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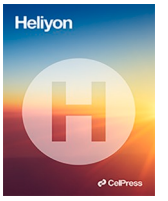

Review article

Next generation probiotics for human health: An emerging perspective

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ABSTRACT

Over recent years, the scientific community has acknowledged the crucial role of certain microbial strains inhabiting the intestinal ecosystem in promoting human health, and participating in various beneficial functions for the host. These microorganisms are now referred to as next-generation probiotics and are currently considered as biotherapeutic products and food or nutraceutical supplements. However, the majority of next-generation probiotic candidates pose nutritional demands and exhibit high sensitivity towards aerobic conditions, leading to numerous technological hurdles in large-scale production. This underscores the need for the development of suitable delivery systems capable of enhancing the viability and functionality of these probiotic strains. Currently, potential candidates for next generation probiotics (NGP) are being sought among gut bacteria linked to health, which include strains from the genera Bacteroids, *Faecalibacterium*, *Akkermansia* and *Clostridium*. In contrast to *Lactobacillus* spp. and *Bifidobacterium* spp., NGP, particularly Bacteroids spp. and *Clostridium* spp., appear to exhibit greater ambiguity regarding their potential to induce infectious diseases. The present review provides a comprehensive overview of NGPs in terms of their health beneficial effects, regulation framework and

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risk assessment targeting relevant criteria for commercialization in food and pharmaceutical markets.

1. Introduction

The conventional probiotics initially sprang from Elie Metchnikoff's report in 1907. The prevailing consensus held that the consumption of fermented dairy products, like yogurt, kefir, sauerkraut, tempeh and kombucha which are rich in lactic acid bacteria (LAB), provides health benefits. Probiotics are viable microorganisms which administered in sufficient quantities, contribute a health advantage to the host. These benefits can include improving digestion, supporting immune function, and contributing to overall well being. The Food and Agriculture Organization (FAO) and World Health Organization (WHO) collaborative group established criteria that probiotics must meet, which is the strain should be deemed safe for consumption [1]. Probiotics are formulations containing living microorganisms, such as bacteria, yeasts, or a combination of all, that commonly present in the natural gut microbiota [2]. The use of appropriate probiotic strains at sufficient doses is the first prerequisite for creating a probiotic food product. The primary criteria for choosing appropriate probiotic bacterial strains are their capacity to remain viable under food processing and storage conditions, their ability to survive during intestinal transit, and their potential to improve consumer health [3]. Additionally, recent clinical trials show significantly enhanced reporting of adverse events [4]. Recent advancements in methods such as metabolomics, gnotobiotics and next-generation sequencing have facilitated a more comprehensive understanding of topics like colonization resistance, susceptibility to external microorganisms, biogeographical diversity, variation in individual microbiome structures, and their potential impact on treatment outcomes [5]. The term NGPs was introduced by O'Toole PW (2017) that NGPs are live bacteria identified based on comparative microbiota analyses that when administered in right amounts, confer a health advantage on human health. On the other hand, live microorganisms in biological products are applicable to the prevention of disease in humans, and are not vaccines [6]. Over the past few years, the scientific community has been accumulating a growing body of knowledge about the mechanisms involved in metabolic and inflammatory disorders. These rapidly escalating conditions are reaching epidemic levels, posing fresh challenges for both clinicians and researchers. Gaining a comprehensive understanding of the exact roles and controlling characteristics of beneficial or probiotic bacteria in the gut ecosystem seems to be essential in the effort to prevent inflammatory and diet-related disorders. *Akkermansia muciniphila, and Eubacterium hallii* and *Faecalibacterium prausnitzii,* have been pinpointed as potential NGPs that hold great promise in preventing and treating diseases associated with dysbiosis [7] (Fig. 1).

Nevertheless, these microorganisms pose difficulties in handling because of their high susceptibility to oxygen exposure and

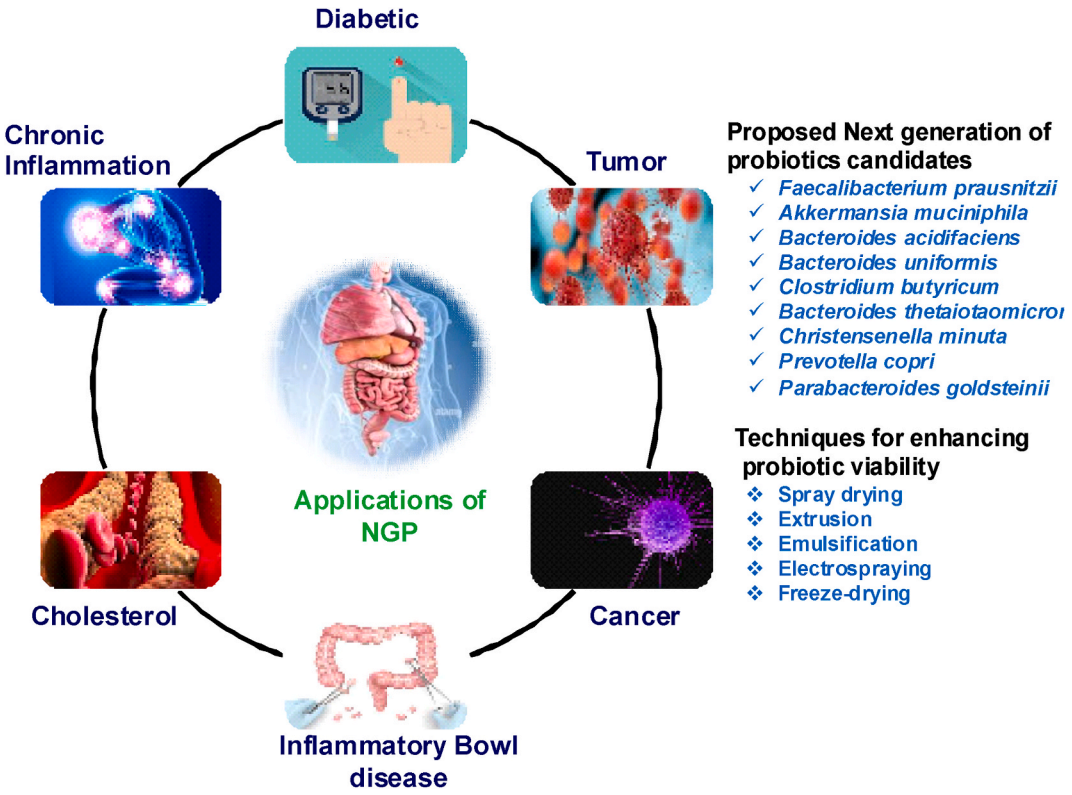

Fig. 1. Next generation probiotics for prevention of disease.

frequently to the gastric conditions they encounter post-ingestion [8]. One characteristic of certain NGPs is their ability to generate short-chain fatty acids, among which butyrate, in particular, is recognized for its role in promoting immune balance and human intestinal well-being [9]. The emerging knowledge is providing a basis for the selection of NGPs. The proposed candidates for NGP include *Akkermansia muciniphila*, *Bacteroides thetaiotaomicron*, *Bacteroides acidifaciens*, *Bacteroides uniformis*, *Clostridium butyricum*, *Christensenella minuta*, *Faecalibacterium prausnitzii*, *Prevotella copri*, and *Parabacteroides goldsteinii.* These selections are primarily based on their potential to prevent and alleviate conditions such as colitis, obesity, liver disease and diabetes [10]. Conversely, the use of conventional probiotics does not target particular diseases. In light of these circumstances, there is an urgent requirement for the

Table 1
Microbial strains for next generation probiotics.

S. No	Strain	Host	Benefit	Clinal Trails	References
1.	*Bacteroides fragilis*	Human feces	Enhances phagocytosis and polarises M1 macrophages	LoVo cells	[22]
2.	*Bacteroides dorei*	Human feces	Cholesterol reducing	Human	[21]
3.	*Bacteroides ovatus*	Human Gut	Reduces Intestinal Inflammation	Mice	[27]
4.	*Bacteroides ovatus*	–	Reduces Intestinal Inflammation	Mice	[28]
5.	*Lactococcus lactis*	GMO(Food)	Reduces inflammatory bowel diseases	Mice	[29]
6.	*Faecalibacterium prausnitzii*	Human feces	Mainly IBD, but also asthma, eczema and Type II diabete	Human	[30–32]
7.	*Bacteroides ovatus*	Human feces	Reduces the risk of certain types of cancer	–	[33]
8.	*Clostridium butyricm*	Human	Prevention of pouchitis and alteration of the microbiota profile in patients with ulcerative colitis	Human	[23]
9.	*Bacteroides acidifaciens*	Mouse feces	Clearance of infectious agents	–	[34]
10.	*Oscillospira* sp.	Human Gut	Improved diabetes, obesity and reduced systematic chronic inflammation	–	[35]
11.	*Akkermansia muciniphila*	Human Gut	Improves key components of metabolic syndrome, such as reducing fat mass, plasma glucose, gut permeability and metabolic inflammation	Mice	[36]
12.	*Bacteroides fragilis*	Human feces	Antibiotic-associated diarrhea	Rat	[25]
13.	*Bacteroides fragilis*	Human Gut	Oxazolone-induced experimental colitis	Mice	[37]
14.	*Bacteroides fragilis*	Human feces	Vibrio parahaemolyticus infection	Mice	[24]
15.	*Bacteroides uniformis*	Human feces	Overweight-associated disorders	Mice	[38]
16.	*Akkermansia muciniphila*	Human Gut	Develop live biotherapeutic product	–	[39]
17.	*Ruminococcus bromii*	Human Gut	Develop live biotherapeutic product	–	[39]
18.	*Faecalibacterium prausnitzii*	Human Gut	Develop live biotherapeutic product	–	[39]
19.	*Anaerobutyricum hallii*	Human Gut	Develop live biotherapeutic product	–	[39]
20.	*Roseburia intestinalis*	Human Gut	Develop live biotherapeutic product	–	[39]
21.	*Faecalibacterium prausnitzii*	Human gut	Reduced in patients with hyperlipidaemia, prediabetes and type 2 diabetes, non-alcoholic fatty liver diseaseand inflammatory bowel disease	Mice and Human	[40]
22.	*Lactococcus lactis*	Fecal	Induced Parkinsonism are mediated by modulating oxidative stress, inhibiting ferroptosis, and redressing dysbiosis	Human	[26]
23.	*Bifidobacterium* sp.		Promotes antitumor immunity and facilitates anti–PD-L1 efficacy	Mice	[41]
24.	*Bifidobacterium longum*	Human Blood	Robust $CD8^+$ T cell response and better prognosis in HBV-related hepatocellular carcinoma	Human	[42]
25.	*Enterococcus hirae*	Human Blood	Robust $CD8^+$ T cell response and better prognosis in HBV-related hepatocellular carcinoma	Human	[42]
26.	*Lactobacillus rhamnosus*	Human blood	Improve immune system	Human	[43]
27.	*Bifidobacterium lactis*	Human blood	Improve immune system	Human	[43]
28.	*Akkermansia muciniphila*	–	Combat cancer disease	Mice	[44]
29.	*Faecalibacterium prausnitzii*	Human	Anti-tumor response	Mice	[45]
30.	*Akkermansia muciniphila*	–	Reducing systematic inflammation and potentially lowering cancer risk	Human	[46]
31.	*Clostridium butyricum*	Stool samples	CBM reduced the changes in the intestinal flora and decreased the incidence of gastrointestinal side effects	–	[47]
32.	*Clostridium butyricum*	–	Showed Antitumor effects by enhancing the release of TRAIL from neutrophils through MMP-8 and novel intravesical therapy for bladder cancer	Human	[48]
33.	*Clostridium butyricum*	–	Reduces the incidence of diarrhea in digestive diseases, including inflammatory bowel disease	Human	[49]
34.	*Eubacterium limosum*		Increases mucosal integrity and shows anti-inflammatory action modulation of mucosal defense system via TLR4	Mice	[50]
35.	*Eubacterium hallii*	–	Improves insulin sensitivity and increases energy metabolism in severely obese and diabetic	Mice	[51]
36.	*Akkermansia muciniphila*	–	Enhance the efficacy of cancer immunotherapy's	Mice	[52]
37.	*Enterococcus hirae*	–	Th1 Cell Immune Responses in Chemotherapy-Treated Cancer	Mice	[53]
38.	*Barnesiellaintestinihominis*	–	Th1 Cell Immune Responses in Chemotherapy-Treated Cancer	Mice	[53]
39.	*Bacteroides fragilis*	Feces of a healthy breast-fed infant	Enhances the phagocytic functions of macrophages, polarising them to an M1 phenotype		[22]

discovery and profiling of new NGPs that are tailored to specific diseases [11]. To attain the objectives of pinpointing NGPs, the initial step involves uncovering whether there exist noteworthy correlations between the microbiota and the host across the various study groups, including the healthy, diseased, and experimental cohorts. These connections can be gleaned from either animal or clinical investigations [12]. The Human Genome Project, has led to a rise in next-generation sequencing technology that has enhanced the depth and velocity of phylogenetic analysis [13].

Due to the favorable results in manipulating gut microbiota for the management and prevention of numerous conditions, food nutraceutical firms and pharmaceutical companies may express keen interest in potential probiotic strains. Nonetheless, for the introduction of these advanced probiotics, also known as live biotherapeutics products [6], in the market a full assessment of safety parameters is mandatory. NGPs are microorganism species that align with the conventional probiotic criteria but have yet to establish a history of use in promoting health. NGPs also closely adhere to the description of live biotherapeutic products (LBPs) as outlined by the US Food and Drug Administration, which defines them as biological products that: "comprises living organisms, including microbes; are pertinent to preventing, treating, or alleviating human diseases or conditions; and are not a form of vaccination" [14]. This paves the way for the exploration of NGPs, given their suitability for pharmaceutical applications rather than being mere dietary supplements [15]. The present review deals with overall perspective of NGP candidates in terms of their health beneficial effects, related regulatory framework, and risk assessment criteria relevant for commercialization in food and pharmaceutical markets.

2. Microbial strains for next generation probiotics

Human are recognized as "Superorganisms", and closely associated with microbiomes [16]. The human gastrointestinal tract (GIT), is home to 100 trillion microorganisms (bacteria, fungus, viruses, and protozoa), as revealed by research carried out by the human microbiome study [17]. Due to the dense population the bacteria residing in the gastrointestinal tract and the absence of prior expertise regarding their nutritional requirements and proper culture conditions, it can be challenging to grow every bacterium. The development of bioinformatics tools and nucleic acid sequencing techniques has allowed researchers to overcome this shortage by enabling them to detect and measure the numerous constituents of the gut microbiota [18]. Approximately 90 % phylogenetic analysis indicates that the gut bacteria are categorized within the Firmicutes and Bacteroidetes phyla [19]. The remaining bacteria include members of the Proteobacteria, Actinobacteria, Verrucomicrobia, and Fusobacteriota phyla. During infancy, the composition of the gut microbiota is relatively clear and includes a notable number of microorganisms such as *Veillonella*, *Clostridium botulinum*, *C. coccoides*, *Bacteroides*, and *Akkermansia muciniphila* [20].

The evidence of benefit of NGPs on human health is available from various clinical trials conducted on humans and mice over past few decades. Several clinical trials have been conducted on human and mice for treatment of many diseases. In a report by Gérard et al. [21], isolated *Bacteroides* sp. from human faces and the report concluded that it was the first cholesterol reducing bacterium. Similarly, *Bacteroides fragilis* was sorted out from a healthy breast fed infant. This bacterial strain showing the ability to enhances phagocytosis, polarises M1 macrophages and improve immune imbalance, inflammatory disease and mental disorders [22]. In another report, *Clostridium butyricum* was isolated and evaluated in patients with ulcerative colitis. The result during clinical trial showed prevention of pouchitis and alteration of the microbiota profile in patients [23]. In another clinical study of Li et al. [24] revealed that the strain inhibited *Vibrio parahaemolyticus* infection in mice. Zhang et al. [25] reported that *Bacteroides fragilis* isolated from human feces protects against antibiotic-associated diarrhea in rats by modulating intestinal defenses. Another study concluded that bacterial strain *Lactococcus lactis* induced Parkinsonism by inhibiting ferroptosis, redressing dysbiosis and oxidative stress in human [26] (Table 1).

In a finding, the clinical study evaluated the effect of *Clostridium butyricum* on human, showing that it reduced the incidence of diarrhea in digestive diseases, including inflammatory bowel disease [49]. In a different finding five bacterial strains *Roseburia intestinalis, Anaerobutyricum hallii, Faecalibacterium prausnitzii, Ruminococcus bromii,* and *Akkermansia muciniphila* were isolated from human gut and developed as live biotherapeutic product [39]. In a study, *Faecalibacterium prausnitzii* was isolated from the human gut, and a clinical trial was conducted on mice and humans. The study revealed that patients treated with this strain showed a reduction in non-alcoholic fatty liver disease, hyperlipidaemia, prediabetes, inflammatory bowel disease and type 2 diabetes, demonstrating its potential as an efficient NGP strain [40]. In summary, NGP is still in its early stages as a medical concept, but it shows great promise and will require much investigation before it can be used in preventive care.

3. Characteristics of next generation probiotics

NGPs' functioning mechanisms in the gut are more complex than those of traditional probiotics, and they are far more susceptible to the harsh conditions found in the human gastrointestinal tract. It has been established that NGPs' are essential for enhancing the efficacy and survivability of beneficial gut bacteria. Probiotics, which are defined as substrates that the host microbes specifically use to provide a health benefit, are also crucial for NGPs [54]. Probiotics have the potential to be beneficial to health in part because they aid in the growth and activity of beneficial gut microbes through fermentation [55]. Additionally, encapsulating materials for probiotics it has been shown that giving inulin (a fructan) orally can greatly increase the proliferation of *Faecalibacteriumprausnitzii* and *Bifidobacterium adolescentis* in the human gut microbiota [39]. Remarkably, a different study showed that adding riboflavin, cysteine, and inulin increased the survival rate of *F. Prausnitzii* in the air by 70 %. *F. prausnitzii* is capable of surviving in partially oxygenized environments such as the gut mucosa through the transfer of electrons to oxygen. For this purpose, the bacterium utilizes extracellular antioxidants, including cysteine and riboflavin that are abundant in the gut. These antioxidants can maintain the viability of *F. Prausnitzii* in ambient air [56]. Galacto-oligosaccharides are frequently added to meals and are thought of as prebiotics. Probiotic development in the complex gut environment may be stimulated by galact-oligosaccharides [57].

Probiotics have garnered ongoing interest due to their ability to ferment in the colon, promoting bacterial activity that may positively impact on colon health, even though they are not widely recognized as prebiotics [58]. When it comes to gut microecology, vitamin D has been extensively studied and is one of the well-researched vitamins. Studies have shown that vitamin D deprivation exerts a noteworthy influence on the diversity and makeup of microbiome. For instance, vitamin D3 treatment was observed to increase the proportional prevalence of Bacteroidetes, while decreasing certain of Proteobacteria in an interventional, open-label pilot investigation [59]. The human body often obtains vitamin K via food supplements. The gene necessary for vitamin K synthesis is also present in the gut microbiota [60], like *Bacillus subtilis*, *Eubacterium rectal*, and various species of *Bacteroides* have the ability to reshape dietary vitamin K into menaquinones, which can control the gut microbiota [54]. The small intestine absorbs just 5–6% of the polyphenols, and very few are eliminated with feces. The remaining polyphenols are then available to support probiotics by the gut microbiota in the colon or large intestine [61].

Plant polyphenols also have an attractive antioxidant impact that may increase the viability rates NGPs sensitive to oxygen within the gastrointestinal tract. Polyphenol-rich extracts, such as those derived from berries, grapes, and caffeic acid, could enhance the growth of *Akkermansia muciniphila* within the microbiome [62]. In animal models, this has been demonstrated to improve colonic inflammation and metabolic disorders, and other diseases [63]. A common plant polyphenol among vegetables and fruits, resveratrol has shown promising effects when used to enhance the activity of NGPs. Research findings indicate that resveratrol modifies the physicochemical attributes of the microbial surface, and promotes *Lactobacillus paracasei* ATCC334 adherence and biofilm formation [64]. Consuming anthocyanins has been associated with an increase in *Bifidobacterium* spp. abundance in the gut microbiota [65]. While anthocyanins have been demonstrated to exhibit antioxidant and anti-inflammatory properties in mice, their impact on NGPs has not yet been assessed. While the small intestine is the primary site of mineral absorption, the gut microbiota's composition in the colon can alter the mineral bioavailability [66].

During food processing, storage, and gastrointestinal transit, the ratio of live probiotics is typically significantly decreased. NGPs have demonstrated effectiveness in treating a variety of disorders associated with the gut microbiota; however, this positive outcome is only likely to occur when a sufficient number of live bacteria enter the intestinal tract and effectively establish residence in the gastrointestinal tract [67]. Tragically, bile salts, gastric acids, and oxygen can all cause severe sensitivity in NGPs such *A. muciniphila* and *F. Prausnitzii* [54]. Combining different probiotics with probiotics during therapy has been shown to increase probiotic colonization and survival [54].

4. Mechanisms of action of next generation probiotics

The vital roles of the human gut microbiota encompass the management of systemic immunity, assisting in nutrient absorption by the host, safeguarding the intestinal barrier to facilitate the establishment of indigenous flora, and competing with external pathogenic bacteria [68]. The substantial influence of the gut microbiome on human well-being is widely recognized [69]. The human digestive system hosts a plethora of microorganisms that have forged intricate connections with the host. Significant attention is dedicated to understanding the composition and function of the gut microbiota in both states of health and disease [70]. The human gastrointestinal microbiota, commonly referred to as the "overlooked organ" of the human body, remains inadequately characterized, even with regard to its composition [71]. Certainly, changes in the composition of the gut microbiome, known as dysbiosis, have been associated with various intestinal and systemic disorders, such as obesity, inflammatory bowel disease, diabetes, allergies, immune disorders, metabolic syndrome, cardiovascular diseases and Crohn's disease [72,73]. Apart from their immune-regulating properties, the gut microbiota also enhance the host's well-being by providing a protective barrier against pathogens, assisting in the process of digestion by breaking down indigestible food components and generating vital metabolites [74]. Furthermore, these metabolic and inflammatory conditions have been associated with substantial changes in both the abundance and diversity of the human gut microbiota [75]. The microbiota assist in the process of digestion, contributes to nutrition, and plays a role in shaping our immune system [76]. It is acknowledged that diet is a fundamental factor that influences the makeup of the gut microbiome. Over a prolonged duration, a consistent dietary pattern shapes both the structure and operations of the gut microbiome [77].

Faecalibacterium prausnitzii, *Eubacterium hallii* and *Akkermansia muciniphila*, are frequently found in the human microorganisms identified for their potential as probiotic candidates [78]. *Akkermansia muciniphila* can degrade components of intestinal mucin, resulting in a competitive inhibitory effect on other pathogens that also degrade mucin [79]. It is a common resident of the human gastrointestinal tract, representing roughly 1–3% of the total gut microbiota [80]. Recent discoveries have revealed that *A. muciniphila* can act as a marker for a favorable metabolic profile in a host. Indeed, a decrease in the presence of *A. muciniphila* in the gut has been linked to a range of metabolic and inflammatory conditions, including obesity, type-2 diabetes, and inflammatory bowel disease [81]. *Faecalibacterium prausnitzii* serves as the primary source of butyrate, with the capacity to influence the expression of tight junction proteins and holds the potential to improve the integrity of the intestinal barrier in people dealing with IBD [82]. This bacterial species ranks among the most prevalent microorganisms in the human gut, comprising approximately 5–20 % of the complete microbiota found in the feces of healthy individuals [83]. Furthermore, it has been documented that *F. prausnitzii* can metabolize the degradation byproducts of complex carbohydrates, including glucose, maltose, and N-acetylglucosamine, a constituent of glycoprotein's present in the gut mucosa [84]. *Eubacterium hallii* engages in nutrient exchange within the gut microbiota by producing lactate and acetate [85]. Recently, various strains from the *Bacteroides* genera were isolated from the fecal samples of healthy individuals using high-throughput in vitro screening assays. These strains exhibited anti-inflammatory characteristics and were regarded as promising NGPs [86]. Most *Clostridium* species are commensal bacteria with the ability to activate intestinal epithelial cells, fortify the intestinal barrier's integrity, and produce short-chain fatty acids [87].

Propionibacterium plays a crucial part in immunomodulation through the expression of dihydrolipoamide acetyltransferase,

resulting in the proliferation of Th17 cells and ultimately decreasing the mortality linked to necrotizing enterocolitis [88]. *F. prausnitzii*, *E. hallii* and *A. muciniphila* are standout contenders among the identified keystone species, and they hold great promise for making a significant contribution to combating diseases stemming from the dysbiosis of inflammatory and metabolic origins. One of the most effective methods to induce beneficial alterations in the gut microbiome is through dietary modification, achieved by avoiding processed, high-carbohydrate, or high-fat foods, as well as artificial sweeteners and sugar, and by increasing the intake of vegetables, fermented foods and fibers that encourage the growth of beneficial bacteria [89]. Although positive outcomes have been observed with probiotics across various circumstances [90], the means by which they provide these benefits to humans remain poorly understood. Furthermore, it is acknowledged that the impact of probiotics depends on the precise strain and dosage, which may, to some extent, explain the varying results observed when using different probiotic strains, even if they belong to the same genus or species. Moreover, multiple factors could potentially impact the outcomes observed in clinical trials involving probiotics, such as the utilization of different probiotic strains, either on their own or in combination with other therapies: The host's initial health status, the capacity of the host's microbiota to permanently accommodate new microorganisms, and the ecological niche created (and controlled) by the host's immune system during the early stages of life [91] (Fig. 2).

5. Techniques for enhance viability and stability of next generation probiotics

The use of appropriate probiotic strains at sufficient doses is the first prerequisite for creating a probiotic food product. The primary criteria for choosing appropriate probiotic bacterial strains are their capacity to remain viable under food processing and storage conditions, their ability to survive intestinal transit, and their potential to improve consumer health. Strain-specificity governs the ability of bacteria in the food matrix to survive against various extreme conditions during product production, processing, and storage [3]. Since prolonged storage is frequently required, commercial probiotic products must have an extended shelf life. Lowering the water activity (aw) to about 0.1 and the intracellular moisture level below 4 % inhibits cellular functions and maintains the cells in an inert condition [92]. Microencapsulation is among the most effective methods for enhancing the survival and durability of probiotic strains under industrial processing conditions, while also providing protection from the gastrointestinal environment [93]. Probiotics are microencapsulated to protect certain compounds or biological cells from external factors that could destroy their essential components. During the formulation development process, it enhances the flow characteristics and shields the bacteria from heat, oxygen, and moisture [94]. It has been demonstrated that probiotic encapsulation technology can improve the biological activity and survival of the microorganisms when utilised as a carrier or targeted delivery system [95]. In general, a minimum level of more than 10^6 live probiotic bacteria per millilitre or gram of food product is approved, while the exact number of cells needed to generate therapeutic effects is unknown and may vary depending on the strain and the desired health effect [96]. As viability is usually regarded as a requirement for probiotics' efficacy in relation to their health-promoting qualities for consumers, it represents an industrial hurdle. Numerous studies have shown the impact of live cells on the functional attributes of probiotics [97]. An effective microencapsulation strategy must protect the probiotics from the harsh conditions of upper gastrointestinal tract, release them within the colon, maintain their stability during storage, and ultimately improve their ability to adhere to mucosal surfaces for colonization [98].

5.1. Spray drying

Spray drying (SD) is a commonly used method for microencapsulation. The fundamental idea underlying this is the exchange of mass and heat between the air and the atomized droplets, and vice versa [99]. This special drying method allows for the continuous

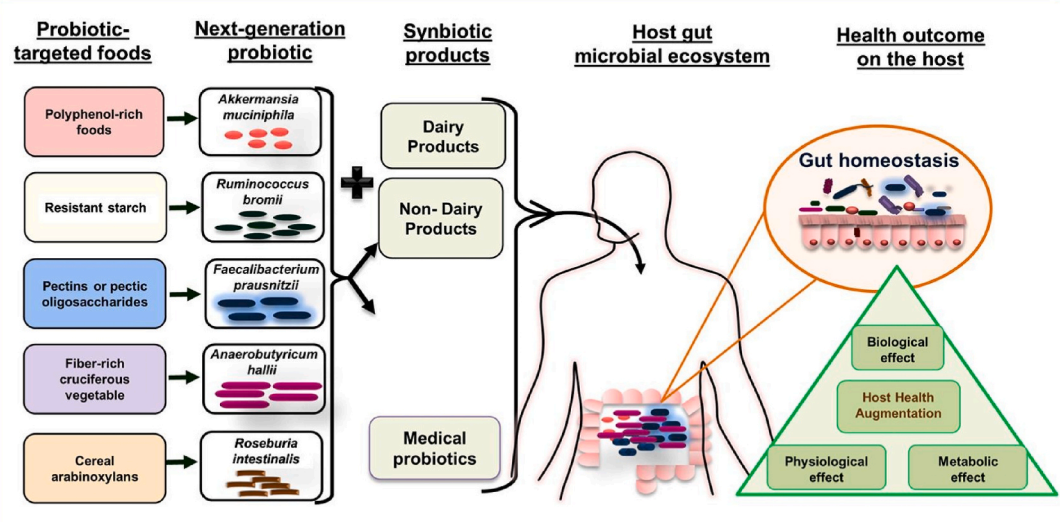

Fig. 2. Mechanism of actions of next generation probiotics. Adapted with permission from Ref. [39].

creation of probiotic powdered particles, which is followed by the internal spraying of liquid stock culture within the drying chamber [100]. According to the numerous authors, enveloping lactic acid and diverse probiotic cultures using a range of carrier substances through the spray drying process is long-term, cost effective, safe and energy-efficient preservation technique [101]. Spray drying involves three stages: atomization, which creates droplets; mixing, which evaporates water between droplets and hot air; and separation, which gathers the dried powders from the cyclone separator [102]. Spray drying provides a number of benefits over other techniques. These consist of low cost, short drying time, and continuous operation capability; together, they allow drying huge quantities of suspension within a relatively brief timeframe. It is also possible to alter the characteristics of the powder, and the scaling-up process is relatively straightforward [103]. The benefits of spray drying, including its elevated efficiency, cost-effectiveness, and good powder characteristics, have made it a potential method for producing probiotic powders. However, the adverse environmental conditions from digestion and drying can substantially lower cell viability, resulting in poor bioaccessibility and bioavailability of living cells. Thus, in order to preserve bacteria and their physiological processes in the targeted regions, efficient targeted delivery systems utilising spray drying must be developed [104]. The main disadvantage of this method is that it uses high temperatures, which might negatively impact encapsulation efficiency [105]. There is a need to concentrate on more practical desiccation techniques like freeze-drying because spray-drying requires high temperatures and oxygen, which makes it unsuitable for next-generation probiotics. The protective effects of antioxidants, osmoadaptation and stress therapy during the freeze drying of next-generation probiotics should be studied in order to optimise this process [8].

5.2. Extrusion

Extrusion is the predominant technique for encapsulating probiotic microorganisms within hydrocolloid gel matrices. This method, also known as sprinkle, is easy to use, inexpensive and produces probiotics with a high rate of encapsulation retention due to its mild environmental conditions [106]. Extrusion offers good cell viability and is a simple method to execute. Encapsulated gel beads are created during the extrusion process by dripping or spraying the feed solution via a nozzle at high pressure. The pulsation or vibration technology used in this method is described as a prilling or vibrational jet that may produce capsules in a standardised manner without compromising the viability of the microflora [107]. Despite the previously noted favorable conditions, its drawbacks include slowness, which hinders its large-scale application; inefficiency in producing microspheres smaller than 500 μm and the requirement for low to moderate viscosity hydrocolloid solutions [108].

5.3. Emulsification

Another low-cost approach to the probiotic microencapsulation is emulsification, which is more readily scaled up than extrusion. Probiotic cells and coated polymer are combined in both combining aqueous and oil phases to generate a substance resembling a "solution," comprising minute droplets. Upon the introduction of cross-linking agents, the water-soluble polymer transitions into an insoluble state, leading to the creation of gel particles within the oil phase. Subsequently, microcapsules can be retrieved through the filtration process [109]. Although this encapsulating method is typically employed in lab settings, there are certain drawbacks for probiotic cell and food sector applications [110]. *L. casei* and *Lactiplantibacillus plantarum* can be effectively utilised when RS-4 (phosphorylated starch type 4) is employed; encapsulation is achieved through the emulsion technique. These probiotics are effectively shielded from gastrointestinal conditions, exhibiting robust survival capacity even under harsh heat treatments and prolonged storage [111].

5.4. Electrospraying

Electrospraying is a cutting-edge drying technique employed in nutraceutical and food industries. It relies on the electrohydrodynamic process, involving the application of a high-voltage electrical field. The electrical interactions between charged particles in a fluid medium are the foundation of electrohydrodynamic approach. Research investigations have recently shown a great deal of interest in food drying using this method. This method provides inexpensive, quick drying times, efficient encapsulation, and great product quality [112,113]. This approach has a number of benefits, including high adaptability, simplicity, and ease of scaling up. The encapsulated probiotic cells in this technology suffer the least amount of thermal damage because heat is not involved [114]. This approach is simple, easy to regulate, and free of serious hazards, making it a potentially useful substitute for encasing delicate substances. This method can be utilised to successfully encapsulate medicinal molecules in micro- and nanoscale forms by adjusting the process variables, solvent type, and process parameters [115]. Due to its basic design, electrospraying may produce particles with a monodisperse distribution and is easy to operate in moderate weather situations [116]. The biological macromolecule encapsulation of food bioactive components by the electrospraying approach has garnered significant attention in the field of food science [117]. Due to its lack of necessity for elevated temperatures, pressures, or harsh chemical environments, research is currently underway to produce drug and probiotic-laden particles using electrospraying [118].

5.5. Freeze-drying

This procedure was initially commercialized during World War II to maintain the stability of penicillin and blood plasma. Afterwards, freeze-drying technology was employed by French virologist Charles Merieux to preserve vaccines. In 1938, Max Mortgenthaler, a scientist, pioneered freeze-dried coffee, paving the way for the development of powdered food item. The low operating

temperature of the freeze-drying process reduces product denaturation, which is typically a problem with other drying techniques [119]. Lyophilisation, also known as freeze drying, is a popular technique for dehydrating probiotic bacterial cells so that their storage durability is guaranteed. Three steps make up the freeze-drying process: freezing the cell culture, sublimation, and final drying. Typically, the initial stage is carried out beyond the drying apparatus. In the subsequent phase of this method, sublimation under reduced pressure is employed to eliminate the frozen water, while the ultimate stage involves desorption to remove the non-frozen water, resulting in the desired final water content [120,121]. Foods, medicines, and biological materials that are heat-sensitive are frequently dried via freeze drying method [122]. Since freeze drying doesn't require any freezing temperatures while the product is being distributed, it's the most practical method for protecting probiotic bacteria. However, in comparison to other drying techniques, the freeze drying procedure is more costly (4–7 times) and time-consuming [123]. The two main disadvantages of the freeze-drying method are its increased drying time and power usage [124]. When probiotics are freeze-dried, their encapsulated structure becomes more porous, negatively impacting their barrier strength [94]. According to reports, probiotics with a significant air-solid interface area during storage die off more quickly [125] (Table 2).

6. Regulatory framework of next generation probiotics

Probiotic regulations vary from nation to nation; no single framework is accepted worldwide. Within the European Union, food supplements and probiotics are subject to the regulations outlined in the Food Products Directive and Regulation (2000/13/EU; Regulation 178/2002/EC). The EFSA must approve every health claim related to probiotics. The qualified presumption of safety for a number of microbial cultures has been published by the EFSA [134]. All of the probiotics' filed health claims have been rejected by EFSA so far. As a result, while product claims are subject to strict inspection, the manufacturing process is not heavily regulated, and there is hardly any post-marketing regulatory follow-up [135]. After reviewing over 400 probiotic applications, the EFSA panel on dietetic products, nutrition, and allergens was unable to find any evidence supporting any health claim. "In reality, an adjustment regarding the use of general descriptors has essentially rendered the use of the term 'probiotic' unlawful" [136]. It remains uncertain whether any NGPs would be subject to further regulatory oversight [6]. Government bodies such as the Food Safety and Standards Authority of India (FSSAI), the U.S. Food and Drug Administration (FDA) and the Dietary Supplement Health and Education Act (DSHEA) in the United States, The European Food Safety Authority (EFSA) in Europe, the Joint Health Claims Initiative (JHCI) in the UK, the State Food and Drug Administration (SFDA) in China, the Canadian Food and Drugs Act Under Natural Health Products Regulations in Canada, and the Food Safety and Quality Division (FSQD), Food for Specified Health Use (FOSHU) in Japan and the National Health Surveillance Agency in Brazil have gained international recognition to describe the regulatory pathways for probiotics marketed as medicinal products including clinical trial data or as components in functional foods [137]. Regulatory challenges affecting the commercialization of NGP's include their classification which can vary across regions (e.g., as drugs or dietary supplements), resulting in diverse market pathways and compliance requirements. Standards for safely and efficacy also vary, complicating and increasing the cost of meeting regulatory expectations globally. Restrictions on health claims concerning probiotics add complexity to market positioning and consumer comprehension. Navigating labelling requirements is crucial to ensure compliance and uphold consumer trust in product benefits. These challenges highlight the importance of harmonized regulatory approaches to promote the global acceptance and market success of NGP's.

7. Safety and effectiveness considerations for next generation probiotics

The idea of NGPs was first formally proposed by Nature Microbiology in 2017. They believe that NGPs are distinct from conventional probiotics and meet the criteria for "active biological agents" as per the US FDA guidelines [138]. The NGPs should undergo clinical trials and need to be approved by relevant regulatory authorities prior to being released onto the market [139]. Potential NGPs are currently required to satisfy the following criteria: safety, individualised treatment, and internal interaction within the flora [140]. In addition to the functional examination of individual bacterial strains, *Lactobacillus rhamnosus* and *Bifidobacterium lactis* have been extensively studied in clinical trials to assess their safety profile, demonstrating high gastrointestinal tolerance and minimal risk of adverse effects in infants and elderly individuals. However safety considerations may vary greatly among different strains, even within the same species. Therefore safety appears to be the most crucial factor in the development of NGPs. These NGP candidates still need to be advanced clinically for the purpose of treating chronic inflammation-related disorders [141]. The safety evolution of NGP varies in different countries. New food products, such as NGP, must be safety evaluated by the European Food Safety Authority (EFSA). Key

Table 2
Techniques of next generation probiotics.

S.No	Food	Techniques	Probiotic Strains	References
1.	Apple juice	Spray drying	*Lactobacillus rhamnosus* GG	[126]
2.	Ice cream	Emulsion	*Lactobacillus casei* Lc-01 and *Bifidobacterium lactis* Bb-12	[127]
3.	kefir	Extrusion	*Bifidobacterium animals*	[128]
4.	Yogurt	Ionic gelation and complexation	*Lactobacillus acidophilus* LA-5	[129]
5.	Yogurt	Extrusion	*Bifidobacterium bifidum F-35*	[130]
6.	Carrot juice	Extrusion	*Lactobacillus acidophilus*	[131]
7.	Fruit juices	Freeze drying	*Bifidobacterium longum, Bifidobacterium breve*	[132]
8.	Mango juice	Gelation	*Lactobacillus plantarum*	[133]

elements of the assessment of microbes include clear species-level taxonomic classification, whole-genome sequencing analysis to fully characterise strains, antibiotic resistances and their potential horizontal transfer, and other potentially harmful metabolic properties like those associated with obesity, diabetes, and metabolic syndrome etc. [142]. In addition to safety concern, the NGP's attributes must include a comprehensive understanding of the diseases it targets, as well as the genetic characteristics and physiological attributes of the bacteria, such as growth dynamics and antibiotic sensitivity patterns. Furthermore, it is necessary to define the underlying molecular ameliorative pathways. The next step in achieving this goal is to perform strict functional validation of the novel probiotics using state-of-the-art NGS (next generation sequencing) and bioinformatics methodologies to screen and isolate the NGPs [11]. Testing genetic stability and conducting human clinical trials underscore the importance of rigorous assessment methods to ensure the safety and efficacy of NGP's. These measures help establish their reliability and effectiveness across various health applications.

Significant studies on NGPs utilise a variety of methods to evaluate effectiveness and safety. These include clinical trials, such as randomized controlled trials and longitudinal studies, which employee validated outcome measures like symptom severity scores, biomarkers, and assessment of quality of life. Animal models are also employed to explore mechanisms of action and establish initial safety profiles before proceeding to human trials. Participant selection criteria usually encompass age, health status, and specific conditions being studied, while interventions involve the controlled administration of probiotic strains or formulations.

8. Potential health benefits and applications of next generation probiotics

The human gut microbiota is essential for regulating systemic immunity, promoting nutrient uptake by the host, preserving the integrity of the gut barrier, allowing for the colonization of native flora, and posing a threat to external pathogenic bacteria [143]. New developments high-throughput DNA sequencing, culturing methods, and molecular analysis technologies have enabled the collection of sufficient data to distinguish functionally distinct bacterial species. The past decade has seen a rapid development of microbiota related analysis platforms, leading to a quick unravelling of the composition, structure, and roles of gut microbial communities [144]. Microbiota based strategies are employed to improve intestinal barrier integrity, reduce inflammation, and ameliorate various diseases [145]. Among them, the fast developing practise of fecal microbiota transplantation (FMT) involves transferring the microbiota from a healthy donor to a recipient who suffers from a medical condition associated with a dysbiotic, diseased gut microbiome. A review of recent developments show that FMT has the most effective results when treating *Clostridium difficile* infections associated with recurrent antibiotic use [146].

There is growing interest in the human gut microbiota as an aspect of the environment that might impact either wellness or disease [147]. The creation of NGP represents a practical method for modifying the gut microbiota and improving human health [39]. Researchers like Neef, Sanz [148] have paved the way for the discovery of NGPs following the pharmaceutical regulatory guidelines outlined by both the food and drug administration and the European pharmacopoeia, NGPs have been identified as live biotherapeutic products (LBPs) since they are more appropriate for pharmaceutical use rather than as dietary supplements. Developing NGP strains is closely associated with addressing specific diseases such as bowel diseases, neuropsychiatric diseases, chronic inflammation, metabolic syndromes, inflammatory asthma, dysbiosis, cardiovascular disorders, and cancers [11].

However, a number of important prospective NGPs are strictly anaerobic and might need to grow in concert with other bacteria to perform at their most effectively [6]. In addition to standard probiotics, the functions of newly discovered, unconventional, indigenous gut microbiota bacteria for the promotion of health and potential medicinal applications have quickly generated increased excitement. Currently, strains of gut bacteria associated with health, such as those from the genera such as *Akkermansia, Faecalibacterium, Bacteroides, Clostridium, Eubacterium, Propionibacterium* and *Roseburi*as, as well as genetically modified (GM) strains are being looked at as potential next-generation probiotics (NGPs) [39]. Appropriate accumulation of comprehensive physiological and molecular data is enabling the separation, recognition, and functional analysis of these different bacteria. These potentially advantageous bacteria are gradually being categorized to create the NGPs [54]. Several NGP bacterial strains belong to different family such as Actinobacteria, Bacteroidetes, Firmicutes and Verrucomicrobia [141]. Significantly, NGPs might be subject to drug-like regulations; consequently, the criteria for categorizing NGPs are considerably more rigorous compared to conventional probiotics [149]. Extensive interpretation of effectiveness in the improvement of disease, physiological, safety, and metabolomics characteristics, as well as the drug vulnerability pattern, drug resistance genes, and potential severity, is required [7]. Addressing the interaction between NPGs and the host to uphold intestinal immunity and host stability is a topic that needs attention. While most NGP products are not yet commercially available, research and development in this field continue to advance [39].

The high sensitivity of nearly all of these putative NGPs to oxygen will significantly impact their growth in pure culture and make large-scale production more challenging [150]. The development of NGPs for additional disease areas is rapidly expanding, in contrast to standard probiotics that target a general population and emphasise gut health [151]. NGPs for gastrointestinal issues, allergies and eczema in children, prevention of skin infections and allergies, and pregnancy and nursing are just a few of the constantly expanding categories in which these products are being developed [152]. NGPs targeted at various life phases are also expected to see significant development as more and more scientific information rapidly accumulates. Next generation probiotics offer innovative approaches to improving health beyond traditional benefits examples include precision targeting probiotics designed to address specific conditions or symptoms such as gastrointestinal disorders, immune modulation probiotics that enhance immune function by supporting the gut microbiota, reducing the risk of infections and autoimmune diseases, mental health support contributing to alleviating symptoms of anxiety, depression or stress and nutrient synthesis etc.

NGP's such as *Lactobacillus*, *Bifidobacterium*, *Akkermansia muciniphila*, and *Faecalibacterium prausnitzii*, demonstrate promising health benefits in scientific studies [153]. *Lactobacillus* and *Bifidobacterium* are recognized for enhancing gut health and immune function, with certain strains proving effective in conditions such as IBS and IBD. *Akkermansia muciniphila* promotes gut barrier

function and metabolic health, aiding individuals dealing with obesity and metabolic disorders. *Faecalibacterium prausnitzii*, known for its anti-inflammatory properties, holds promise for managing inflammatory bowel diseases.

9. Conclusions

In recent times, there has been a notable surge in research interest regarding the influence of commensal gut bacteria on enhancing health, surpassing the focus traditionally placed on disease-related studies. These non-traditional germs that promote health are commonly known as NGPs, and if they are utilised for pharmaceutical purposes, they are subject to FDA live biotherapeutic products demands. The main obstacle lies in the identification of NGPs, as the approach is heavily reliant on assumptions and predominantly built upon correlation studies that compare the relative abundance of microbes in healthy individuals and those with diseases. After being identified, the organism needs to undergo testing using suitable in vitro, and *in vivo* models for a variety of functional, safety, and technological criteria. To produce LBP on a large scale, the unusual growth requirements must be considered, and the composition must guarantee the culture's viability and bioactivity until it is consumed. The produced product needs to clear regulatory approval requirements and undergo phase 1–3 clinical studies to confirm dose, assess safety, and evaluate efficacy. Although there is a wealth of research, further work is necessary to progress beyond the established correlation between gut microbiota in a healthy state and one in a diseased condition. The main reason could be that a harmonious intestinal microflora plays a role in establishing a balanced host microbiome environment that is linked to good health, which could be shown by the abundance of these health-associated bacteria. Another possible cause for the anomalous "immune set point" could be that a smaller number of these NGP candidates have been responsible. Nonetheless, further investigation is required to ascertain whether a solitary bacterial strain can offer such beneficial effects or if a consortium is necessary to achieve the intended outcomes of live bacterial biotherapeutics. Further research is needed to determine whether to use NGPs as preventive medicine, and this will involve the use of preclinical models and clinical trials to distinguish between all of the possibilities.

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The authors declare that they have no known competing financialinterestsor personal relationships that could have appeared to influence the work reported in this paper.

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