835	53	10 weeks	Obesity and type 2 diabetes	Live and heat-killed	Oral gavage	2×10^8	N.A	4 weeks	Reduced body weight, improved body composition; Improved gut barrier and metabolic parameters	[34]

Table 1 (continued)

	Number of animals	Age	Study details	Condition of the microorganism	Method of administration	Dose	Frequency	Treatment length	Results	References
A. muciniphila ATCC BAA-835	20	6 weeks	Healthy	Live	Oral gavage	2×10^8	Daily	5 weeks	Reduced fat mass and increased lean mass; Improved glucose homeostasis; Reduced metabolic endotoxemia and inflammation	[45]
A. muciniphila ATCC-BAA-835	24	6 weeks	High-fat diet	Live, supernatant or purified protein	Oral gavage	4×10^8	Daily	14 weeks	Reduced body mass; Improved glucose tolerance; increased serum concentrations of insulin and glucagon-like peptide-1 (GLP-1)	[46]
A. muciniphila ATTC BAA-835	21	8 weeks	Obese	Pasteurized	Oral gavage	2×10^8	Daily	5 weeks	Reduced body weight gain and fat mass gain without affecting cumulative food intake	[47]
A. muciniphila ATTC BAA-835	125	10–11 weeks	Obesity and diabetes	Live, pasteurized and purified protein Amuc_1100	Oral gavage	1×10^9–1×10^{10} for live *Akkermansia*; 1×10^{10} for pasteurized *Akkermasia*; 3 µg of purified protein	Daily	1st experiment 4 weeks, 2nd and 3rd experiment 5 weeks	Live and pasteurized *A. muciniphila* reduces body weight, fat mass gain, improve glucose intolerance and insulin resistance	[48]

Table 1 (continued)

	Number of animals	Age	Study details	Condition of the microorganism	Method of administration	Dose	Frequency	Treatment length	Results	References
A. muciniphila ATCC BAA-835	36	20 weeks	*Porphiromonas gingivalis* induced periodontitis	Live and purified protein Amuc_1100	Oral gavage	1×10^9	Three times a week	6 weeks	*A. muciniphila* and Amuc_1100 reduces alveolar bone loss and periodontal inflammation	[49]
A. muciniphila ATCC BAA-835	24	22 weeks	Obesity	Live	Oral gavage	1×10^9	Daily	2 weeks	Inflammation reduction; reduced soft and hard tissue damage and alveolar bone loss	[50]
A. muciniphila ATCC BA-835	36	6–8 weeks	Diabetes	A. muciniphila-derived extracellular vesicles	Oral gavage	10 µg	Daily	2 weeks	Reduction of gut permeability	[51]
A. muciniphila CIP 107961 ^{T}	24	25 weeks	Diabetes	Centrifugated	Oral gavage	2×10^8	Three times a week	From 3 weeks of age to 10 weeks	Delayed onset of diabetes; reduced serum endotoxin levels	[52]
A. muciniphila BAA-835	36	8 weeks	Endotoxemia-Induced Inflammation in Apoe −/−	Live and heat killed	Oral gavage	5×10^9	Daily	8 weeks	A muciniphila improved both aortic and systemic inflammation, reduced gut permeability	[53]
B. fragilis ATCC 25285	40	N.A	Graft-versus-host disease (GVHD)	Live	Oral gavage	1×10^9	Three times a week for 1 week and weekly for 30 days	33 days	Improved acute and chronic GVHD development	[54]

Table 1 (continued)

	Number of animals	Age	Study details	Condition of the microorganism	Method of administration	Dose	Frequency	Treatment length	Results	References
B. acidifaciens JCM10556	38	24 weeks	Obese	Live	Oral gavage	5×10^{9}	Daily	10 weeks	Reduced body weight and fat mass; Improved hepatic and peripheral insulin sensitivity	[55]
B. uniformis CECT 7771	28	6–8 weeks	High-fat diet induced obesity	Live	Oral gavage	5×10^{8}	Daily	7 weeks	Reduced body weight gain, liver steatosis; improved immune system and glucose oral tolerance	[56]
B. uniformis CECT 7771	30	6–8 weeks	Obese	Live	Oral gavage	5×10^{7}	Daily	17 weeks	Body weight and adiposity reduction; improved oral glucose tolerance; reduced gut permeability, plasma cholesterol and triglycerides	[57]
B. uniformis CECT 7771	40	6–8 weeks	Obese	Centrifuged and re-suspended in 10% skimmed milk	Oral gavage	1×10^{8}	Daily	14 weeks	Reduced body weight gain, plasma cholesterol, triglycerides, glucose and leptin	[58]
B. thetaiotaomicron DSM 2079	75	8 weeks	High-fat diet	Live	Oral gavage	1×10^{10}	Daily	8 days	Decrease of body weight, serum triglycerides, insulin	[59]
B. thetaiotaomicron VPI-5482	60	8 weeks	High-fat diet	Live and heat killed	Oral gavage	5×10^{8}	Three times a week	7 weeks	Alleviated diet-induced body-weight gain and adiposity	[60]

Table 1 (continued)

	Number of animals	Age	Study details	Condition of the microorganism	Method of administration	Dose	Frequency	Treatment length	Results	References
F. prausnitzii A2–165	30	6 weeks	Asthma	Live, supernatant and dead	Oral gavage	1×10^9	Daily	22 days	Decreased inflammation; increased fecal short-chain fatty acids	[61]
F. prausnitzii A2–165 (DSM 17677) or *B. thetaiotaomicron* VPI-5482 (ATCC 29148)	64	N.A	Gnotobiotic animals	Live	Oral gavage	*B. thetaiotaomicron* 1×10^7; *F. prausnitzii* 7×10^9	Once a week	Until F. prausnitzii was established in a donor rat	Increased colonic mucus production	[62]
F. prausnitzii A2–165	80	6 weeks	Induced inflammation	Live	Intragastrical	1×10^9	Daily	10 days	Reduction of inflammation	[63]
F. prausnitzii ATCC 27766	60	N.A	Induced colitis	Live and supernatant concentrated	Oral gavage	1×10^9	Daily	7 days	Reduced weight loss and inflammation in colitis	[64]
F. prausnitzii A2–165	96	6–8 weeks	Induced colitis	Bacterial strains or supernatant	Intragastrical	1×10^9	Daily	7 days for sever protocol and 10 days for moderate protocol	Reduced weight loss and inflammation in colitis	[65]
F. prausnitzii ATCC27766	35	6 weeks	Induced colitis	Fresh and fresh culture supernatant	Oral gavage	1×10^9	Daily	7 days	Reduced inflammation; increased short-chain fatty acids	[66]
F. prausnitzii A2-165; HTF-F	50	2 months	Induced colitis	Live and its extracellular polymeric matrix	Intrarectal	3×10^9 of *F. prausnitzii*; 50 µg of its extracellular polymeric matrix	Daily	For ten days prior the DSS exposure and during the eight days of DSS treatment	Attenuated clinical symptoms in DSS-colitis; decreased inflammation	[67]
F. prausnitzii strain N.A	24	8 weeks	Diabetes	Purified microbial anti-inflammatory molecule (MAM) from *F. prausnitzii*	N.A	200 µL at a concentration of 1 µg/µL	Daily	4 weeks	Restoration of the intestinal barrier; decreased inflammation	[68]

Table 1 (continued)

	Number of animals	Age	Study details	Condition of the microorganism	Method of administration	Dose	Frequency	Treatment length	Results	References
F. prausnitzii strain N.A	30 calves	Newborn	Healthy	Live culture	Oral gavage and intrarectal	40 mL	One dose in the first week of life and a second dose 1 week later	2 weeks	Decreased incidence of severe diarrhea and related mortality rate	[69]
F. prausnitzii A2–165	80	6–8 weeks	Acute induced colitis	Live and supernatant	Intragastrical	1×10^9	Daily	10 days	Decreased intestinal permeability; decreased inflammation	[70]
F. prausnitzii A2–165	29	7–8 weeks	Gnotobiotic animals	Concentrated colture	Intragastrical and intrarectal	1×10^9	N.A	4 weeks	Reduced weight loss and inflammation	[71]
F. prausnitzii ATCC 27766	18	8 weeks	High-fat diet	N.A	Intragastrical	2×10^8	Twice a week every 2 weeks	13 weeks	Increased insulin sensitivity; decreased inflammation in the visceral adipose tissue	[72]
F. prausnitzii A2–165	102	N.A	Radiation-induced inflammation	Live	Intragastrical	1×10^9	Daily	6 days	Reduced severity of the histological damage and epithelial permeability	[73]
E. hallii L2–7	32	12 weeks	Obesity and diabetes	Active and heat-inactivated	Oral gavage	1×10^8	Daily	4 weeks	Reduced blood glucose levels; reduced hepatic triglyceride levels; increased fecal butyrate	[74]
C. butyricum MIYAIRI 588	18	5 weeks	High-fat diet	Spores	Oral gavage	1.4×10^9	Daily	12 weeks	Decreased plasma cholesterol levels and enhanced bile acid excretion	[75]

Table 1 (continued)

	Number of animals	Age	Study details	Condition of the microorganism	Method of administration	Dose	Frequency	Treatment length	Results	References
R. intestinalis DSMZ-14610	24	6 weeks	Induced colitis	Supernatant	Oral gavage	0.2 mL of 5× concentrated growth supernatant	Daily	7 days	Reduced intestinal inflammation; increased short-chain fatty acids	[76]
P. copri DSM 18205	12	12–14 weeks	High-fat/high-sucrose diet + fructo-oligosaccharides	Live	Oral gavage	N.A	Daily	7 days	Improved glucose homeostasis and insulin tolerance	[77]
P. copri DSM 18205	20	6–8 weeks	Healthy	Live	Oral gavage	1×10^8	Daily	4 weeks	Increased production of Th17 cells in the gut (improved immune response)	[78]
P. copri DSM 18205	10	10 to 12 weeks	High-fat diet	Live or heat-killed	Oral gavage	1×10^8	Daily	1st experiment: 7 days 2nd:7 days 3rd: single gavage	Improved of glucose tolerance only with live *P. copri*	[79]
P. copri CB7	12	10 weeks	High-fat diet	Live	Oral gavage	5×10^8	Twice a week	3 weeks	Increased insulin resistance	[80]
P. copri CB7	N.A	N.A	Induced colitis	Live	Oral gavage	1×10^7	Single gavage	Single gavage	Increased inflammation, more severe colitis	[81]

the use of *A. muciniphila* as probiotic to ameliorate the metabolic state associated with obesity and diabetes. However, a recent study also highlighted that *A. muciniphila* was able to reduce the decline associated with aging, attenuating inflammation, immune disorders, and intestinal mucus layer thinning, thus promoting healthy aging [37]. Moreover, the positive effect of the consumption of *A. muciniphila* on experimentally induced periodontitis was also suggested: the gavage with *A. muciniphila* in mice infected by *Porphyromonas gingivalis* (a primary periodontal pathogen), reduced the bone loss typical of this condition compared with controls not receiving the microbial supplement [38]. Finally, the positive effect on reducing colitis and associated tumorigenesis was also suggested [39, 40].

The mechanisms leading to these beneficial outcomes have not been fully elucidated yet. A primary role in mediating these effects was given to the protein Amuc_1100, present on the bacterium outer membrane, that seems to be able to interact with the intestinal Toll-like receptors (TRL2) and promote tight junctions occlusion, thus restoring the gut barrier function. Interestingly, some studies highlighted that the positive effects mediated by *A. muciniphila* supplementation were also obtained by the pasteurized bacterial cells [41, 49] or the purified Amuc_1100 protein [40, 49], supporting the important role played by the cell membrane components. In addition, a recent study identified a novel peptide secreted by *A. muciniphila* (named P9) that can improve glucose homeostasis and promote thermogenesis, thus counteracting obesity in high-fat fed mice [44].

To date, only one pilot *A. muciniphila* intervention study on human exists. Depommier et al. [43] carried out a randomized, double-blind, placebo-controlled study in overweight/obese volunteers with metabolic syndrome, that consumed live or pasteurized *A. muciniphila* (10^{10} CFU/day) for 3 months [43]. The authors demonstrated that both the formulas were safe and well tolerated by humans, and that the intervention reduced inflammation and improved insuline sensitivity, with the pasteurized bacteria showing a better effect than live cells [43]. Indeed, the use of the pasteurized *A. muciniphila* as novel food was recently approved by EFSA, making this species the first next-generation probiotic that will be soon available on the market (https://open.efsa.europa.eu/questions/EFSA-Q-2019-00767). This result will surely boost further investigations on this microbe as NGP directed to the prevention or treatment of diabetes and metabolic syndrome.

Faecalibacterium prausnitzii

Faecalibacterium prausnitzii is a Gram-positive bacterium belonging to the *Ruminococcaceae* family, also known as *Clostridium* cluster IV (phylum Firmicutes). *F. prausnitzii* is considered as extremely sensitive to oxygen and is the only isolated species of the *Faecalibacterium* genus [47]. However, a recent study based on genomes reconstruction from human gut metagenomes highlighted the presence of at least 12 different species commonly found in the human gut, most of them never isolated, and suggested the definition of *Faecalibacterium* complex [48]. The interest in *F. prausnitzii* is associated with its capacity to produce beneficial metabolites, mainly the short-chain fatty acid butyrate, that is known to play several health-promoting effects. SCFAs have an anti-inflammatory, anti-carcinogenic and immunomodulatory activity, it is an energy source for the colonocytes, and it can improve the metabolic syndrome [46, 82]. Consistently, *F. prausnitzii* is usually considered as a biomarker of intestinal health, since it is depleted in inflammatory states, such as IBD/IBS (Fig. 2) [46], while a diet rich in complex fiber can promote its growth [5, 8, 11]. Indeed, several trials on mice demonstrated a protective role of *F. prausnitzii* in experimentally induced colitis (Table 1). A treatment with *F. prausnitzii* or concentrated growth supernatant were able to reduce inflammation and tissue damage in mice with induced colorectal colitis [83–85]. In addition, *F. prausnitzii* gavage in high-fat fed mice was also associated with a reduction of visceral adipose tissue inflammation and fibrosis [86]. Besides butyrate, several other metabolites may be implicated in these beneficial effects. An uncharacterized peptide [66] or salicylic acid [64] were both identified in *F. prausnitzii* culture supernatant and were shown to exert an anti-inflammatory activity and to prevent colitis in mice. Nevertheless, contrasting results about this species are present in literature. In fact, higher *F. prausnitzii* abundance has been reported in allergic diseases [65, 72]. However, these discrepancies might be due to the presence of different and unidentified species/strains. As reported above, at least 12 different species closely related to *F. prausnitzii* were recently identified [48]. The same study also suggests that a misidentification of some *F. prausnitzii* strains likely occurred and some of them may belong to different species [48]. These species may be differently linked with health and disease [48]. In addition, different *Faecalibacterium* species may co-occur in the same subject. A decrease in *Faecalibacterium* diversity was found in obesity and inflammatory diseases, while the consumption of a diet rich in fiber may promote it [48]. These considerations should guide the development of NGPs, that should include more than one strain to take advantage of the wide diversity existing in this species. Therefore, although further investigations are needed, *F. prausnitzii* can be considered as a promising NGP for IBD/IBS and other inflammatory conditions.

Prevotella copri

Prevotella copri (Bacteroidetes phylum) is an obligate anaerobic Gram-negative rod and it is one of the dominant taxa in

the human gut microbiome. *P. copri* is traditionally considered as a beneficial microbe, since it is often associated with a diet rich in fiber from vegetable products and normally shows higher levels in non-Western populations [87]. The interest in *P. copri* is due to the proposed positive effect in modulating glucose homeostasis, as recently demonstrated in a cohort of more than 1000 subjects [71]. Indeed, subjects with higher basal levels of *P. copri* showed higher glucose tolerance and insulin sensitivity upon a 3-day intervention with barley kernel fiber [88]. This mechanism seems to be linked with the ability to promote glycogen storage in the liver, probably activated by the production of succinate [89]. In addition, other studies demonstrated that a *Prevotella*-rich microbiome predisposes to higher weight loss [77, 79, 90, 91] or cholesterol decrease [92] upon the consumption of a fibre-rich diet. Consistently, mice gavaged daily with *P. copri* showed improved glycemic control [88, 89] (Table 1). However, also in this case literature data about the role of *P. copri* in relation to human health are contrasting [93]. Subjects with higher *P. copri* abundance reported higher serum levels of branched-chain amino acids (BCAA) that promote insulin resistance [94]. The same authors demonstrated that *P. copri* was able to produce BCAA and that mice fed with one *P. copri* strain for 3 weeks aggravated glucose tolerance, increased insulin resistance and showed higher circulating levels of BCAA [94] (Table 1). In addition, higher baseline abundance of *P. copri* was associated with a lower decrease in insulin resistance in obese subjects following a Mediterranean diet intervention [8]. *P. copri* was also linked with arthritis onset [95] and gavage with *P. copri* in mice with experimentally induced colitis exacerbated colitis gravity and inflammation [95] (Table 1). Interestingly, the same *P. copri* strain (*P. copri* CB7, Table 1) was tested in these two studies [94, 95], demonstrating that different strains may explicate totally opposite effects. Indeed, a recent study highlighted that different *P. copri* strains have a specific functional potential and may be selected by diet [96]. In addition, it was demonstrated the presence of at least four different species closely related to *P. copri* (*P. copri* complex) [97], suggesting that isolated strains previously identified as *P. copri* might belong to different species. Specific *P. copri* strains may be selected by diet [80, 96] and display a different polysaccharides utilization pattern [80]. Therefore, although *P. copri* might be a promising taxon to be used as NGP for glucose metabolism regulation, this beneficial activity cannot be generalized to all strains and further investigations are needed.

Bacteroides spp.

Bacteroides spp. are anaerobic, non-spore-forming, Gram-negative rods and some species (*B. uniformis, B. fragilis, B. xylanisolvens, B. thetaiotaomicron*) are considered interesting as NGP [81]. *B. fragilis* has been considered a pathogen for several years. Indeed, some *B. fragilis* strains can produce a zinc-dependent metalloprotease that is considered a toxin and can disrupt the intestinal mucosa. Therefore, according to the occurrence of the toxin-encoding gene *bft*, *B. fragilis* has been classified into two subgroups: non-enterotoxigenic (NTBF, lack of *bft*) and enterotoxigenic (ETBF, with *bft*) *B. fragilis*. Other pathogenic factors are associated with the presence of lipopolysaccharide (LPS) or ferritin that should also be considered in *B. fragilis* safety evaluation [98]. However, NTBF strains may exert several beneficial effects owing to an anti-inflammatory and immunomodulatory activity [99] (Table 1). This activity seems to be mediated by the production of a capsular polysaccharide A that showed these properties even when purified and administered to mice [100].

Among other *Bacteroides* species, *B. uniformis* and *B. thetaiotaomicron* were suggested as NGP for the management of metabolic syndrome, glucose homeostasis, and obesity in mice fed with high-fat diet (Table 1). Indeed, oral gavage with *B. uniformis* can reduce liver steatosis, weight gain, and immune dysfunctions associated with obesity [101], while an intervention with *B. thetaiotaomicron* reduced adiposity and weight gain [102]. However, a *B. thetaiotaomicron* isolate was reported to induce colitis in mice [103].

All these findings suggest that, although *Bacteroides* spp. are potentially interesting as NGP, the strains should be carefully evaluated for safety both in vitro and in vivo.

Eubacterium hallii

Eubacterium hallii (Firmicutes, Clostridium cluster XIVa) includes non-spore forming, obligately anaerobic rods and is considered a beneficial microorganism since it can produce several SCFAs [104], that play a major role in the modulation of gut inflammation, promoting epithelial integrity and regulating the immune response. Several studies report a decrease in *E. hallii* abundance in IBD/IBS and a reduction of SCFA producers, including *Eubacterium*, in diabetic subjects (Fig. 2) [56, 60]. Consistently, oral administration of *E. hallii* to obese and insulin-resistant mice improved insulin sensitivity and energy metabolism [105]. In addition, it was reported an increase in *Eubacterium* spp. and an improvement in insulin sensitivity after a fecal microbiota transplantation from lean to obese donors [106]. Although the mechanism was not yet fully elucidated, it seems that SCFA can bind to receptors, regulating satiety hormones such as ghrelin and glucagon-like peptide-1 (GLP-1), thus, inhibiting food intake [107].

Current issues and future paths

NPGs are attracting more and more interest both at academic and industrial research levels. However, several points should be addressed before proceeding to their introduction on the market.

First of all, wider and thorough studies about safety and tolerability of these novel microbial taxa need to be carried out, by both animal and human trials. Trials involving humans are still not available for most of the candidate NGPs and when performed, they are mainly exploratory, with small sample sizes and do not include sensitive populations (frailty subjects, elderly, or children). These studies should also consider that different subjects may show a specific response to the same strain. Indeed, the same drug, dietary treatment or probiotic supplementation may have a subject-specific effect, that may be caused by several factors, including genetics and gut microbiome composition. Therefore, a personalized application of NGPs should also be considered. In addition, an update in current regulation would be necessary. Indeed, the introduction of new taxa on the market may follow the novel foods framework or the pharmaceutical path, being commercialized as LBPs. In both cases, a thorough characterization of several strains from these new species will be required, including phenotypic and genomic analyses, with a focus on the research for the presence of genes related to antibiotic resistance, toxin production, virulence factors, and mobile elements. For this purpose, large-scale culturomics studies are extremely important [74, 108], not only to discover novel interesting strains, but also to highlight the wide diversity existing within each species and characterize the largest possible number of strains of the candidate NGP species. Finally, our knowledge about NGP mode of action is still scarce. In vitro and in vivo trials, as well as genomic screening, are needed, to understand the functional mechanisms leading to a positive effect on human health.

Another issue is related to NGP cultivation and stabilization for storage. Indeed, all these taxa are extremely sensitive to oxygen, much more than common probiotic LAB, that constitute the major hurdle to be overcome for their production and commercialization. Microbial biomass production usually takes place in bioreactors that can work anaerobically. However, guaranteeing strict anaerobiosis in the following phases, such as during microbial cells collection, freeze-drying and storage during the product shelf life, can be more challenging. In addition, the viability of the strains after the gastrointestinal passage should also be evaluated, as well as the number of cells to be assumed to obtain the desired effects. The use of appropriately designed coating systems might be tested to protect cell viability during shelf life and gastrointestinal transit [109].

Although there are several obstacles that need to be overcome before these products can be introduced into the probiotics products market, the development of NGPs hold promises for innovation in both food and pharmaceutical industry and it will be possible in following years as an output of interaction between research centers, regulatory boards, and industry.

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Declarations

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