Review Article

Next-Generation Probiotics: Promising Therapeutic Candidates for Metabolic and Gastrointestinal Disorders

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Most of the probiotic bacterial candidates currently available in the market consist of various strains belonging to different classes. Nevertheless, the gastrointestinal microbiome is a collection of undefined microbial agents that may contribute some medical benefits to human beings. Hence, currently, researchers from different corners are centered on investigating and identifying gastrointestinal-derived probiotic strains for the advancement of next-generation probiotics. The term next-generation probiotics refers to genetically modified microorganisms created by deleting, adding or modifying specific genes to produce a probiotic strain that modulates the metabolism, gastrointestinal health and delivered directly to the mucosa. Next-generation probiotics generated from different probiotic strains are intended to provide one or more health benefits to a host and for the efficient control and/or treatment of multiple diseases. Even though some next-generation probiotics are auspicious of the control and treatment of several chronic sicknesses, studies on human beings are still sporadic and confirmations from regulatory authorities are thus rare. Furthermore, some problems need to be resolved by releasing their broad application to the public. Probiotic strains such as *Faecalibacterium prausnitzii*, *Prevotella copri*, *Bacteroides uniformis*, *Bacteroides thetaiotaomicron*, *Bacteroides acidifaciens*, *Clostridium butyricum*, *Christensenella minuta*, *Akkermansia muciniphila* and *Parabacteroides goldsteinii*, have been postulated as next-generation probiotic candidates, as a result of their therapeutic or preventive effects on diseases such as colitis, obesity, diabetes and liver diseases. This review highlights the probiotic potential of next-generation probiotics and discusses the potential existing and emerging next-generation probiotics.

Key words: Lactic acid bacteria, butyrate, next-generation probiotics, gastrointestinal tract

It has been estimated that the human microbiota contains 100 trillion bacteria and forms a symbiotic relationship with the host by controlling both onset and progression of illness as well as the promotion of health[1,2]. Bacteria that colonize the intestinal tract are involved in biological processes that control metabolic phenotype, epithelial lining development and innate immunity. It has been reported that intestinal dysbiosis (altered composition of intestinal microbiota) has the capability to produce a multitude of disorders such as obesity, diabetes mellitus, neurodegenerative diseases, asthma, and inflammatory bowel disease[3]. The identification of

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beneficial bacterial candidates that promote health and those that can be used to treat intestinal dysbiosis has been achieved through an in-depth understanding of the intestinal microbiome[4].

Medical experts and the public in general use the term "probiotics" to describe a means of improving human and/or animal health. The term "probiotic" is often used in reference to both foods and medications[5]. According to World Health Organization/Food and Agriculture Organization probiotics are defined as "living microorganisms that, when introduced into the body in adequate quantities, provide health benefits"[6].

Most of the bacterial strains licensed and sold as probiotics in the market today belong to the Lactic Acid Bacteria (LAB) group, which is mainly designated by the genus *Lactobacillus*[7]. They are metabolically recognized by the production of lactic acid from carbohydrates, producing an acidic milieu that inhibits the emergence of some disease-causing bacterial species[8]. They may also generate secondary metabolites such as bacteriocins, exopolysaccharides and enzymes, all of which are beneficial to human health[9].

Despite the benefits mentioned above, current probiotic development trends seek to reduce the usage of probiotic groups like *Lactobacillus* and enhance the use of other genera and species of bacteria that are more suited to the intestinal environment[10]. These bacteria are termed Next-Generation probiotics (NGPs). The growing popularity of NGPs in recent years can be linked to the various benefits they provide over conventional probiotics[11,12]. In-depth research into this new generation of probiotics will allow for the development of more advanced tools to aid in the treatment of emerging and re-emerging illnesses[13]. The aim of this review is to highlight the different types of NGPs and their benefits to human health.

Probiotics display numerous modes of action, including the regulation of intestinal health, and its pH over the secretion of Short-Chain Fatty Acids (SCFAs), inhibition of the growth and occupation of gastrointestinal (GIT) pathogens, and help to prevent related illnesses[14]. It has been found that butyrate, produced from SCFAs, reduces the proliferation of pro-inflammatory cytokines and supports the expression of antimicrobial substances in the intestinal system[15]. Moreover, it facilitates the differentiation, proliferation and physiology of the epithelial cells of the immune and mucosal system. Butyrate facilitates the propagation and the intestinal integrity in Crohn's disease patient[16]. Bacterial candidates such as *Bacteroides uniformis*, *Bacteroides thetaiotaomicron*, *Bacteroides acidifaciens*, *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, *Clostridium butyricum* (*C. butyricum*), *Prevotella copri* (*P. copri*), *Christensenella minuta* (*C. minuta*) and *Parabacteroides goldsteinii* (P. goldsteinii), have been hypothesized as NGP candidates, due to their soothing and defensive effects on diseases such as colitis, diabetes, obesity and liver diseases[17,18]. This review highlights the probiotic potential of NGPs and discusses the potential existing and emerging NGPs.

WHAT ARE PROBIOTICS

Probiotics are live microbial agents, primarily bacteria and yeasts that generate health benefits when up taken in sufficient concentration. Mostly present in fermented products like yogurt, kefir, sauerkraut and supplements[19]. Probiotics promote a conducive gut microbiome niche, facilitate digestive function, strengthen immune response and may prevent or treat certain GIT issues, such as diarrhea and Irritable Bowel Syndrome (IBS)[20].

Physiological homeostasis, enhancement of intestinal integrity, and antimicrobial peptide production are all benefits of probiotics and their metabolites[21,22]. Probiotics are efficiently maintaining the levels of microflora of the intestinal tract[23]. Traditional Probiotics (TPs) have a long history of safe utilization with a broad range of health-promoting effects, such as preventing neonatal Necrotizing Enterocolitis (NEC)[24], alleviating the frequency intestinal colic in infants[25], uplifting the quality of life in IBS patients[26], preventing children's diarrhea[27] and reversing antibiotic induced intestinal inflammation[28]. In the last few years, probiotics have become very popular and are becoming a multibillion-dollar business around the world, which is expected to exceed $65.9 billion by 2024. Probiotics categorized by constituent type (yeast and bacteria), by preparation form (dry or liquid probiotic), by application (dietary supplements, food & beverages, and animal feed), by end user (Animal or human probiotics): Global industry perspective, comprehensive analysis and forecast, 2019–2026.

Most of the TPs which are available on the market are derived from the conventional *Streptococcus*, *Lactobacillus*, *Bacillus*, *Bifidobacterium* and yeast[29]. For example, *Streptococcus thermophilus* secreted

β-galactosidase in yogurt can degrade lactose into galactose and glucose, which is crucial process for those with lactose intolerance. Nevertheless, probiotics are not considered as antibiotics in several countries and are not regulated very well[30]. Consequently, a cocktail of probiotic products is mostly promoted to buyers without consistent proof of safety and efficiency[5]. NEC represents a severe intestinal disorder predominantly affecting preterm infants and is exemplified by abdominal distension, eating intolerance, high mortality, dysentery and unknown etiology[31]. Previous meta-analyses study revealed that the supplement of probiotic minimized the occurrence of NEC in newborns (<1500 g birth weight) ranging from 6 %-2 %, nonetheless *Lactobacillus* and *Bifidobacterium* are administered individually[32]. However, a phase III clinical trial indicated that no significant reduction was detected linked to the use of *Bifidobacterium brevis* BBG-001[33]. Thus, there are scarce of studies on the probiotic potential of *Lactobacillus rhamnosus* (*L. rhamnosus*) ATCC 53103, *L. rhamnosus* R0011, *L. rhamnosus* ATCC 53103, *Saccharomyces cerevisiae*, *Saccharomyces boulardii* and *Lactobacillus helveticus* R0052 as probiotics[34]. In United States of America, according to the Gastroenterological Association, the use of probiotics for children with acute gastroenteritis is not suggested or recommended[34]. Hence, even if probiotics are crucial in many different aspects, the research findings on their effectiveness are inconstant. Additionally, all human beings have a typical gut microflora; therefore, the probiotic profile can vary from individual to individual. For those reasons, thorough investigations to explore the actual profile and capacity of probiotics are necessary in future. The impacts of TPs on the human gut microbiota are insufficient and the therapeutic potential of gut flora intervention is mainly treated at the level of strains.

Closely 80 % of the gut microflora are uncharacterized[35], and several types of immune and metabolic illnesses are linked with the total mass of flora in the body[36]. Though, very limited investigations have been carried out on probiotics because these agents are highly sensitive to oxygen which makes it difficult to generate their pure isolates.

With the introduction of culturomics, pure bacterial isolates such as *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, *Eubacterium hallii* (*E. hallii*), *Bacteroides fragilis* (*B. fragilis*) and *Roseburia* sp. have efficaciously been attained *in vitro*. These have been termed as NGPs[37]. Nature Microbiology officially introduced the idea of NGPs in 2017 for the first time[37]. They realized that NGPs differ from TPs and conceptually refer to "active biological entities" which fulfil the suggestion presented by United States Food and Drug Administration guidelines. Comprise live microbial agent; they are utilized for treatment, prevention, control of a disease in humans and they are not vaccine. These days, NGPs candidates are being extensively investigated and reported. NGPs suggested overcoming the deficiencies of the existing TPs and can contribute an imperative role in the prevention or treatment of human diseases all over the globe[38].

OVERVIEW OF THE MODE OF ACTION OF PROBIOTICS

Probiotics exert their beneficial effects through diverse mechanisms. The mode of action of probiotics involve colonization and maintaining balanced gut microbial populations in both adults and children; suppression of intestinal bacteria and bacteriocin synthesis; regulation of enzymatic pathways linked to the metabolization of several number of toxic substances and carcinogens; and synthesis of volatile fatty acids, branched chain fatty acids and SCFAs, which contribute a substantial benefit in the preservation of energy homeostasis and management of the activity of the peripheral tissues. Besides, probiotics enhance adhesion in the enterocytes and mucin generation and regulate the action of gut-linked lymphoid tissue and the immune system[39].

The immunomodulatory activity of probiotics is mainly because of the interaction of probiotic bacteria with DCs, epithelial cells, and with monocytes/macrophages and lymphocytes[40]. Likewise, probiotic metabolites can interact with the brain-gut axis and play a role in behavior[39]. This multifaceted mechanism underscores the potential of probiotics in preserving gut health.

NGPs:

The term NGPs consider the Genetically Modified Micro-organisms (GMMs) which have been developed either by deletion, addition, or upregulation of specific genes to generate an efficient probiotic candidates in terms of metabolism, GIT survivability, technological stress tolerance and mucosal directed delivery of prophylactic and/or therapeutic agents to confirm one or multidimensional benefits on the host (also called "bio-drug") for the treatment or prevention of various illnesses[41].

While NGPs have not yet been functioning as health regulators, they have the potential to serve as

alternative modulators for conventional probiotics. NGPs are probiotic which comprised strains such as *Bifidobacterium*, *Lactobacilli* etc., nevertheless large-scale genomic manipulation have identified potential probiotic candidates with considerable health benefits, mostly from the genera Verrucomicrobia, *Bacteroides*, *Akkermansia,* Firmicutes, *Eubacterium* and *Faecalibacterium*[42].

B. fragilis is one of the promising NGPs candidates which has been modulating the immune system associated with the T-cell immune response[43]. Likewise, *Bacteroides acidifaciens* have been recognized to promote the production of Immunoglobulin (IgA) in murine models and as a result uplifting the IgA^+ B cells and B cells production which is crucial in maintaining homeostasis of the intestine and avoiding the pathogen attachment in the GIT[44]. Investigations have indicated that the NGPs candidate, *Akkermanisa*, has the potential to regulate obesity, diabetes and inflammation in humans[45]. In endurance athletes, *Akkermansia muciniphilia* plays an important role in maintaining gut barrier function[46], and glucose homeostasis and its direct relation to the capability of the athletics[47], and most importantly it has the capacity to induce the immune system[48]. Recent research findings indicated that the bacteria *Akkermansia muciniphilia* synthesize Vitamin B12, but the product's efficiency in humans has yet to be determined[49].

Another potential NGP is *Faecalibacterium prausnitzii* which has played immunodulatory activities *via* induction of T-cell and interleukin-10 responses in murine and human dendric cells[50]. Another worthy NGP *E. hallii* L2-7 has been reported to enhance insulin sensitivity (IS) and raise the metabolism of energy in diabetic and obese murine models[51], *E. hallii* DSM 17630 and *E. hallii* DMS 3353 have been suggested to generate Vitamin B12 and sustain intestinal homeostasis *via* the consumption of glucose and several fermentation intermediates like lactate and acetate *in vitro* investigation[52].

Probiotics of the new generation appear to be beneficial in preliminary studies, however, more testing and proof is needed to confirm their effectiveness and safety in humans[53]. *Lactobacillus* sp. and other TPs are biologically safe and some are practically effective. According to evidence-based medicine, a statistically insignificant effect is likely to result from their use. Moreover, TPs are also not implemented to cure certain disorders[54]. Thus, in the current scientific landscape, there is a critical need to identify and use more potent and disease-specific NGPs.

By using modern next-generation sequencing techniques, many previously unknown probiotic bacterial candidates have been identified from the intestinal microbiota and these NGPs have become ideal sources for novel therapeutic agents for several diseases in humans[53]. In comparison to TPs, NGPs have several benefits. To date, many metabolites such as indoles, secondary bile acids, folate, serotonin, Trimethylamine-N-Oxide (TMAO), Gamma-Aminobutyric Acid (GABA), SCFAs acetate, butyrate, propionate and others have been identified from NGPs, all of which can contribute a significant role in maintaining the physiological host phenotype (fig. 1)[55].

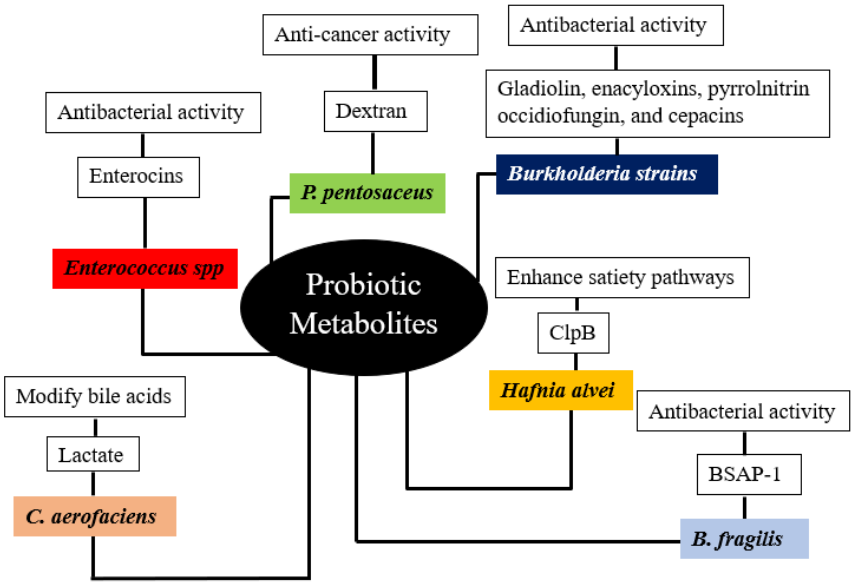

Fig. 1: Schematic representation summarizing the probiotic potential of different bacterial candidates (emerging NGPs)

NGPs strains:

***B. fragilis*:** *B. fragilis* is the species within the different species found under the class Bacteroides. Documented findings indicated that enterotoxin gene lacking strain *B. fragilis* show relatively several benefits[56]. The capsular Polysaccharide (PSA) of this strain has been recognized as the structure which is typically involved in the interaction to the host cell. PSA boosts the anti-inflammatory memory of T-cell[57].

C. minuta: *C. minuta* is a gram-negative bacterium, was recently discovered as a member of the *Christensenella* genus and the *Christensenella*ceae family. *C. minuta* was first introduced from the stool of an apparently healthy individual. This bacterium is a natural inhabitant of the human GIT which is a conducive niche for it[58]. *C. minuta* is the member of the Firmicutes family and has been known to have probiotic potential against metabolic illnesses and obesity as well. According to reports, the population of *Christensenella*ceae was found to be higher in individuals whose body mass index is lower than those weighing higher[59]. It has also been proven that the usage of *C. minuta* may enhance microbiota related with obesity[60] and it's also been discovered that taking *C. minuta* increases the formation of SCFAs.

***P. copri*:** *P. copri* is non-spore forming anaerobic, gram-negative bacterium and belonging to Bacteroidetes phylum. *P. copri* is a common inhabitant of the intestinal microbiome of humans that has been both negatively and positively linked with the health of the host[61]. Like other anaerobes, it can perpetuate easily and efficiently in the GIT of humans. This probiotic candidate can enhance glucose tolerance and the level of glycogen in the liver[62]. *P. copri* has been documented as a potential curing agent for metabolic sicknesses including obesity and type-2 diabetes[63]. Its NGP potential is mainly associated with its ability to enhance glucose homeostasis through intestinal gluconeogenesis. Moreover, *P. copri* is involved in intensification of glucose tolerance and boost insulin resistance which happens before the progression of type 2 diabetes and cardiovascular sickness.

***P. goldsteinii*:** *P. goldsteinii* is an anerobic, gram-negative bacterium in the family Porphyromonadaceae and belongs to the genus *Parabacteroides*. It is considered as an NGP for obesity[64]. Mice fed a high-fat diet had significantly lower *P. goldsteinii* concentrations in the microbiota, while mice treated with prebiotic PSA showed significantly higher levels. The reduction in the weight of mice has been tied to augmented intestinal permeability, inflammation, and metabolic endotoxemia, which culminates in insulin resistance and obesity reversing. This NGP candidate has also been reported to possess insulin stimulating and anti-inflammatory properties[42].

***E. hallii*:** *E. hallii* is an anaerobic, gram-positive bacterium pertaining to the phylum Firmicutes and the family Lachnospiraceae. *E. hallii* has the capability to ferment carbohydrates and generate butyrate as a product[65]. *E. hallii* is advantageous in the intestinal food chain. The organism can influence metabolic balance and gut microbiota structure by generating various SCFAs from the host and/or dietary PSA[52]. It has been documented that daily oral dose of *E. hallii* enhances IS and upgrade metabolic energy in diabetic and obese mice. Interestingly, increasing the dosage of *E. hallii* did not affect the body weight or food intake of the treated mice, indicating that this bacterium may serve as a novel, safe and potential probiotic candidate for enhancing IS in the treatment of obesity and diabetes[51].

In the gut microbiota and breast milk, Bifidobacteria (naturally strain) can break down complex carbohydrates into monosaccharides. These monosaccharides can then be utilized by *E. hallii* to produce SCFAs[66]. This symbiotic relationship between Bifidobacteria and *E. hallii* suggests a significant and advantageous association for the host.

***C. butyricum*:** *C. butyricum* is an obligatory anaerobe, gram-positive and spore-producing bacterium. The name 'butyricum' is derived from its ability to produce substantial amounts of butyric acid[67]. This specific strain has the sole future to metabolize non-carbohydrate substrates, resulting in the production of SFA, primarily butyric acid. In a study by Cao *et al*.[68], oral administration of *C. butyricum* after gastrectomy reduced early postoperative inflammation, boosted the immune system, maintained GIT microbiota, raised intestinal SCFAs, minimized the postoperative problems, and finally helped the quick recovery[68].

Documented reports indicated that that *C. butyricum* displays notable potential in plummeting the occurrence of GIT tumors in mice that are induced by a high-fat diet. Therefore, it could be utilized in the prevention and treatment of cancer. Besides, *C. butyricum* has been recorded to inhibit the propagation of GIT tumor and facilitate apoptosis[69]. Additionally, in the context of depression, combining therapy with *C. butyricum* strains

and antidepressants has shown significant improvement in individuals suffering from depression[70].

***Odoribacter laneus* (*O. laneus*):** *O. laneus* is a rod-shaped, anaerobic, gram-negative bacterium that was first detected from the fecal maters of a healthy donors in Japan[71]. In a recent investigation performed by Hueber-Ruano *et al*.[72], *O. laneus* was determined as an NGP because of its capability to enhance the sensitivity for insulin and minimize the inflammatory markers in a mouse model. The researchers introduced *O. laneus* to the obese mice *via* oral gavage and visualized a considerable decline in the levels of serum succinate. They postulated that raised succinate levels might be due to a compromised integrity of intestinal barrier, chiefly in cases of dysbiosis of the gut. The increase in serum succinate levels is correlated with situations such as obesity and type 2 diabetes mellitus (T2DM), which are known by chronic inflammation[73]. Additionally, the activation of Succinate Receptor 1 (SUCNR1) in macrophages is linked to the development of obesity and T2DM, causing the adipose tissue inflammation and infiltration by inflammatory cells[73]. In general, *O. laneus* displays promising therapeutic power in the treatment of T2DM and obesity (fig. 2).

EMERGING NGPs:

Emerging NGPs are probiotic strains that go beyond TPs in their capabilities and therapeutic potential. These NGPs include specific bacterial species and engineered microbes that are designed to target and modulate gut microbiota, enhance immune responses and improve metabolic health. Unlike conventional probiotics, emerging NGPs typically include strains mostly encompassing lesser-known and newly discovered bacterial species as discussed below and summarized in fig. 1.

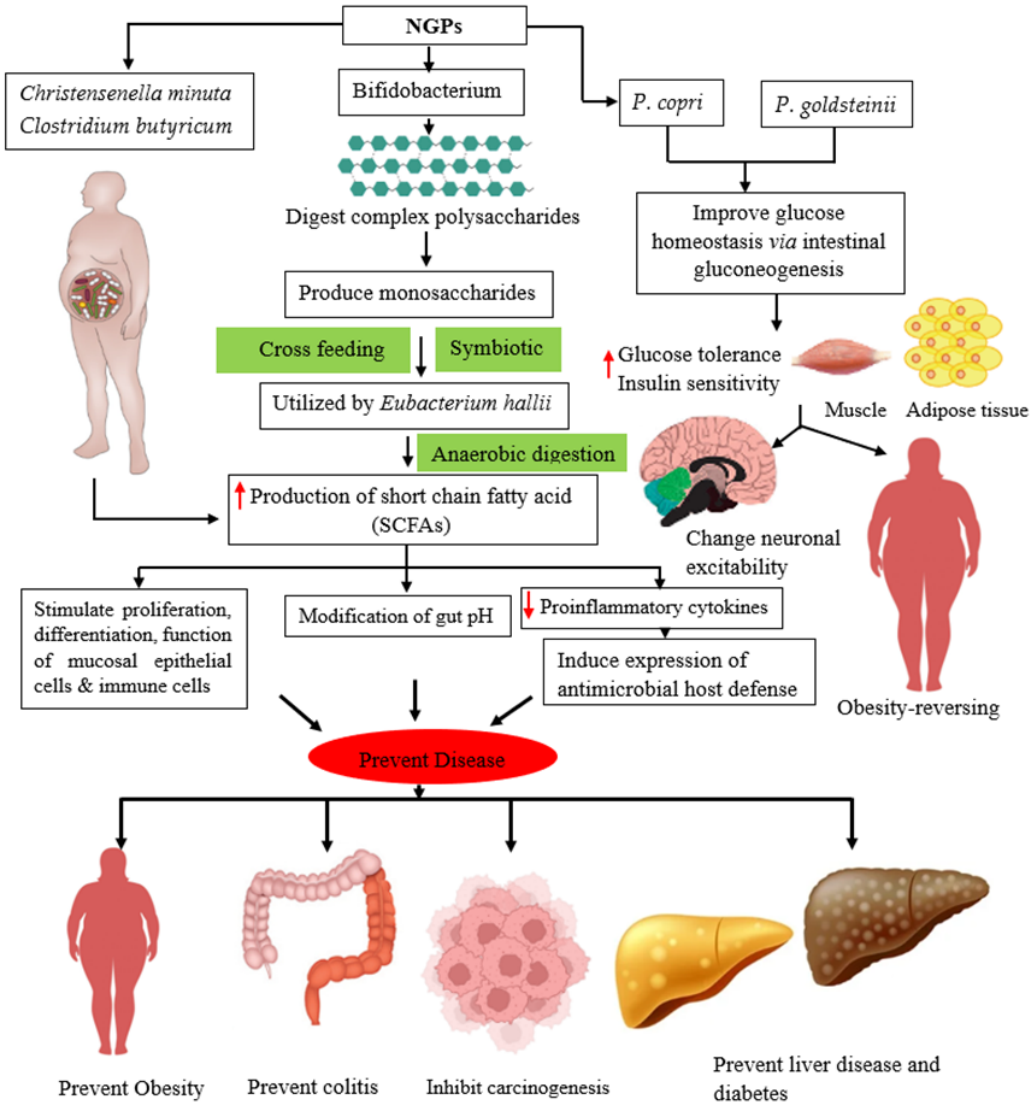

Fig. 2: Schematic representation of the multifunctional roles of NGPs

***Eubacterium*:**

Eubacterium sp. are anaerobic, rod-shaped gram-positive bacteria that are commonly found in the oral cavity and GIT. These bacteria are considered beneficial microbes and are part of the core human gut microbiome[74]. Within the genus *Eubacterium*, there are 26 officially recognized species, but the key genotypes are limited to *Eubacterium callanderi*, *Eubacterium barkeri*, *Eubacterium limosum* and *Eubacterium aggregans*[75]. *Eubacterium* spp. has been associated with human health, particularly in relation to Colorectal Cancer (CRC) development. Notably, *Eubacterium rectale*, *E. hallii* and *Eubacterium ventriosum* are found in reduced abundance in CRC patients[76], and metagenomic investigations have consistently shown that *Eubacterium ventriosum* is more prevalent in healthy control groups, indicating its potential as a biomarker for lower CRC risk[77]. Additionally, *Eubacterium* sp. are known producers of SCFAs, including butyrate, acetate and formic acid, with butyrate playing a role in inhibiting carcinogenesis and inducing apoptosis in cancer cells[78].

***Collinsella* aerofaciens (*C. aerofaciens*):**

C. aerofaciens is a gram-positive, anaerobic bacterium commonly found in the human gut microbiota. It plays a crucial role in the digestive process by helping to break down complex carbohydrates and produce SCFAs, which are vital for health. *C. aerofaciens* is also involved in the modulation of the immune system and maintaining the integrity of the gut barrier[79]. Within the human colon, *C. aerofaciens* plays a significant role in the metabolism of lactose. Numerous studies have indicated that *Collinsella* and *Bifidobacterium* have the ability to modify host bile acids, thereby influencing the pathogenicity and virulence of enteric pathogens[80]. More recently, it has been suggested that variations in the abundance of *Collinsella* may also impact the levels of plasma cholesterol in the host[81].

***Burkholderia* sp.:**

Bacteria belonging to the *Burkholderia* genus are renowned due to their adaptive metabolic pathways and varied ecological niches[82]. The taxonomical revisions within this genus have resulted in the use of the term "*Burkholderia*" to encompass the *Burkholderia* sensu lato, acknowledging its heterogeneity[83]. These bacteria are commonly found in terrestrial and aquatic ecosystems and can exist as free-living organisms or establish close associations with protozoans, fungi, animals, plants, and humans[84]. Such connection can have either advantageous or detrimental effects on the eukaryotic host. For instance, candidates of the *Burkholderia cepacia* complex, which comprises no fewer than 22 taxonomically related species, act as opportunistic pathogens, particularly in individuals with compromised immune systems like those with cystic fibrosis[85].

Various strains of *Burkholderia* exhibit killing properties by generating specialized metabolites such as pyrrolnitrin, occidiofungin and cepacins[86]. Despite prior studies chiefly aimed at eco-friendly management of phytopathogenic fungi, there is a growing interest in utilizing *Burkholderia* bacteria for the discovery of novel antibiotics. For example, *Burkholderia ambifaria* produces enacyloxins that exhibit activity against gram-negative pathogens, including *Acinetobacter baumannii*[87]. Additional illustrations involve gladiolin synthesized by *Burkholderia gladioli* and thailandamides produced by *Burkholderia thailandensis*, both of which demonstrate encouraging efficacy against *Mycobacterium tuberculosis* and *staphylococcus aureus*, respectively[88]. These recent findings, coupled with the identification of numerous 'cryptic' clusters of genes governing biosynthetic pathways within *Burkholderia* genomes, highlight the potential of these organisms as a valuable resource for drug discovery[89].

***Enterococcus* sp.:**

Enterococci, which are LAB, encompass a wide range of microorganisms that can be both pathogenic and commensal. They are commonly found in various environments, including the gut as symbionts. *Enterococcus* sp. strains have developed a high tolerance to salts and acids, making them well-suited for adaptation to different food systems. They play a role in the fermentation process of traditional cheese and dry sausages, where they are thought to provide a peculiar sensory characteristic of these dairy products[90]. Additionally, numerous strains of *Enterococcus* have been recognized for their antimicrobial substance, including bacteriocins. Bacteriocins could be applied for preserving a range of food commodities and are now known as a potential probiotic agent[91]. Furthermore, these biomolecules are being determined as promising alternative therapeutic agents in combating the development of antimicrobial resistance[92].

Enterococcus strains, belonging to the *Enterococcus* genus, produce a diverse array of bacteriocins often referred to as enterocins. These bacteriocins have been extensively studied, particularly for their activity

against gram-positive foodborne bacteria such as *L. monocytogenes*[93]. Two *Enterococcus* strains mainly *Enterococcus faecium* and *Enterococcus faecalis*, are the chief producers of enterocins in comparison to the contributions obtained from *Enterococcus hirae*, *Enterococcus avium*, *Enterococcus mundtii* and *Enterococcus durans*. According to reports, the bacteriocins generated from *Enterococcus faecalis* and related isolates have clinical relevance and are considered as emerging NGP candidates[94].

***Ruminococcus* sp.:**

Ruminococcus genus is characterized as obligatory anaerobic, gram-positive, non-motile cocci that do not form endospores. Their growth is dependent on fermentable carbohydrates. Several species of *Ruminococcus* are present in significant quantities in the human gut microbiota and are essential for proper digestion. Recent advances in next-generation sequencing have revealed their wide distribution among various animal hosts. Among these species, *Dysosmobacter welbionis*, a member of the Ruminococcaceae family, has been identified as a novel bacterium that produces butyrate[95].

This newly discovered bacterium has been detected in 62.7 %-69.8 % of healthy individuals. Notably, in obese individuals with syndrome of metabolic dysfunction, the abundance of *Dysosmobacter* genus is inversely correlated with body mass index, fasting glucose levels and glycated hemoglobin[96]. Live *Dysosmobacter welbionis* J115 supplemented mice, but not with pasteurized bacteria, partially mitigated the development of diet-induced obesity, fat mass gain, insulin resistance, white adipose tissue enlargement and inflammation. Furthermore, administration of live *Dysosmobacter welbionis* J115 protected mice from inflammation in brown adipose tissue, accompanied by increased mitochondrial count and enhanced non-shivering thermogenesis. These effects were observed with minimal impact on the composition of the mouse gut microbial community. These findings indicated that *Dysosmobacter welbionis* J115 has a direct and beneficial influence on host metabolism and holds promise as a potential NG beneficial bacterium for addressing obesity and associated with metabolic disorders. The presence of *Ruminococcus* bacteria in the gut microbiome is crucial for the digestion of resistant starches. The slow digestion of these specific carbohydrates by *Ruminococcus* has been related to a variety of wellness benefits, including the reversal of infectious diarrhea and a reduced risk of diabetes and colon cancer[97].

***Pediococcus pentsaceus*:** According to Jiang *et al*.[98], *Pediococcus pentosaceus* (*P. pentosaceus*) is a non-motile, gram-positive, cocci-shaped, homofermentative LAB with facultative anaerobic metabolism and carbohydrate catabolism features. The ability of some *P. pentosaceus* strains to be used in fermentation, as a bioactive growth enhancer for animals and as a probiotic was already established in the 1990s[99]. Nevertheless, most of *P. pentosaceus*' characteristics were not thoroughly researched at the time. Many additional previously unknown traits of *P. pentosaceus* have also been researched after more than 20 y of research. As of today, there are still issues with the actual application of *P. pentosaceus* as a probiotic, such as a lack of understanding of processes, adverse effects, usage and dose. There is mounting information that *P. pentosaceus* and its bacteriocins are effective for maintaining intestinal health as well as the food industry[100].

P. pentosaceus, a member of LAB, has been gaining increasing attention, resulting in a notable surge in experimental research. When employed as an additive, *P. pentosaceus* enhances the flavor and nutritional value of food, as well as improving the preservation of animal-sourced products. Scientific evidence suggests that *P. pentosaceus* produces substances known as bacteriocins or bacteriocin-like compounds, which demonstrate effective antibacterial properties within the microbial environment. Moreover, numerous strains of *P. pentosaceus* have been recognized for their potential as probiotics due to their abilities to reduce inflammation, combat cancer, provide antioxidant effects, aid in detoxification and lower lipid levels[101,102].

In recent years, *P. pentosaceus*, a specific type of LAB, has gained significant importance in LAB applications. This bacterium has been found in various sources, including fermented food, raw animal and plant products, aquatic products, as well as feces, with some strains showing association with the human GIT[99]. There is a widening body of experimental evidence suggesting that *P. pentosaceus* could be utilized as a potential bio preservative for foods, animals, or plants, as well as a potential probiotic candidate.

P. pentosaceus has displayed positive activity on intestinal substance absorption and excretion, along with the ability to enhance detoxification processes in the liver by reducing levels of blood ammonia, heavy metal ions, and endotoxins[103]. Additionally, *P. pentosaceus* has exhibited anti-inflammatory properties

by regulating Lipopolysaccharides (LPS) and cytokines in the host[104]. Recent *in vitro* study indicated that the *P. pentosaceus* strain OBK05 displayed strong antidiabetic activity by inhibition of α-glucosidase and α-amylase activity[105].

***Butyricoccus pullicaecorum* (*B. pullicaecorum*):**

B. pullicaecorum, anaerobic, gram-positive, non-motile coccoid cells typically arranged in pairs, displayed potential for therapeutic interventions in various bladder cancers and Colorectal Cancers (CRC). This is primarily due to its ability to secrete butyrate. An oral dose of *B. pullicaecorum* or its metabolites has demonstrated improved clinical outcomes in CRC by activating secrete butyrate transporters and/or receptors, indicating its potential as an anti-CRC probiotic. Moreover, *B. pullicaecorum* displayed a probiotic characteristic with positive effects on chronic inflammations. In a rat colitis model, oral dose of *B. pullicaecorum* exhibited a marked protective effect, reducing lesion sizes and inflammation. Additionally, the supernatant of *B. pullicaecorum* cultures withstand cytokine-initiated deterioration of epithelial integrity in an *in vitro* experimental model[106].

The production of butyrate, known for its beneficial properties in maintaining GIT health, has led to the exploration of butyrate-producing bacteria as the NGPs. *B. pullicaecorum*, belonging to clostridial cluster IV, emerges as a promising probiotic candidate for individuals with inflammatory bowel disease. However, before generating a stable formulation for oral dose, understanding its bile and intrinsic acid tolerance is crucial[107].

Clinical trials have shown that *B. pullicaecorum*, a safe butyrate-producing microbe, may potentially reduce cancer progression, offering opportunities for therapeutic interventions in different types of bladder cancers *via* the secretion of butyrate[108].

***Hafnia alvei* (*H. alvei*):**

H. alvei is a rod, gram-negative bacteria which belongs to the genus Hafnia under the order Enterobacterales. Lucas *et al*.[109], displayed that the gavage of the *H. alvei* HA4597™ strain in High fat diet-mice caused a reduction in food intake and reduced fat mass as well as weight gain[109]. Besides, the treatment group that acquired *H. alvei* HA4597TM exhibited reductions in triglycerides, serum glucose and the level of anino-transferase[109].

Legrand *et al*.[110], reported that oral administration of *H. alvei* in High fat diet-mice for 18 d and 46 d, respectively, reduced the mass of fat in treated mice and lessened food intake in 16 d of gavage mice. In general, the gavage of *H. alvei* HA4597™ had weight-dropping effects[110]. In a different study, Dechelotte *et al*.[111], documented the effect of orally administered *H. alvei* HA4597® for 236 overweight patients coupled with slightly hypocaloric food for a period of 12 w. They encountered a significant body weight loss (around 3 %) in the original body weight. A weight loss of 3 %-5 % of body weight is suggested by international baseline for overweight individuals. Moreover, Dechelotte *et al*.[111] reported a reduction in the circumference of hip and a significant decline in the circumference of waist and the level of serum glucose. The documented decline in body weight may be accredited to metabolic activity of the ClpB protein generated by *H. alvei* which improve satiety pathways through melanocortin receptor activation (essential for energy metabolism) [110]. This pathway is associated with the conduction of anorexigenic signals and a rise in the expenditure of energy linked with peripheral lipolytic effects[111]. As well, obese individuals have been reported to display a low concentration of bacterial strains encoding ClpB protein. A high number of bacteria encoding for ClpB protein in the intestinal microbiota may be attributed to a decline in the human body weight[112]. Thus, *H. alvei* could be a potential NGP bacterium for obesity and other illnesses in humans.

CONCLUSION

In conclusion, next-generation and emerging probiotics hold significant present as viable therapeutic effect for metabolic and GIT disorders, offering innovative solutions through their ability to maintain gut flora, immune responses and metabolic pathways. This review addressed different bacterial species which have probiotic potential, highlighting their diverse mechanisms of action and therapeutic benefits. With continued interdisciplinary collaboration and rigorous scientific investigation, NGPs have the potential to revolutionize the management and treatment of metabolic and GIT disorders, improving patient outcomes and overall health.

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Conflict of interest:

The authors declared no conflict of interests.

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