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Recent developments in probiotics: An emphasis on *Bifidobacterium*

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ABSTRACT

Microorganisms colonize the human gastrointestinal tract. These microbes may vary depending upon age, food habits, and health conditions. Uses of probiotics and probiotic-containing foods are increasing with our understanding towards the beneficial associations of gut colonizing microbes and the human body. Numerous fermented products and dietary supplements contain beneficial probiotic microbial strains. *Lactobacillus* and *Bifidobacterium* are the most common genera, which have been used as commercial probiotics. This review highlights recent progress related to the application of *Bifidobacterium* probiotic strains, their biofunctional attributes, safety evaluation, antibiotic resistance and the possibility to transfer antimicrobial resistance genes to other gut colonizing microbes. Further, few recently developed encapsulation methods to enhance the survivability of *Bifidobacterium* based probiotic formulations have also been discussed.

1. Introduction

Microorganisms have always been associated with human food. These microorganisms also colonize the human gastrointestinal tract and contribute some health benefits. It was suggested that the microbial particles, which are derived from the mother can be transported to the fetal side during the early stage of the fetus development. Such "microbial priming" plays an important role to establish a successful host-microbe relation after birth (Senn et al., 2020). A number of bacterial genera primarily belonging to *Enterococcus, Enterobacter, Escherichia, Bifidobacterium,* and *Lactobacillus* colonize the human gut. Among these bacteria, *Bifidobacterium* is one of the most abundant bacteria of healthy breast-fed infants. This bacterium has demonstrated notable physiological and genetic features along with the adhesion ability to epithelial cells and metabolism of host-derived glycans. *B. bifidum* and *B. breve* are the most frequently shared gut colonizing species between mothers and their corresponding children (Turroni et al., 2019).

Probiotics are defined as 'live micro-organisms, which when consumed in adequate amounts confer a health benefit on the host' (FAO/WHO, 2001, pp. 1–4). Fermented dairy products are the key sources of probiotic bacterial strains. Lactic acid bacteria including probiotic *Lactobacillus* spp. have been widely used as starter culture in several fermented dairy products (Minj, Chandra, Paul, & Sharma, 2020). *Bifidobacterium* along with *Lactobacillus* seems to be the most promising microbial genera in health-promoting dairy foods formulations (Linares et al., 2017). Functional attributes of these bacteria contribute directly or indirectly to several health benefits including the protection against pathogenic microbes, hypertension, inflammation, diabetes, oxidative stress, etc. These microbes are also involved microbiome modulation, immune modulation, and anti-cholesterolemic activity (Novik & Savich, 2020).

Bifidobacteria may synthesize and produce vitamins like riboflavin, thiamine, vitamin B6, and vitamin K and related bioactive molecules like folic acid, niacin, and pyridoxine. Bifidobacteria containing fermented milk is rich in free amino acids and vitamins. As compared to lactic acid bacteria, bifidobacteria preferentially produce L(+)-lactic acid, which is more easily metabolized by humans and may be important in the case of infants or the people having metabolic acidosis. Bifidobacteria containing food products may also improve the bioavailability of minerals by facilitating their ionization (McCartney, 2003). *Bifidobacterium* containing probiotic formulations include single bacterial strain, in combination with other probiotic microbes, encapsulated bacterial cells, and co-encapsulated cells with prebiotics. Most common *Bifidobacterium* species are found to colonize the human gut and used in probiotic formulations including *B. animalis*, *B. adolescentis, B. bifidum, B. breve, B. infantis,* and *B. longum* (O'Callaghan & van Sinderen, 2016). Most of these bacteria have demonstrated their role as probiotic strains as well as postbiotics. Antibiotic resistance and horizontal gene transfer of antibiotic resistance gene into other gut microbiota or pathogenic microbes maybe lead to developing new antibiotic resistant strains. Thus, confirmation of non-transferable antibiotic resistance must be a criterion from safety aspect, while developing any antibiotic resistant

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strain as a probiotic. Probiotics are consumed orally, which is often challenging in terms of loss of viability during its exposure to the harsh gut conditions in the upper gastrointestinal tract. Highly acidic gastric fluids in the stomach may directly reduce microbial viability and alter the probiotic associated properties. This problem may be solved by developing a gastric fluid-resistant probiotic formulation through encapsulation technology (Yus et al., 2019). A lot of literature is available on the probiotics, while this review summarized the recent work and development on different probiotics *Bifidobacterium* strains along with an emphasis on antimicrobial properties, antibiotic resistant strains and encapsulation strategies.

2. Bifidobacterium as probiotic

Most of the gut colonizing bacteria are obligate anaerobes including genus *Bifidobacterium*. Bifidobacterial species have been used in fermented dairy products traditionally and certain strains are 'Generally Recognized As Safe'. This has promoted the application of bifidobacteria as probiotic agents (Picard et al., 2005). Most of the probiotic strains have demonstrated their positive effect on human health. Some commercially used bifidobacterial species and strains including few recently confirmed probiotic strains of bifidobacteria have been studied (Table 1).

2.1. Bifidobacterium animalis

Bifidobacterium animalis has been used in fermented dairy products for a long time. Most of the *Bifidobacterium animalis* strains show high gastrointestinal survival and confirmed probiotic properties during their survival in the GIT. Earlier, *Bifidobacterium animalis* and *Bifidobacterium lactis* were categorized as two distinct species and now considered as *B. animalis* having two subspecies: *animalis* and *lactis*. Among different commercially available strains, *B. animalis* spp. *lactis* BB-12 and *B. animalis* spp. *lactis* DN-173010 have been studied extensively (Quigley, 2017).

Attachment of the probiotics with intestinal epithelial cells is an important factor. This attachment potential is influenced by a number of factors including the interaction of probiotic strain with dietary fibers. *Bifidobacterium animalis* subsp. *lactis* JCM 10602 demonstrated a great adhesion potential to dietary fibers present in the intestinal tract, which may further affect the adhesion to intestinal epithelial cells. The adhesion mechanism primarily involved hydrophobic and electrostatic interactions in the case of cellulose and chitin, respectively (Taniguchi, Nambu, Katakura, & Yamasaki-Yashiki, 2020). Fermentation with probiotic *Bifidobacterium* strains may improve the bioactivity of functional foods. As observed in the case of *Bifidobacterium animalis* subsp. *lactis* LT 19-2, which exhibited β-glucosidase activity with strong acid tolerance altered the aglycone profile of ginsenosides and improved immunomodulatory effect in fermented red ginseng (Kim, Jeong, Lee, & Byun, 2019).

Bifidobacterium animalis subsp. *lactis* HN019 reduced the plaque index and marginal gingival bleeding. This probiotic significantly reduced the adhesion of *Porphyromonas gingivalis* to buccal epithelial cells and also demonstrated antimicrobial activity against periodontopathogens. Thus, suggested to be used in non-surgical periodontal therapy of patients with generalized chronic periodontitis (Invernici et al., 2020). Probiotics have also been reported to be associated with the alleviation of constipation. *Bifidobacterium animalis* subsp. *lactis* MN-Gup improved constipation-related issues including defecation frequency, stool consistency, straining, and incomplete feeling during defecation. An increased concentration of acetate also confirmed the alteration in gut microbiota and a significant increase in acetate-producing bacteria (R. Wang et al., 2020).

Probiotics have been associated with improvements in mental health-related issues. *Bifidobacterium animalis* subsp. *lactis* BPL1 has been shown to improve the central adiposity in adults with simple

Table 1
Recently reported biofuctional attributes of different *Bifidobacterium* strains.

S. No.	Bacterial strain	Key Functional attribute	Model	Reference
1.	*Bifidobacterium bifidum* ATCC 29521	anti-inflammatory role by modulating miRNA-associated TJP and NF-κB regulation and, restoring dysbiosis	Male C57JBL/6 mice	Din et al. (2020)
2	*Bifidobacterium breve* NCIM 5671	prophylactic effects in terms of downregulating arthritis markers	Male Wistar rats	Achi, Talahalli, and Halami (2019)
3	*Bifidobacterium bifidum*	Controlling and inhibiting the tumor growth by elevation of antigen-specific IL-12, IFN-γ and lymphocyte proliferative	C57BL/6 mice	Abdolalipour et al. (2020)
4	*Bifidobacterium lactis* V9	regulate the levels of sex hormones during polycystic ovary syndrome	Women with polycystic ovary syndrome	Zhang et al. (2019)
5	*Bifidobacterium breve* A1 (MCC1274)	improving memory functions	Healthy human adults suffering from mild cognitive impairment	Xiao et al. (2020)
6	*Bifidobacterium longum* subsp. *longum* 35624™	impacted hypothalamic-pituitary-adrenal axis functioning in male animals and tended to reduce anxiolytic behavior in the OFT	Sprague Dawley rats under control or "stressed" conditions	Haas et al. (2020)
7	*Bifidobacterium lactis BB12*	Modification of oral biofilm (reduction in salivary *S. mutans* and lactobacillus)	18–30 years students with initial stages of dental caries	Zare Javid et al. (2020)
8	*Bifidobacterium animalis* subsp. *lactis* CECT 8145	obesity management (reduced anthropometric adiposity biomarkers)	Abdominally obese individuals	Pedret et al. (2019)
9	*Bifidobacterium bifidum*	Modulated humoral and cellular immune responses and balanced Th1/Th2 immune responses against infuenza infection	Six- to eight-week-old female Balb/c mice	Mahooti et al. (2019)
10	*Bifidobacterium longum* subsp. *longum* YS108R	alleviated DSS-induced colitis by protecting mucosal barrier integrity	Male C57BL/6J mice	Yan et al. (2020)
11	*Bifidobacterium animalis* subsp. *lactis* BB-12®	Reduced infant colic (Modulation of gut microbiota structure and function)	Breastfed infants with infant colic	Nocerino et al. (2020)
12	*Bifidobacterium longum* 1714™	Modulated neural responses during social stress	Healthy human volunteers	(H. Wang, Braun, Murphy, & Enck, 2019)

obesity. In children suffering from Prader–Willi syndrome, a rare genetic disorder, the probiotic consumption decreased abdominal adiposity and improved fasting insulin concentration and insulin sensitivity along with modest improvements in some mental health symptoms (Amat-Bou et al., 2020).

2.2. *Bifidobacterium adolescentis*

Probiotics have a proven role in inflammation modulation by modifying the gut microbiota. Preventive and therapeutic treatment with *Bifidobacterium adolescentis* on collagen-induced arthritis revealed that early administration of *B. adolescentis* (before CIA) performed better than late administration of *B. adolescentis* in terms of reduced clinical symptoms, rebalanced pro- and anti-inflammatory responses, maintained fecal short-chain fatty acids concentration along with restored intestinal dysbiosis (Fan et al., 2020). Similarly, *Bifidobacterium adolescentis* CGMCC15058 demonstrated a preventive as well as therapeutic effects against liver failure. Administration of this bacterial strain significantly reduced the elevated levels of alanine aminotransferase, lipopolysaccharide-binding protein, and total bile acid in serum. It also exhibited anti-inflammatory properties by decreasing the levels of inflammatory cytokines and increasing the levels of the anti-inflammatory cytokine interleukins in the liver. *B. adolescentis* colonization significantly altered the gut microbial community by depleting some common pathogenic bacterial population (Li et al., 2019 b).

The gut microbial composition may ameliorate atopic dermatitis clinical symptoms during the probiotic intervention. *Bifidobacterium adolescentis* treatment reduced ear and skin thickness and suppressed eosinophils and mast cells infiltration. Immunomodulation potential of *B. adolescentis* promoted Treg differentiation and suppressed Th2 responses. It altered gut microbial colonization by increasing the proportion of *Lactobacillus*, which was positively correlated with increased propionic acid production (Fang et al., 2020). With expanding research on probiotic strains and their performance in the human gut; understanding and application of prebiotics are also expanding. *Bifidobacterium adolescentis* P2P3 efficiently degraded resistant starch. This bacterium also demonstrated immunomodulatory activity through stimulated secretion of Th1 type cytokines from mouse macrophages (Jung et al., 2019). Probiotic microbes may negatively affect some pathogenic microbes including fungus. Production of organic acids (acetate and lactate) and decreased pH during fermentation seems to be a key mechanism for their antagonistic activity. *Bifidobacterium adolescentis* not only inhibited *Candida albicans* growth but also showed an immunostimulatory effect by inducing the killing activity of human-macrophages to eliminate adherent-invasive *Escherichia coli* (Ricci et al., 2020).

Probiotics are widely been explored towards their role in the gut-brain axis to deal with psychological disorders. *Bifidobacterium* may influence the functioning of the brain and central nervous system, leading to the changes in behavior, nociception, and cognitive abilities of humans and animals. Gamma aminobutyric acid (GABA) is the principal inhibitory neurotransmitter playing a key role in anxiety and depression disorders in mammals, which is produced by bifidobacterial strains. Among different bifidobacterial strains, *Bifidobacterium adolescentis* represents a model GABA producer in the human gastrointestinal tract. Supplementation of *B. adolescentis* PRL2019 and *B. adolescentis* HD17T2H confirmed the capability of these probiotic microorganisms to stimulate the *in vivo* production of GABA during an *in vivo* trial on Groningen rats (Duranti et al., 2020). Similarly, *Bifidobacterium adolescentis* 150 being an efficient GABA producer, reduced depressive-like behavior during the forced swimming test conducted on BALB/c mice (Yunes et al., 2020). In the mice model, *B. adolescentis* exhibited anxiolytic and antidepressant effects, which was related to the reduction in inflammatory cytokines and rebalancing the gut microbiota (Guo et al., 2019). Thus, *Bifidobacterium* containing probiotic formulations may be developed to deal with psychological disorders.

2.3. *Bifidobacterium bifidum*

Probiotics including *Bifidobacterium* strains are known to be beneficial in preventing several diseases including inflammatory bowel disease in model animals. *B. bifidum* ATCC 29521 demonstrated its role as an anti-inflammatory probiotic strain by modulating miRNA-associated tight junction proteins and inflammatory genes (Din et al., 2020). *Bifidobacterium bifidum* G9-1 successfully managed the irritable bowel syndrome by reducing the hypersensitivity to restraint stress in terms of serum corticosterone level and fecal frequency in rats subjected to maternal separation (Fukui et al., 2018). Non-viable, heat-inactivated *B. bifidum* MIMBb75 has been shown to be effective in the treatment of irritable bowel syndrome, which pointed towards the beneficial effects of bacterial strains are independent of cell viability (Andresen, Gschossmann, & Layer, 2020). Thus, it demonstrated probiotics along with their postbiotic potential applications.

Balance of the intestinal microbiota seems to be important in diarrhea treatment, which is largely caused by dysbiosis along with the hyperproliferation of *E. coli* in the intestine. Probiotic *B. bifidum* G9-1 remarkably improved the dysbiosis, jejunal villus length, and alleviated diarrhea symptoms in rat models (Makizaki et al., 2019). Paradoxically exacerbate aspirin-induced small intestine injury was well treated by the administration of *B. bifidum* G9-1. This bacterium inhibited the growth of *Akkermansia muciniphila* (a human intestinal mucin-degrading bacterium), which resulted in the reduction of thinning of the mucus layer (Yoshihara et al., 2020). *B. bifidum* TMC3115 demonstrated a beneficial effect on the serum cholesterol metabolism of subjects with dyslipidemia by increasing Firmicutes, Bacteroides, and Actinobacteria, while decreasing Proteobacteria and Fusobacteria in the intestine (Wang et al., 2020 a).

Bifidobacterium has shown its role in colorectal cancer and the use of probiotics might be a promising intervention method. The manipulation of the gut microbial composition using probiotic *B. bifidum* CGMCC 15068 showed a promising prevention strategy for colitis-associated colorectal cancer. Thus, all these findings supported the beneficial role of *B. bifidum* containing probiotics on intestinal health by modulating dysbiosis and the microbe-associated gut metabolic profile (Wang et al., 2020 a). Formulations consist of prebiotics and probiotics are gaining a lot of importance. Recently, xylanase treated oat β-glucan has been evaluated for its prebiotic effect on human colon *B. bifidum* CICC 6168. It was observed that production of lactic and acetic acid reduced the pH of fermentation broths. The prebiotic also promoted the proliferation of *B. bifidum* probiotic (Qiu et al., 2020).

2.4. *Bifidobacterium breve*

Bifidobacteria showed dominance during the early colonization of intestinal microbiota in infants. *Bifidobacterium breve* has been commonly isolated from the intestines of healthy breastfed infants and also from human milk. It was reported that the allergy prevalence may be a consequence of early intestinal dysbiosis. The infant formulations containing probiotic *Bifidobacterium breve* strains along with the prebiotic oligosaccharides may be useful in allergy management, especially in the case of non breastfed infants (Cukrowska, Bierła, Zakrzewska, Klukowski, & Maciorkowska, 2020). Intake of *Bifidobacterium breve* M-16V modulated the expressions of cytokines and reduced allergic lung inflammation in mice model when exposed to air pollution during pregnancy. Maternal intake of this bacterium successfully demonstrated the beneficial effects in neonate mice by alleviating allergic reactions accelerated by prenatal exposure to residual oil fly ash air pollution (Terada-Ikeda et al., 2020). *B. breve* seems to be neuroprotective for preterm neonates because of its anti-inflammatory effects and ability to facilitate nutrition. Contrary, there was no significant effect on neurodevelopment was observed in the children, who participated as preterm neonates in the randomized controlled trials administered with *B. breve* M-16V. However, the validity of these results is highly restricted because

of the high rate of loss to follow up (Agrawal et al., 2020).

Administration of *Bifidobacterium* containing probiotics may be used as an effective therapeutic strategy towards managing cognitive function, anxiety, and depression-like symptoms in humans. The therapeutic potential of *B. breve* A1 has been reported for preventing the cognitive impairment in Alzheimer's disease by using mice model as well as on elderly human with mild cognitive impairment. Thus, oral supplementation of *B. breve* A1 suggested its potential for improving cognitive function (Kobayashi et al., 2019). *B. breve* A1 also showed its potential in improving anxiety and depressive symptoms in patients with schizophrenia (Okubo et al., 2019).

Hypertension and obesity have also been cured during clinical trials conducted on animal models. *B. breve* CECT7263 attenuated endothelial dysfunction and increased blood pressure in the low-renin form of hypertension. These protective effects were mediated by increased acetate and reduced trimethylamine production by gut microbiota (Robles-Vera et al., 2020). A clinical study on pre-obesity subjects revealed the anti-obesity effect of *B. breve* B-3 and a possible increase in muscle mass. Oral administration of heat-killed *B. breve* B-3 significantly increased muscle mass, activated serine/threonine protein kinase, and phosphorylated AMP-activated protein kinase in male rodents. Thus, suggesting the potential of heat-killed *B. breve* B-3 in promoting muscle hypertrophy and modifying metabolic functions (Toda et al., 2020).

2.5. *Bifidobacterium longum*

Several strains of *B. longum* and *B. longum* subspecies *infantis* (*B. infantis*) have been used as probiotics. Production of exopolysaccharides by *B. longum* is closely associated with its adhesion property. On the other hand, *B. infantis* is well adapted to the infant's gut as it has co-evolved with the mother-infant dyad because of its ability to metabolize complex carbohydrates found in human milk. *In vivo* attachment of *B. longum* B-11 to rat's intestine has been confirmed by scanning electron micrographs, which suggested it to be a potential probiotic (Yasmin et al., 2020). *B. longum* 51A demonstrated promising results in colitis treatment. Oral administration of *B. longum* 51A showed a decrease in intestinal permeability and reduced the levels of IL-1β, eosinophil peroxidase, and myeloperoxidase (Abrantes et al., 2020).

Rotavirus infection causes diarrheal disease in children. However, recent research confirmed the relationship between rotavirus and probiotics, which was effective against rotavirus mediated diarrhea. A clinical trial reported the anti-rotaviral effect of *B. longum* BORI and successfully eradicated diarrhea induced by rotavirus. *B. longum* BORI dose was reported to be interfering with the interaction of virus and host cell. Thus, proven to be a safe and effective probiotic strain (Han et al., 2019).

B. longum has several beneficial health effects including stress management. Oral administration of *B. longum* subsp. *longum* 35624™ to male and female Sprague-Dawley rats under control or "stressed" conditions revealed that the probiotic dose was not able to rescue depressive-like behavior in males or females, but influenced hypothalamic pituitary adrenal axis functioning in male rats and reduced anxiolytic behavior (Haas, Wang, Saffar, Mooney-Leber, & Brummelte, 2020).

B. longum was also found to be effective in balancing and restoration of gut microbiota, which was disturbed by amoxicillin treatment. Mice were treated with amoxicillin showed increased β-lactam resistance and efflux resistance genes in the gut microbial population. However, treatment with *B. longum* along with inulin and fecal matter transplantation showed restoration of Gut microbiota (Lin et al., 2020). Tolerance to acid stress by bifidobacteria is crucial to survive and then exert the beneficial effects during gut colonization. This acid stress tolerance in probiotic strain *B. longum* JDM301A was enhanced by successive batch cultures, which influenced the transcriptional and physiological responses, including alteration in the bacterial cell wall and cell membrane, metabolism of amino acids, and neutralization of internal pH by increased production and transport of NH_3 (Wei, Gao, Liu, Li, & Liu, 2019). Genetically engineered probiotic bifidobacterial strains may provide additional benefit to their host. Transformation of plasmids pBPES-tu and pBPES-groEL into *B. longum* JCM1217 demonstrated increased phytase production and could efficiently degrade phytate. It was thus suggested an application of recombinant live probiotic strain *B. longum* JCM1217 for phytase secretion and phytate degradation in the host gut (Sun 2019).

Probiotics in a combination with other compounds like fungal extract and antibiotics may provide additional benefits to the host. A probiotic formulation Bifidus BB536 (containing *B. longum*) demonstrated enhanced probiotic effects when administered in a combination of standardized extract of cultured *Lentinula edodes* mycelia. This combination modulated T cell and dendritic cell phenotypes, and cytokine profiles to support anti-inflammatory response when followed by antibiotic dose (Chowdhury et al., 2019).

Bifidobacterium longum subspecies *infantis* (*B. infantis*) is well known as symbiotic bacteria having a human host that suppose to protect the preterm or term neonate by nourishing healthy gut microbiota. Several strains of *B. infantis* have been developed and commercialized (Chichlowski, Shah, Wampler, Wu, & Vanderhoof, 2020). *Bifidobacterium infantis* NLS super strain alleviated gastrointestinal symptoms in newly diagnosed coeliac disease patients consuming gluten. Administration of *B. infantis* decreased the abundance of *Ruminococcus* sp. and *B. adolescentis*. *B. infantis* NLS-SS improved specific coeliac disease symptoms in a subset of highly symptomatic treated patients. However, the study suggested a large level trial with detailed observation and analyses of different associated parameters (Smecuol et al., 2020). *B. infantis* was effective in improving psychological symptoms and quality of life of individuals, who are suffering from flood-affected irritable bowel syndrome. *B. infantis* M-63 effectively improved the mental health of individuals, who developed irritable bowel syndrome probably by restoring the gut microbial balance and gut-brain axis (Ma et al., 2019). Similarly, *B. infantis* alleviate intestinal epithelial injury and maintain intestinal immune tolerance in mouse model suffering from inflammatory bowel disease. Thus seems to be a potential therapeutic strain in the treatment of immune damage (Zhou, Liu, Xie, Yao, & Li, 2019).

Goat milk oligosaccharides increased the attachment of *B. longum* subsp. *infantis* ATCC 15697 to intestinal epithelial cells *in vitro*. The same strain of *B. infantis* when pre-treated with goat milk oligosaccharides significantly prevented the attachment of *Campylobacter jejuni* to intestinal HT-29 cells. Early exposure to goat milk oligosaccharides modulated the adhesion of *B. infantis* along with the utilization of carbohydrates present in goat milk. Thus, provides a synbiotic formulation including oligosaccharides sourced from goat's milk and probiotic *B. infantis* as a functional food (Quinn, Slattery, Walsh, Joshi, & Hickey, 2020).

3. *Bifidobacterium* spp.: an important factory of antimicrobials

Proteinaceous antimicrobial compounds i.e. bacteriocins are produced by bifidobacteria. These bacteriocins are ribosomally-synthesized antibacterial peptides having a significant potential in the fields of food preservation, and health care applications. However, the antimicrobial activities of these compounds are strain-dependent. *Bifidobacterium*-associated bacteriocins have demonstrated their antimicrobial activity against pathogenic microorganisms e.g. *Clostridium perfringens, Listeria monocytogenes*, and *Escherichia coli* (Martinez, Balciunas, Converti, Cotter, & De Souza Oliveira, 2013). However, cytotoxicity of the probiotic bacteriocins seems to be concentration depended (Todorov et al., 2017). On the other hand, lectins are glycoproteins, which are noncovalently attached to the carbohydrates. Probiotic bacterial lectins have demonstrated different biofunctional propertied including immunomodulatory, antibacterial and antifungal. Lectin produced by *B. adolescentis* possessed significant antibacterial activity against a clinically isolated

multidrug resistant *S.* Typhi (Kadhem et al., 2019). *B. infantis* (ATCC No. 15697) produced indole-3-lactic acid, a metabolite having anti-inflammatory property. However, the practical application has been recommended only after safety evaluation and clinical studies (Meng et al., 2020).

Cell free culture supernatant of *B. breve* YH68 inhibited the growth of *Clostridioides difficile* ATCC 9689 by inducing the leakage of a large amount of intracellular K^+, which enhanced cell membrane permeability, and eventually resulted in cell disintegration (Yang & Yang, 2019). Antibiotic resistant clinical isolates including *S. aureus* and *S. epidermidis* responsible for bacterial conjunctivitis were successfully inhibited by the cell-free extracts of *B. longum* Reuter 1963AL EMCC 1547 and *B. bifidum* (Tissier 1900) EMCC 1334 (Mohamed, Elmohamady, Abdelrahman, Amer, & Abdelhamid, 2020), which indicate towards the application of probiotic *Bifidobacterium* against pathogenic microbes.

Recently two bacteriocin gene clusters from the genome of *B. bifidum* VKPM=Ac-1784 has been identified, which indicated the antibiotic production potential of this strain (Korzhenkov et al., 2021). Bacteriocinogenic *Bifidobacterium* spp. have successfully demonstrated the inhibitory action towards pathogenic microbes including *E. coli*, *L. monocytogenes*, *Salmonella* spp., *B. cereus*, *Erwinia* spp., *Xanthomonas* spp., and *L. innocua*. However, these pathogenic and spoilage-associated bacteria showed increased levels of resistance to the bacteriocin-like substances (Voidarou et al., 2020). As a probiotic, it is advantageous for the *Bifidobacterium* to produce antimicrobial compounds against foodborne pathogens. Bifidocinp-A, a bacteriocin produced by *B. animalis* BB04, demonstrated significant antimicrobial activity against a wide range of foodborne bacteria, which further endorse its application in the processing and storage of set yogurt as a natural bio-preservative (Qiao et al., 2020).

Probiotic *Bifidobacterium* strains have also demonstrated antifungal activity and suggested to be used as biocontrol agents against mycotoxin producing fungi. *Bifidobacterium bifidum* PTCC 1644 inhibited the growth of *Aspergillus parasiticus* and also reduced the aflatoxin production by the fungus (Ghazvini et al., 2016). Similarly, *B. adolescentis* CCFM1108 inhibited the growth of a mycotoxin (patulin) producing fungus *Penicillium expansum*. Multiple antifungal compounds were produced by this bacterial strain including lactic acid, 3-phenyllactic acid, acetic acid, and *p*-hydroxyphenyllactic acid. *B. adolescentis* CCFM1108 supernatant disrupted plasma membrane integrity of the fungus and significantly reduced patulin production (Qiao et al., 2020).

Safety is a major concern associated with the consumption of probiotics. It is always recommended to confirm the safety of these bacterial strains to be used as probiotic. *B. bifidum* BGN4 and *B. longum* BORI are commonly used probiotic strains, which neither showed hemolytic activity nor mucin degradation activity and did not produce ammonia or biogenic amines (Kim et al., 2018). Viable cells of *Bifidobacterium breve* BBG-01 have been used as pediatric medicinal supplements to treat clinical conditions like intractable infantile diarrhea, preterm status, and pediatric surgery. Clinical data revealed that the adverse effects of this probiotic dose occurred only in extremely premature infants with functional ileus, and in surgical neonates. Thus, this study confirmed the safety of *Bifidobacterium breve* BBG-01 as probiotic preparation for infants (Kitajima & Hirano, 2017). Similarly, *B. infantis* EVC001 supplement was safely consumed and well-tolerated by healthy infants. No unexpected adverse events were noticed during the clinical trial of this strain (Smilowitz et al., 2017). Thus, it seems to have a lower risk associated with the consumption of these probiotic *Bifidobacterium* strains, however a critical safety evaluation must be performed for an individual strain before their clinical trials.

4. Antibiotic-resistant *Bifidobacterium* probiotic strains

Gut microbial communities retain a reservoir of antibiotic resistant genes. There is always a risk involved related to the genetic transfer of these resistance genes between microbial populations. The occurrence of antibiotic resistance genes in the different bifidobacterial strains has been evaluated for their possible genetic mobility to other human gut colonizing microbes (Duranti et al., 2017). Recently, a study depicted antibiotic resistance in genus *Bifidobacterium* by combining the phenotype dataset and in silico genotype predictions. Most of the *Bifidobacterium* strains were found to be sensitive to beta-lactams, chloramphenicol, glycopeptides, and rifampicin, while resistant to aminoglycosides, quinolones, polypeptides, and mupirocin. Bifidobacterium strains generally contain cmX and tetQ genes in resident plasmids, while the two most abundant antibiotic resistance genes tetW and ermX were encoded in the genome (Cao et al., 2020). Detailed mechanism related to antibiotic resistance governed by these genes has been represented in Fig. 1.

Probiotic bacteria must be characterized and proven safe for consumers' health through multiple safety analyses mainly including antibiotic resistance, toxin production, hemolytic activity, and infection-causing ability in immune-compromised individuals, any side effect or adverse outcome. Among different safety parameters, the horizontal transfer of antimicrobial resistance plasmid among the microbial population through transferable drug resistance plasmid containing probiotic strains is an alarming concern. Thus, it is important to confirm the nontransferable nature of such elements, which must be a criterion for developing commercial probiotic formulations. Commercially produced *B. bifidum* BGN4 and *B. longum* BORI when evaluated for their antibiotic resistance, *B. bifidum* BGN4 showed resistance to gentamicin, while *B. longum* BORI has a *tet*(W) gene in its genome and demonstrated tetracycline resistance. However, these antibiotic resistance genes were not transferrable via conjugation to *Lactobacillus fermentum* AGBG1 (a gut colonizing sensitive strain) (Kim et al., 2018). Similarly, *Bifidobacterium animalis* subsp. *lactis* AD011 suggested to be a potential probiotic microorganism after carrying out several safety parameters including ammonia synthesis, antimicrobial susceptibility, biogenic amine production, mucin degradation property, hemolytic activity, ability to transfer antibiotic resistance gene to other gut colonizing or probiotic microorganisms along with maintenance of genetic stability (Ku et al., 2020).

Rifaximin along with a probiotic dose is quite common in patients suffering from symptomatic uncomplicated diverticular disease. Rifaximin resistant probiotic strain *B. longum* W11 is routinely used in such cases. Patients treated with concomitant dose antibiotic and rifaximin-resistant probiotic *B. longum* W11 demonstrated better clinical outcomes. Thus it was suggested to use probiotic strain demonstrating a strong non-transferable resistance to a particular antibiotic should be used with that specific antibiotic (Di Pierro, Bertuccioli, Pane, & Ivaldi, 2019). An oral dose of *Bifidobacterium* containing probiotics has also been found to reduce the antibiotic-resistant gene in gut colonizing microbes. Supplementation with activated *B. longum* subsp. *infantis* EVC001 significantly reduced the antibiotic resistance genes among breastfed infants as compared to unsupplemented controls. These genes were associated with the resistance to a wide range of antibiotics including beta-lactams, fluoroquinolones, and macrolides. Gut colonization by *B. longum* subsp. *infantis* EVC001 effectively reduced the pathogenic microbes (*Clostridium, Klebsiella, Staphylococcus, and Streptococcus*), which might be containing the antibiotic resistance genes. Thus, its colonization significantly influenced the infant gut microbiome and provided immediate clinically relevant benefits in the treatment of nosocomial infections (Casaburi, 2018). Recently identified antibiotic resistant bifidobacterial strains along with the possibility to transfer antibiotic resistance gene have been enlisted in Table 2.

5. Recent encapsulation strategies used for probiotic *Bifidobacterium* strains

As discussed above, Bifidobacteria probiotics demonstrated a significant health impact on its host. However, this ability may be restricted

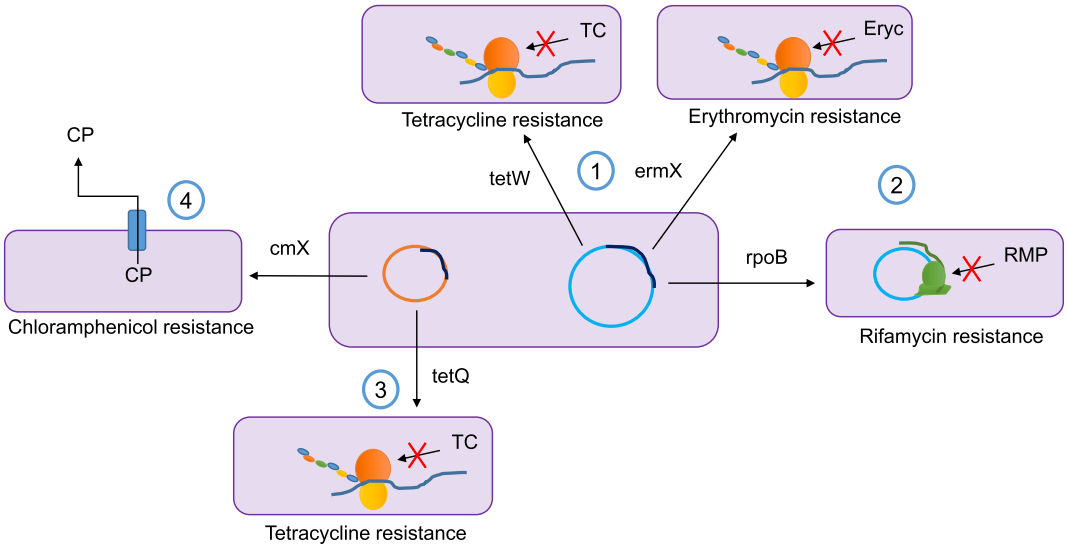

Fig. 1. Common antimicrobial resistance genes and their mechanism of action in *Bifidobacterium*; tetW, ermX and rpoB are generally present in genome: (1) tetW and ermX provide resistance against tetracycline and erythromycin, respectively, by modifying the ribosomal subunit, (2) rpoB expression results into rifamycin resistance by protecting RNA polymerase, (3) tetO present in the plasmid, provide resistance against tetracycline by modifying ribosomal subunit, (4) cmX is also found in the plasmid and provides chloramphenicol resistance by enabling antibiotic transport efflux pump.

Table 2
Antimicrobial resistance in *Bifidobacterium* strains.

S. No.	Bifidobacterial strain	Antibiotic resistance	Antibiotic resistance transfer potential	Reference
1	*Bifidobacterium animalis* subsp. *lactis* AD011	Tetracycline	NO	Ku et al. (2020)
2	*Bifidobacterium animalis* subsp. *lactis* Bl-04	Tetracycline	NO	Morovic et al. (2017)
3	*Bifidobacterium longum* LTBL16	Tetracycline	NA	Huang, Pan, Zhu, and Li (2020)
4	*Bifidobacterium breve* CECT7263	erythromycin and clindamycin	NO	Martínez et al. (2018)
5	*Bifidobacterium breve* NRBB51 and *Bifidobacterium breve* DRBB26	erythromycin	NA	Bottacini et al. (2018)
6	*Bifidobacterium breve* 139W4-23	Tetracycline	NA	Bottacini et al. (2018)
7	*Bifidobacterium breve* CNCM I-4321 and *Bifidobacterium breve* DRBB28,	aminoglycoside (streptomycin; Str)	NA	Bottacini et al. (2018)
8	*Bifidobacterium longum* W11	rifampicin	NO	Di Pierro and Pane (2021)
9	*Bifidobacterium breve* INIA P734	No resistance gene	NO	Rodrigo-Torres et al. (2021)
10	*Bifidobacterium adolescentis* 150	Amikacin Gentamicin Kanamycin Neomycin Polymyxin Streptomycin	NA	Yunes et al. (2020)

NA: No data available.

by the extreme gastrointestinal environment. To address this issue, encapsulation seems to be an effective method for entrapping the probiotics using natural or synthetic cross-linking polymers as packaging materials. Probiotic bacterial strains can be embedded and separated from the external environments for enhancing their ability to tolerate acids, bile salts, and other adverse gastrointestinal conditions (Table 3). Among different encapsulating materials, sodium alginate, a polysaccharide derived from brown algae or bacteria, is considered a biocompatible, safe, non-toxic, and economic material (Ji et al., 2019). Recently, encapsulation of *B. animalis* subsp. *lactis* BB12 in milk protein

Table 3
Different *Bifidobacterium* strains and materials used for encapsulation in the past two years.

S. No.	Bacterial strain	Encapsulating material	References
1	*Bifidobacterium pseudocatenulatum* BPG7	Alginate microgels	Gu et al. (2019)
2	*Bifidobacterium pseudocatenulatum* G7	Alginate microgels	Gu et al. (2019)
3	*Bifidobacterium animalis* subsp. *lactis* BB12	Chitosan (CS)/poly (vinyl alcohol)	Mojaveri et al. (2020)
4	*Bifidobacterium animalis* subsp. *lactis* BB12	Alginate–goats' milk–inulin matrix	Pradeep Prasanna and Charalampopoulos (2019)
5	*Bifidobacterium animalis* subsp. *lactis* BB12	Alginate-jaboticaba peel blend	Cedran, Rodrigues, and Bicas (2020)
6	*Bifidobacterium longum* DD98	Chitosan-Coated Alginate Microcapsules	Ji et al. (2019)
7	Bifidobacterium animalis subsp. *lactis* BB12	W1/O/W2 emulsion formulations	Frakolaki et al. (2020)
8	*Bifidobacterium bifidum*	Sodium alginate and zein	Riaz et al. (2019)
9	*Bifidobacterium bifidum* ATCC 35914	Polysaccharide-Protein Matrix	Iqbal, Zahoor, Huma, Jamil, and Ünlü (2019)
10	*Bifidobacterium breve* CICC 6182	Low methoxyl pectin	M. Li et al. (2019)
11	*Bifidobacterium breve* ATCC 15700	Polymeric matrices of high-amylose starch	Murúa-Pagola, Castro-Becerra, Abadía-García, Castaño-Tostado, and Amaya-Llano (2020)
12	*Bifidobacterium longum* CICC 6259	Alginate oligosaccharide (AOS), chitosan oligosaccharide	Chang, Wang, Sun, Shen, and Jiang (2020)

matrix or alginate matrix with the addition of inulin and ascorbic acid provided resistance against the harsh gastrointestinal conditions. However, protein capsules provided higher viability of the probiotic strain as compared to the alginate matrix (Kumherová, Veselá, Jokešová, Klojdová, & Horáčková, 2020). Similarly, a combination of β-cyclodextrin with whey protein isolate and sodium caseinate as encapsulating agent demonstrated a high survival rate of microencapsulated *B. bifidum* BB12 under harsh gastric conditions (Arslan-Tontul, 2020).

B. longum subsp. *infantis* CCUG 52486 has been successfully microencapsulated using the extrusion method in various matrices, including sodium alginate, sodium alginate-cow milk, sodium alginate-goat milk, and sodium alginate-casein hydrolysate. Evaluation of the survival of free and encapsulated bacterial cells revealed that cow and goat milk-based encapsulation were more efficient, which demonstrated higher probiotic cell concentrations even after refrigerated storage (Prasanna & Charalampopoulos, 2018). Emulsification and internal gelation have been reported to be efficient encapsulation techniques for the protection *B. longum* during storage and gastrointestinal transit. Sodium alginate and chitosan were used as encapsulating and coating materials. Chitosan-coated alginate microcapsules protected *B. longum* from gastrointestinal fluids like acid and bile as well as high-temperature conditions (Ji et al., 2019). Xanthan-chitosan-xanthan hydrogels have been developed as an encapsulation system, which demonstrated high survivability of *B. bifidum* BB01 under simulated gastrointestinal conditions (Chen et al., 2017). Co-extrusion technology with chitosan coating and incorporation of mannitol as prebiotic has been used for the microencapsulation of *Bifidobacterium animalis* subsp. *lactis* BB-12 (Yong, Lai, Ghazali, Chang, & Pui, 2020). Delivery of *B. longum* CFR815j in alginate starch as microencapsulated probiotic through ice-cream showed high viability and stability in simulated gastrointestinal conditions. Further, it was also observed that this encapsulation did affect the sensory characteristics of the ice-cream (Kataria, Achi, & Halami, 2018).

Inulin, as a prebiotic, has been widely used in encapsulation along with probiotics. A novel nanofiber mats consisting of chitosan/polyvinyl alcohol loaded with inulin and probiotic *B. animalis* subsp. *lactis* BB12 showed an excellent platform for the protection of living bacterial cells. Survivability of these encapsulated cells in electrospun fibers significantly increased in the presence of gastric and intestinal fluids (Mojaveri, Hosseini, & Gharsallaoui, 2020). Edible films made up of prebiotic fibers i.e. inulin and fructooligosaccharides in whey protein isolate and alginate matrices further plasticized with glycerol have been used for the encapsulation of *B. animalis* subsp. *lactis* BB12. The minimum threshold viability (10^6 CFU/g) of this probiotic strain was confirmed even after 60 days of storage (Odila Pereira et al., 2019).

Encapsulation of prebiotics along with probiotics may be beneficial for promoting microbial growth and further survival of probiotics. Several natural plant-based materials have been used for encapsulation purposes. Encapsulated Goji berry extracts consist of different polysaccharides and polyphenols, promoted the proliferation of *B. longum* Bb46. The extract also protected the viability of probiotic strains (Skenderidis, Mitsagga, Lampakis, Petrotos, & Giavasis, 2020). Encapsulation of *B. infantis* in mucilage and soluble protein extracted from chia seed and flaxseed showed high viability after refrigerated storage of 45 days (Bustamante, Oomah, Rubilar, & Shene, 2017).

B. longum encapsulated with glycerol as a cryoprotectant has been used for functional fermented sausage production. Further, it was observed that encapsulated *B. longum* may be used for the production of healthier fermented meat products (Song et al., 2018). An advanced encapsulation technique involving double emulsification well-protected a probiotic strain *B. lactis* BB-12. These encapsulated probiotics could maintain their viability even after 4 weeks of refrigerated storage. This system also provided high survival rates under simulation of the gastrointestinal system at various pH (Frakolaki, Katsouli, Giannou, & Tzia, 2020). Thiolated oxidized konjac glucomannan (sOKGM) microspheres protected the probiotic strains from the harsh gastrointestinal conditions. These microspheres protected *B. animalis* subsp. *lactis* A6 and showed enhanced gastric acid resistance and mucoadhesive properties. These encapsulated probiotics also alleviated constipation by balancing the intestinal flora in mice (Liu et al., 2020).

6. Conclusions

Different *Bifidobacterium* strains have been recommended as a probiotic. Recent research work has been focused on the understanding of mechanisms underlying the biofunctional attribute of probiotic strains. A proper diet plan consists of a suitable probiotic dose seems to be an effective preventive treatment against various infections and inflammatory diseases. It was further observed that researchers are more cautious towards the safety evaluation of the emerging probiotic strains primarily focusing on the antibiotic resistance genes and their potential transferability to other gut microflora. Besides probiotic attributes, its proliferation and survivability under gastrointestinal conditions using prebiotic supplementation and encapsulation strategies are also being explored and continuously moving towards up-gradation and advancement.

Conflict of interest and authorship conformation form

- All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.
- This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue.
- The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript

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