2025 • Vol. 3, No. 2 • pp. 1-12
Trends in Pharmaceutical Biotechnology (TPB)

Trends in Pharmaceutical Biotechnology (TPB)
Print ISSN: 3006-0516 Online ISSN: 3006-0354

Immunomodulatory Effects of *Bifidobacterium Breve*: Mechanism and Therapeutic Potential

Zahraa S. Mohammed[1, *], Ali D. Hasan[2]

[1] *Department of Applied Biotechnology, College of Biotechnology, Al-Qasim Green University, Al-Qasim, Iraq*

[2] *Department of Microbiology, College of Veterinary Medicine, Al-Qadisiya University, Al-Qadisiya, Iraq*

[*] ***Corresponding Email:*** Zahraasami2020@gmail.com

Access this article online

REVIEW ARTICLE
Received: 21.07.2025 **Revised:** 18.08.2025
Accepted: 28.09.2025
DOI: 10.57238/tpb.2025.153196.1031

OPEN ACCESS

ABSTRACT

Bifidobacterium breve is an abundant commensal bacterium in the infant intestine and an important component of many probiotic formulations. Th17 correctness, its plenitude is related to gut harmony and its decline relates to numerous inflammatory and autoimmune pathologies. We draw on a rapidly accumulating body of evidence describing the effects of B. breve on the immune system and revealing the molecular mechanisms underlying these effects. We describe its contribution to improving gut barrier function, modifying the systemic and mucosal immune systems via interaction with Toll-like receptors (TLRs), as well as the better regulation of the intra- and post-translational cytokine landscape, which in turn promoted an anti-inflammatory milieu by inducing IL-10 and TGF-β, while suppressing pro-inflammatory TNF-α, IL-6 and IL-1β. We further discuss its strain-dependent functions with reference to the extensively characterized B. breve M-16V in the treatment of NEC, allergic inflammation and IBD. This review provides detailed insights into these mechanisms and demonstrates the therapeutic potential of B. breve for the treatment of immune-related disorders, and emphasizes the necessity of comprehensive characterization of strain-specific effects in future research and clinical application. Finally Increasing evidence shows that probiotics and gut microbiota can modulate human immune function and protect against diseases mediated by impaired gut barrier or chronic inflammation.

Keywords: Bifidobacterium Breve, Cytokines, Immune-Related Disorders, Immune Response, TLR, TNF-α

1 Introduction

BIFIDOBACTERIUM breve is a common commensal bacterium in the infant gut and is a mainstay in probiotic preparations [1]. What is unique about this species is that it has co-evolved with humans, being established by vertical transmission from mother to child [2]. B. breve ranks among the most prevalent of probiotic organisms with Lactobacilli, reaching its highest levels in infancy and diminishes systematically with aging, a change often associated with increased mucosa permeability and inflammatory diseases [3].

The processes that generate well-known key metabolites such as Short-Chain Fatty Acids (SCFAs)—acetate and butyrate [4]—are central to its beneficial effects on health. Instead of passive end products of fermentation, these short-chain fatty acids represent essential mediators that reinforce gut barrier function and modulate the host immune system6. Morphologically, these Gram-positive, anaerobic bacteria can be rod- or bifid (Y-shaped) [5]. This review will first discuss its interaction with the intestinal mucus layer and its possible role in gut barrier strengthening, and then its immunomodulatory signaling via pattern-recognition receptors. Lastly, we talk about the therapeutic application of the extensively characterized strain B. breve M-16V for immune-mediated diseases [6].

A microbial ecosystem found in the human

gastrointestinal tract, the gut microbiota plays a key role in mediating host health by affecting immunological development, nutrient metabolism, and pathogen resistance [7]. Among these microorganisms are bifidobacteria, a class of Gram-positive anaerobes that play a significant role in the gut microbiota, especially in the early years of life [8]. Breastfed infants are the primary host of the early gut colonizer Bifidobacterium breve, which is established by vertical transmission [9]. The host immune system must be "taught" by this colonization during infancy [10].

The prevalence of many diseases, such as autoimmune disorders, inflammatory bowel disease (IBD), and allergies, has been correlated inversely with Bifidobacterium (including B. breve) populations, which decrease from infancy to adulthood and continue to decline into old age [11]. Since probiotics are defined as "live microorganisms, which when given in a suitable dose, result in a health benefit on the host," this association has generated a lot of interest in using B. breve as a therapeutic probiotic [12]. In this sense, B. breve has emerged as a promising candidate with particular health-beneficial characteristics and co-evolution with humans. Probiotic effects are strain-associated [13].

Bifidobacterium species, which are part of the GIT microbiota, are known to live within the intestinal mucus layer and provide the host with a number of advantageous effects. Gram-positive anaerobic bacteria belonging to the phylum Actinobacteria are known as bifidobacteria. They can be rod-shaped or have the characteristic bifid (or Y) shape. As of right now, Bifidobacterium has 55 known species and subspecies [6]. The advantages of Bifidobacterium strains, which include gut-brain-axis crosstalk, immune cell activation, and epithelial maturation, are particularly noticeable in the early stages of life [14].

Bi-directional communication along the gut-brain axis via the vagus nerve13 Secondly, this axis is influenced by the modulation of systemic inflammation by B. breve, which can potentially affect brain function14. In particular, the B. breve suppresses pro-inflammatory cytokines (TNFα, IL-1, and IL-6) [15]. Thereby relieving neuroinflammation which is a major cause of degenerative diseases [16].In addition, these microbial interactions send signals through the vagus nerve to influence stress and emotional processes in the brain [17].

After weaning and the introduction of solid food, intestinal bifidobacteria levels steadily decline until adulthood, when they are sustained at a relative abundance of roughly 10% for the duration of adulthood [11]. In particular, probiotics based on Bifidobacterium have shown promise in treating gastrointestinal disorders like Helicobacter pylori infections, irritable bowel syndrome (IBS), antibiotic-associated diarrhea, constipation, and inflammatory bowel disease (IBD). By altering the gut microbiota, increasing immunological impact, and fortifying the gut barrier, these advantages are realized [18].

Of all the probiotic organisms, lactobacilli and bifidobacteria are the most common and extensively utilized. The health benefits of bifidobacteria are well established, and they co-evolved with humans, contributing significantly to the early gut microbiota [19, 20]. Bifidobacteria are actually thought to be crucial for controlling the immune response and promoting and sustaining gut physiology, including the synthesis of mucin. Similarly, these microbes may live in the human gut because the host produces prebiotic molecules like mucin that aid in their colonization and survival [6, 21].

Bifidobacteria levels further decline in elderly people, reaching a relative abundance of 0% to 5%. Age-related changes in lifestyle and surroundings have been connected to the decline in bifidobacteria levels in the elderly. It's interesting to note that intestinal mucus thickness decreases and permeability increases in tandem with this drop in Bifidobacterium abundance [11, 22].

Although a direct correlation between reduced mucus and Bifidobacterium is still unknown, this intriguing finding raises the possibility. Although they are more prevalent in the colon, Bifidobacterium species are present in both the small intestine and the colon regardless of age. It has been noted that a number of Bifidobacterium species interact with intestinal mucus, colonize the mucus layer, eat mucus glycans, and modify the mucus layer in ways that are strain-specific. The following Bifidobacterium-mucus interactions are covered in this review of the literature:

- Adhesion of mucus;
- Degradation of mucin glycan;
- Positive modulation of goblet cell cells;
- Retention of goblet cells during inflammation; and
- Inhibition of pro-inflammatory cytokines and generation of anti-inflammatory IL-10 [6].

This connection and the evidence that these microbes are passed from mother to child via vertical transmission mechanisms [18] highlight how bifidobacteria and their human host co-evolved. Numerous illnesses, such as autoimmune diseases, IBD, and possibly cancer, have been adversely associated with the decline in this bacterial population in the gut microbiota of both adults and children [2, 18]. These microbes are therefore thought to be essential for preserving gut health and general homeostasis throughout adulthood [23].

Probiotics, including bifidobacteria, have positive effects on human gut health and have a role in sustaining a balanced microbiota community [17, 18]. Similarly, due to their ability to modulate gut microbiota, improve intestinal barrier function and exert anti-inflammatory properties also play an important hole as relevant ingredients in probiotic formulations. Bifidobacteria have been shown in numerous studies to be effective in promoting immune

function, improving gut health, and averting gastrointestinal disorders [23]

The majority of known and applied probiotic microorganisms in supplements are members of the genera Bifidobacterium and Lactobacillus as well as other lactic acid bacteria from the Lactococcus and Streptococcus genera, the bacterial species Escherichia coli (E. coli) Nissle 1917, Enterococcus fecium, Bacillus coagulans and the yeast Saccharomyces boulardii [24]. Bifidobacteria produces several metabolites, such as lactate, acetate, and indigenous vitamins. and is involved in producing SCFAs, such as butyrate, with the help of cross-feeding interactions with other gut microbes that metabolize acetate, providing health benefits [25, 26].

Bifidobacterium species are present in breastfed newborns starting on the second day of life and quickly become the predominant genus in the gut by the second week. Bifidobacterium species continue to dominate until the introduction of solid foods and the weaning away from breast milk [20]. In addition, C-section infants are still deficient in bifidobacteria at 3 days of age, despite such breastfeeding [27]. The anti-allergic effects of this species have been demonstrated in many in vitro and experimental animal studies [28]. Bifidobacterium breve M-16V was most effective among strains of Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium animalis, Lactobacillus plantarum and Lactobacillus rhamnosus to induce an anti-allergic mechanism in experimental models of FA to ovalbumin (OVA) in mice [20].

Only Bifidobacterium breve M-16V (given via oral route) significantly decreased acute allergic skin reactions to OVA and inhibited airway reactivity to methacholine, in contrast to other assessed bifidobacteria. Additionally, this strain decreased peripheral blood levels of OVA-specific IgE and IgG1, decreased the number of eosinophils in bronchoalveolar lavage fluid, and prevented splenocyte cultures from producing pro-allergic cytokines like IL-4 and IL-5 [28]. In vitro studies revealed that, in more detail, Bifidobacterium breve M-16V influenced the status of systemic Th1/Th2 equilibrium via simultaneous induction of IFN-gamma (but not IL-12) as well as IL-10 secretion along with inhibition of total IgE and IL-4 production in response to OVA stimulation [29].

These findings imply that even in premature newborns, Bifidobacterium breve M-16V can stimulate the production of regulatory TGF-β1 by Treg cells. Since preterm newborns are more likely to develop NEC and late-onset sepsis, the capacity to activate Treg cells is crucial. By colonizing the gut and causing the epithelial barrier to mature, Bifidobacterium breve M-16V may guard against harmful bacteria and their spread. This strain can also trigger anti-inflammatory processes, such as by boosting IFN-gamma secretion [20].

On the other hand, Treg cells elaborate suppressive cytokines such as TGF-β1 or IL-10 ultimately antagonizing the activation of pro-inflammatory cytokine profiles [30]. Alternatively, modification of toll-like receptor (TLR) expression may be a method whereby Bifidobacterium breve modulates the activation of inflammatory processes in the gut epithelium of premature infants. Bifidobacterium breve M-16V strongly diminished TLR-4 and increased TLR-2 expression, and inhibited expression of pro-inflammatory cytokines including IL-1 beta, IL-6, and tumor necrosis factor alpha when NEC was induced in experimental rats, and this was revealed when the probiotic was given orally [31]. TLRs are the major receptors that mediate the interactions between gut microbiota and gut epithelium that promote the immune response and intestinal epithelial barrier development [25], which is well established. In addition, the total number of Bifidobacterium was greater in the colon and caecum in all neonates as compared to the controls, and in neonates the increase lasted through weaning [32]. Furthermore, compared to the control groups, there was a significant increase in Bifidobacterium numbers in the colon and caecum during the neonatal period but not during weaning [32].

The objective of this review is to summarize the currently available knowledge about the immunomodulatory effects of Bifidobacterium breve. We will review its mechanisms of action, namely interaction with the intestinal mucus layer, gut barrier modulation and specific tailoring of the host immune system and, therapeutic potential in inflammation related diseases.

2 Bifidobacterium breve aids in Gut Barrier Function

B. breve promotes host health mainly by reinforcing the intestinal barrier [33]. It engages with the inner mucus layer by means of adhesion, glycan utilization, and goblet cell functional modulation [34]. Importantly, B. breve strains have been demonstrated to enhance the expression of key tight junction proteins, such as Occludin and ZO- [35]. Through these physical barriers, B. breve strengthen intestinal permeability, thereby avoiding pathogen translocation and pro-inflammatory substances, such as lipopolysaccharides (LPS), from passing into systemic circulation [36].

Strengthening the function of the intestinal barrier is one of the main ways that B. breve promotes its positive effects. The first line of defense against luminal pathogens and antigens is the gut epithelium, which is protected by an elastic and relatively viscous layer of mucus [37] as shown in Figure 1. It has been demonstrated that Bifidobacterium species, such as B. breve, are found in the inner mucus layer and interact with it through the following mechanisms:

- Mucusal adhesion,
- Glycan consumption, and

- Advantageous modulation of the goblet cell function [6].

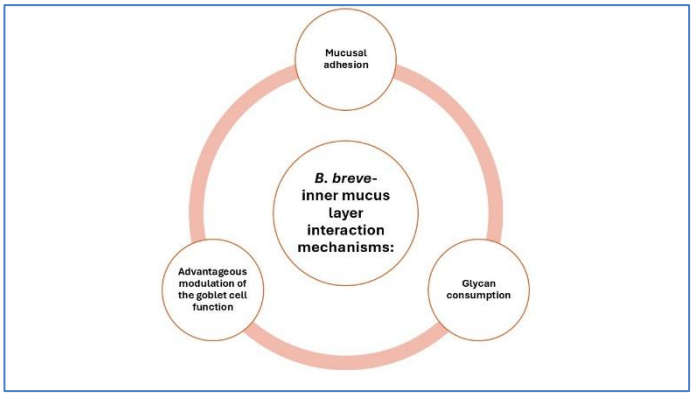

Fig. 1. B. breve-inner mucus layer interaction mechanisms.

Maintaining barrier function requires this kind of interaction. Notably, as people age, their permeability increases at the same time that their Bifidobacterium abundance declines and their intestinal mucus becomes more rarefied. This correlation has causal implications [38]. According to reports, strains of B. breve increase tight junction proteins like occludin and ZO-1, which can reduce intestinal permeability and prevent the translocation of pathogens and pro-inflammatory chemicals (lipopolysaccharides, or LPS) [39]. In addition to preventing the common [29] systemic inflammation linked to a leaky gut, B. breve strengthens this physical barrier, which supports gut homeostasis [40]. Systemic inflammatory disorders linked to gastrointestinal loss [41]. This intricate and dynamic pathway is modulated mainly by the gut microbiota. The gut–brain axis includes mechanisms of communication plus the influence of microbes via neural, immunological, endocrine and hormonal links between the gut and brain. This communication takes place through the vagus nerve, which is a crucial pathway that links the brain and the gut. Signals emitted from the gut including ones that are microbially- mediated or mechanically- induced by stretching- are sent to the brain via the vagus nerve. This pathway influences many brain processes including stress reactions and emotional processes [40]. Thus, it can transmit signals between the brain and help regulate the gut while the gut communicates with the brain by means of the vagus nerve (which has sensory fibers that report on the state of the gut, including fullness and distress).

Additionally, by controlling systemic inflammation, the gut microbiota affects the immune system, which in turn impacts brain function. Neuroinflammation, a crucial aspect of neurodegenerative diseases, is linked to chronic type of low-grade inflammation, which is defined by the ongoing production of pro-inflammatory cytokines such as TNFα, IL-1, IL-6, and interferon-gamma (IFNγ) [42]. In addition, B. breve increased tight junction (TJ) proteins, decreased intestinal epithelial cell damage, and inhibited pro-inflammatory factors. Bile acid profiling suggested B. breve increased bile acids regulatory genus (such as Clostridium sensu stricto 1 and Bifidobacterium) in gut niche and benefited intestinal bile acid deconjugation based on the gut microbiota and metabolome analysis [43]. Products made from Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium infantis, and Bifidobacterium lactic are among them. Benefits vary depending on the type. Bifidobacteria aid in the synthesis or production of B vitamins, such as folate [44]. B vitamins aid in your body's energy production. Additionally, bifidobacteria aid in the digestion of nutrients, increasing their availability to your body. Finally, Bifidobacteria contribute to the synthesis of short-chain fatty acids (SCFAs). SCFAs have been praised by researchers for their ability to improve blood sugar levels and the gut lining., blood pressure, inflammatory response, immune system, and lipid metabolism [45].

3 Immunomodulatory Mechanisms

Bifidobacterium is a Gram-positive, anaerobic, saccharoclastic, and non-motile genus of commensal bacteria. To date, it has the broadest range of any mammalian gastrointestinal tract parasite and ten phylogenetic clusters [46]. Due to Bifidobacteria's need of an oxygen free environment and metabolic precursors, cultivation in vitro requires highly specific conditions [47]. The genomic variations seen in Bifidobacterium are partially due to the gene acquisition processes necessary for the bacteria to flourish in various host ecological niches. Bifidobacterium's varied function in host immunological control is supported by its tropism and niche adaptation.

Bifidobacterium has been identified as a biomarker or immunomodulator of human disease, acting as both a protector and a driver. Many strains are frequently employed as live biotherapeutics and exhibit advantageous anti-inflammatory and immunomodulatory qualities as shown in Figure 2. These include enhanced intestinal barrier function and an increase in suppressive Foxp3+ regulatory T cells (Tregs) [48] and suppression of the Th2 and Th17 processes in the intestines.

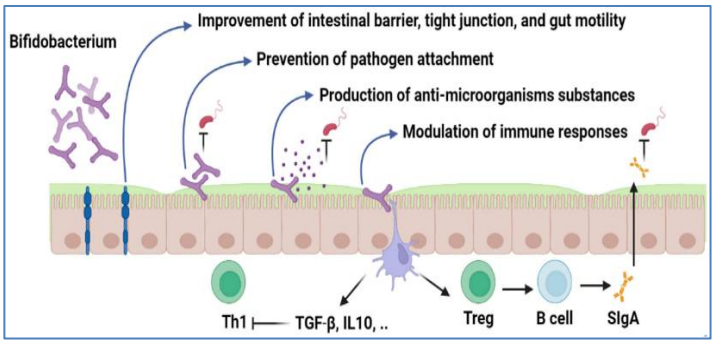

Fig. 2. Immunomodulatory action of *Bifidobacterium*.

However, a number of autoimmune and autoinflammatory diseases in humans have been linked to the lack or decrease of Bifidobacterium species. For example, the microbiome fingerprint of treatment-naïve Crohn's disease (CD) is linked to lower gut levels of many Bifidobacterium species in people [49]. There is growing evidence that the composition of the infant's gut microbiome plays a crucial role in immunological development, especially in the first three months of life, when abnormalities in gut microbial composition have the greatest impact on the immune system's development. In fact, a number of studies have shown how early gut microbiome dysbiosis, which is defined as an excess of proteobacteria [50] and lack of ecosystem function are linked to both acute and chronic immune imbalances, which can result in less common but dangerous immune-mediated disorders like Crohn's disease and type 1 diabetes as well as common conditions like colic, atopic asthma, and allergies]51]. Because it is difficult to collect samples from neonates, human immune development has been poorly known. Recent advances in systems immunology allow for the unraveling of immune cell-regulatory interactions and the tracking of immune development at the systems level [52].

Finding microbial elements that help promote healthy immune system imprinting and potentially prevent cases of autoimmunity, allergies, and possibly other immune system disorders is of tremendous interest [53]. Early-life loss of Bifidobacterium has been linked to a higher incidence of autoimmunity, according to a Finnish birth cohort [54]. Immune development is one of the many physiological processes that depend on the gut-associated bacteria. Acquisition of our earliest pioneer microbial communities, including the dominant early life genus Bifidobacterium, occurs at a critical stage of immunological maturation and training. Bifidobacteria are constituents of the resident microbiota during [55]. The biggest mass of lymphoid tissue in the human body is found in the gut-associated lymphoid tissue (GALT), which is home to a range of immune cells, including T and B lymphocytes, as well as antigen-presenting cells like macrophages and dendritic cells (DC).

The gut mucosa and luminal microbes are shielded by intestinal epithelial cells. For example, to improve defense against luminal bacteria in the gastrointestinal system, Goblet and Paneth cells release mucus layer and antimicrobial peptides, respectively. Additionally, B lymphocytes' secretory immunoglobulin A (sIgA) provides defense against the luminal microbiota [5].

3.1 *Interaction of Pattern Recognition Receptors (PRRs)*

B. breve primarily interacts with the host immune system through Pattern Recognition Receptors (PRRs), such as Toll-like receptors (TLRs) found on immunological and epithelial cells. Controlling immunological responses depends on this conversation. For instance, when B. breve M-16V was given orally to rats with NEC, it dramatically decreased the expression of pro-inflammatory TLR-4 while increasing the expression of TLR-2, which is associated with tissue healing and homeostasis [56]. Ultimately, this shift in TLR expression profile caused microglia to generate less main proinflammatory cytokines (IL-1β, IL-6, and TNF-α) [57]. One of the most significant ways that B. breve reduces excessive pro-inflammatory reactions is through this particular modification of TLR signaling [58]. It has been demonstrated that bifidobacteria interact with human immune cells and alter particular pathways related to both innate and adaptive immunity responses [59]. Responses triggered by the interactions between cells can activate different immune pathways, in a regulated or exaggerated context, and lead to a spectrum of diseases such as allergies, host behavioural alterations, and gut and skin pathology [5]. Recognition receptors are highly expressed in intestinal epithelial cells (IECs) and include pattern-recognition receptors (PRRs), nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs), toll-like receptors (TLRs), C-type lectin receptors (CLRs), RIG-I-like receptor (RLR), absent in melanoma 2 (AIM2)-like receptors (ALRs) and the oligoadenylate synthase receptor (OAS) [60, 61]. Interplay between host and microbe influences T cell development (to TH1, TH2, TH17, and regulatory (Treg) cells dictated by pro-inflammatory (and anti-inflammatory cytokines) such as transforming growth factor-β (TGF β) and interleukin-10 (IL-10) [62]. Bifidobacterium strains are also capable of modulating pro-inflammatory and anti-inflammatory cytokines. Consumption of the dairy products containing B. lactis and other favorable strains increased serum levels of pro-inflammatory cytokines (interferon-γ (IFN-γ) and interleukin 12 (IL12), and immunoglobulin (Ig)), and increased the activity of natural killer cells, indirectly suggesting that Bifidobacterium may play a role in the enhancement of the immune response and NK cell activities [63]. Bifidobacterium strains also can impact host immune responses and release mediators of macrophage function. Moreover, B. pseudocatenulatum, isolated from faecal samples grown with dendritic cells and macrophages, was shown to be a histocompatibility complex (MHC) class I enhancer and TNF, IL1 and nitric oxide (NO) producer [5].

3.2 *Cytokine Modulation and T-Cell Regulation*

A Th bias in the cytokine milieu is another aspect of B. breve's immunomodulatory function, and its capacity to raise secretory immunoglobulin A (sIgA) levels is an essential part of its advantageous action [64].

Probiotics can enhance intestinal epithelium and also modulate innate and adaptive immunity through immune mediators such as Toll-like receptors (TLRs), cytosolic

signaling receptors that includes nucleotide-binding oligomerization domain leucine-rich repeat-containing and pyrin domain-containing (NLRP) and anti-inflammatory cytokines [5]. Intracellular immunological receptors have an amazing ability to detect microbe signals and pathogen-associated molecular patterns (PAMPs). Toll-like receptor (TLR) expression is high in immune (dendritic, macrophage and natural killer (NK) cells) and non-immune (endothelial and epithelial) cells. Accumulation of inflammatory cytokines and other immune mediators triggered by TLRs when they recognize such microbe-related substances drives both innate and adaptive immune responses, through various pathways by TLRs triggering downstream immune responses [65]. Enterocytes (intestinal absorptive cells) express TLR4 as many proteins on their surface and are in close contact with microbial substances in the gut lumen; the outer membrane of the intestine is lined by enterocytes. TLR4 (Toll Like Receptor 4) recognizes LPS (lipopolysaccharide: from Gram-negative bacteria) and activates MYD88 (myeloid differentiation primary response 88) intranuclear protein. Activation of MYD88 leads to degradation of the NFκB/IKB dimer (nuclear factor kappa-light-chain-enhancer of activated B cells)/ (a NFκB inhibitory protein). At this point, the NFκB complex is translocated into the nucleus, where upon the disintegration of the NF-κB/IKB dimer a large number of pro-inflammatory cytokines, tumor necrosis factor-alpha (TNFα), and interleukin gene transcription occur [66].

Bifidobacterium probiotics and bacterial metabolites have been shown to influence innate immune response in the intestine and transcriptional activity of enterocytes. Methods of PCM, such as a diet with a single probiotic strain or a combination of probiotic strain, for example, B. infantis and L. acidophilus produced high expression of inflammatory inhibitors (Tollip and SIGIRR) and significantly decreased expression of IL-1β, IL-8, IL-6, TLR2 mRNA, and high expression of TLR4 mRNA (Thiyagarajan et al. 2023). It was also shown that Tollip and SIGIRR mRNA levels were up-regulated and IL-6, IL-8, and TLR2 were down-regulated in primary enterocyte cultures of NEC tissue exposed to PCM [67].

3.3 Reducing Pro-Inflammatory Cytokines

The ability of B. breve to reduce production of pro-inflammatory and pro-allergic cytokines. In ovalbumin (OVA)-induced allergy models, treatment groups supplemented with B. breve M-16V demonstrated a decrease in OVA-specific IgE and IgG1 in plasma peripheral blood levels and inhibition of IL4 and IL5 producing splenocytes [68]. At the level of the gut mucosa, bifidobacteria also have an impact on immunological responses. Gene expression analysis of the colon homogenates of Bifidobacterium adolescentis-treated mice showed decreased levels of proinflammatory cytokines (TNFα, IL-6, IL-1β, IL-18, IL-22, and IL-9) but increased levels of an anti-inflammatory cytokine (IL-10) as well as Th2-type cytokines (IL-4 and IL-5) as compared with controls. Likewise, colons of colitic mice treated with ATCC15703 show greater numbers of Tregs. Likewise, germ-free mice that were colonized with Bifidobacterium bifidum strain PRI1 have an increased frequency of Tregs in the colonic lamina propria [69]. Colon lamina propria dendritic cells (DCs) show increased expression of early activation markers in mRNA following PRI1 treatment including IL-10, GM-CSF, TGFβ1, Indoleamine 2,3-dioxygenase, PTGS2, and PD-1 along with the co stimulatory markers CD86 and CD40. Upon in vitro treatment of DCs with PRI1 and subsequent co-culture with naïve CD4 T cells, enhanced Treg induction and elevated IL-10 production are observed [47]. At the level of species and strains, Bifidobacterium immunomodulatory programs are diverse in phenotype and robustness, with pro-inflammatory effects reported (70). The phylogeny of Bifidobacterium was proven to be unrelated to its immunomodulatory effect [71]. Cross-feeding is the manner in which microbial species eat through and release metabolites. Bifidobacteria are key genera for metabolite production used in other genus as well as in several Bifidobacterium species and strains [72]. Probiotics have specific cell envelope molecules with immunomodulatory properties that can reduce pro-inflammatory cytokines and increase production of the anti-inflammatory IL-10, induce T regulatory cells (Tregs), and facilitate improvement in protection from radiation response. One of the most extensively studied anti-inflammatory probiotic substances is the capsular polysaccharide A (PSA) of Bacteroides fragilis. Oral administration of PSA, a zwitterionic polysaccharide, is both protective and therapeutic in murine models of multiple sclerosis and colitis, by stimulating IL-10 secretion from Tregs. The requirement of TLR2 and MHCII for PSA protection is likely due to TLR2 signaling in plasmacytoid dendritic cells, which induces Tregs and IL-10 [73]. Furthermore, in a murine colitis model, glycosphingolipids from B. fragilis decrease the levels of invariant natural killer T cell (iNKT) in the intestinal lamina propria (74). Recently, B. fragilis PSA was shown to enhance resistance to viral infection in a mouse model through colonic DC activation and TLR4-dependent IFN-β production by [75].

3.4 Stimulation of Pathways that Promote Anti-inflammatory and Regulatory Pathways

The second function is that B. breve can produce anti-inflammatory cytokines at the same time. It has been shown that this particular strain causes systemic release of IFN-γ and IL-10, which biases the systemic Th1/Th2 balance toward a more advantageous, controlled phenotype [47]. Furthermore, B. Breve can stimulate regulatory T cells (Tregs), a master regulator of

immunological tolerance, to secrete TGF-β1 [76]. Its therapeutic promise for conditions including IBD and allergies is based on the activation of Treg cells, which plays a crucial role in regulating inflammatory processes [77].

3.5 *Production of Beneficial Metabolites*

Some of the metabolites that B. breve releases, including lactate and acetate, can crossfeed on other gut microorganisms and produce short-chain fatty acids (SCFAs), like butyrate, which are advantageous for host health [78]. SCFAs have anti-inflammatory characteristics that include strengthening epithelial barrier, promoting Treg development, and inhibiting histone deacetylases [79]. Additionally, colonocytes, which support intestinal health, use butyrate as their primary energy source [80]. ndustrial applications of Bifidobacteria, one of the dominant genera in the human gut microbiota, include several probiotic strains.

Hexose carbohydrates are fermented by bifidobacteria to produce lactic and acetic acids among other beneficial metabolites [81]. These metabolites support immunological function and intestinal barrier integrity [82]. Bifidobacterial species carry a metabolic pathway to generate aromatic lactic acids (ALAs) from the consumption of dietary aromatic amino acids. Aromatic lactic acids such as indole-3-lactic acid (ILA) have also been found to have anti-inflammatory activities through the aryl hydrocarbon receptor (Ahr) [83, 84]. Some bifidobacteria also create conjugated linoleic acid and vitamins in addition to the metabolites mentioned above [84] which have the ability to influence host physiology and function as signaling molecules [81, 85]. Small intestine microbes are crucial to host physiology, including immunity, metabolism, and gastrointestinal motility [86]. Bifidobacteria have been shown to produce SCFAs and SCFA precursors, such as lactic acid, as well as vitamin B12 and amino acids through fermentation [70]. However, studies have also shown that bifidobacteria are able to shuttle vitamin B12 into the cytoplasm [87].

Therefore, bifidobacteria, which produce lactic acid and acetic acid via the bifidus shunt where 2 moles of glucose yield 3 moles of acetic acid and 2 moles of lactic acid. In the end, genomic analysis has suggested for bifidobacteria the production of all 20 amino acids, with serine being intermediated via glycerate-3-phosphate or proline through 2-oxoglutarate.11 [88].

4 Strain-Specific Effects and Clinical Implications

The therapeutic effects of B. breve are strain-specific, the well-characterized strain B. breve M-16V is superior to other lactobacilli and bifidobacteria in eliciting anti-allergic mechanism potentials [64]. Because it has been shown to reduce allergic skin reactions, suppress airway reactivity, and offer protection against NEC, it is also advantageous in experimental models [89].

Through epithelial barrier maturation and TLR-4 mediated inflammation suppression, B. breve (M-16V) protects preterm newborns against pathogenic bacterial translocation and NEC development, according to preclinical efficacy findings in this work [1].

It may be useful in preventing and treating allergy illnesses including asthma and atopic dermatitis because of its capacity to restore the Th1/Th2 balance and stimulate Treg function [77]. Breastfed infants' guts are dominated by B. breve, which has also been isolated from human milk. It is non cytotoxic, has immune-stimulating properties, has antibacterial efficacy against human infections, and lacks transmissible antibiotic resistance characteristics. The applications of B. breve strains, mostly for the prevention and treatment of pediatric diseases, are discussed in this review. The target pathologies include celiac disease, obesity, allergy and neurological illnesses, and common gut ailments including diarrhea and infant colic [90]. Breve Bifidobacterium A popular probiotic strain for babies is M-16V. It has been shown that M-16V may be able to prevent children from contracting allergy disorders and the deadly necrotizing enterocolitis (NEC). This study understands the potential advantages of M-16V for newborn health, namely in the prevention and treatment of immune-mediated diseases in neonates and premature birth difficulties [1]. Inflammatory bowel disease (IBD): B. breve can target IBD by altering damage-associated molecular patterns (DAMPs), TLR signaling pathways, and immune responses. IBD is characterized by chronic intestinal inflammation and associated disruption of the epithelial barrier function [77, 91]. Analysis of a randomized experiment on the impact of Bifidobacterium breve M-16V supplementation on fecal bifidobacteria in growth-restricted extremely preterm infants [92]. Early M-16V treatment may improve bifidobacterial colonization in preterm infants (gestation < 33 weeks), according to several implementation cohort studies for babies with low birth weights [92, 93].

5 Conclusion

This review demonstrates that Bifidobacterium breve does not only play a role of a symbiotic organism but a key modulator of intestinal immunity and inflammation17. Its action modes are multiple: direct strengthening of the gut barrier, intricate host–microbe communication through Pattern Recognition Receptors (PRRs), and exquisitely tuned cytokine matrix conducive to tolerance18. Here, we confirm the prevention and treatment of immune-mediated diseases19 with specific strains M-16V. Large human clinical trials and the evaluation of synergistic synbiotic combinations are warranted to fully exploit the therapeutic potential of this microbial partner20202020

Bifidobacterium breve is an important

immunomodulator for normal gut homeostasis and gut immune system development; Bifidobacterium breve. It acts by several mechanisms: direct reinforcement of the gut barrier and elaboration of complex signaling with the host through PRRs as well as masterful modulation of the cytokine matrix to inhibit excess inflammation and promote tolerance.

Compelling support exists for B. breve use—especially specific strains such as M-16V—for the prevention and treatment of immune-mediated diseases. Nonetheless, future studies should focus on several aspects, including:

- Large-scale and robust human clinical trials to test the efficacy in target populations;
- More precise understanding of the molecular pathways activated by different B. breve strains; and
- The synergistic combinations between B. breve with a prebiotic (synbiotics) or other probiotic strains to promote its beneficial effects.

Overall, Bifidobacterium breve is a permanent proof by showing how our microbial friends can be used much more creatively for treating many types of inflammatory and immune-related diseases.

Conflict of Interest: The author declares no conflict of interest.
Financing: The study was performed without external funding.
Ethical consideration: The study was approved by Al-Qasim Green University, Al-Qasim, Iraq.

REFERENCES

[1] Wong CB, Iwabuchi N, Xiao J-z. Exploring the science behind *Bifidobacterium* breve M-16V in infant health. *Nutrients*. 2019;11(8):1724. doi: 10.3390/nu11081724

[2] Milani C, Mancabelli L, Lugli GA, Duranti S, Turroni F, Ferrario C, et al. Exploring vertical transmission of bifidobacteria from mother to child. *Appl Environ Microbiol*. 2015;81(20):7078-87. doi: 10.1128/AEM.02037-15

[3] Saturio S, Nogacka AM, Alvarado-Jasso GM, Salazar N, de Los Reyes-Gavilán CG, Gueimonde M, et al. Role of bifidobacteria on infant health. *Microorganisms*. 2021;9(12):2415. doi: 10.3390/microorganisms9122415

[4] Facchin S, Bertin L, Bonazzi E, Lorenzon G, De Barba C, Barberio B, et al. Short-chain fatty acids and human health: from metabolic pathways to current therapeutic implications. *Life*. 2024;14(5):559. doi: 10.3390/life14050559

[5] Sadeghpour Heravi F, Hu H. *Bifidobacterium*: host–microbiome interaction and mechanism of action in preventing common gut-microbiota-associated complications in preterm infants: a narrative review. *Nutrients*. 2023;15(3):709. doi: 10.3390/nu15030709

[6] Gutierrez A, Pucket B, Engevik MA. Bifidobacterium and the intestinal mucus layer. *Microbiome Res Rep*. 2023;2(4):36. doi: 10.20517/mrr.2023.37

[7] Hou K, Wu Z-X, Chen X-Y, Wang J-Q, Zhang D, Xiao C, et al. Microbiota in health and diseases. Sig Transduct Target Ther. 2022;7:135. doi: 10.1038/s41392-022-00974-4

[8] Saturio S, Nogacka AM, Alvarado-Jasso GM, Salazar N, de Los Reyes-Gavilán CG, Gueimonde M, et al. Role of bifidobacteria on infant health. *Microorganisms*. 2021;9(12):2415. doi: 10.3390/microorganisms9122415

[9] Wu S, Luo G, Jiang F, Jia W, Li J, Huang T, et al. Early life bifidobacterial mother–infant transmission: greater contribution from the infant gut to human milk revealed by microbiomic and culture-based methods. mSystems. 2025;10:e00480-25. doi: 10.1128/msystems.-25

[10] Pantazi AC, Balasa AL, Mihai CM, Chisnoiu T, Lupu VV, Kassim MAK, et al. Development of gut microbiota in the first 1000 days after birth and potential interventions. *Nutrients*. 2023;15(16):3647. doi: 10.390/nu15163647

[11] Arboleya S, Watkins C, Stanton C, Ross RP. Gut bifidobacteria populations in human health and aging. *Front Microbiol*. 2016;7:1204. doi: 10.3389/fmicb.2016.01204

[12] Redondo-Useros N, Nova E, González-Zancada N, Díaz LE, Gómez-Martínez S, Marcos A. Microbiota and lifestyle: a special focus on diet. *Nutrients*. 2020;12(6):1776. doi: 10.3390/nu12061776

[13] Kujawska M, Neuhaus K, Huptas C, Jiménez E, Arboleya S, Schaubeck M, et al. Exploring the potential probiotic properties of Bifidobacterium breve DSM 32583—A novel strain isolated from human milk. *Probiotics Antimicro Prot*. 2024;17:4171–85. doi: 10.1007/s12602-024-0346-9

[14] Lin C, Lin Y, Zhang H, Wang G, Zhao J, Zhang H, et al. Intestinal 'infant-type'bifidobacteria mediate immune system development in the first 1000 days of life. *Nutrients*. 2022;14(7):1498. doi: 10.3390/nu14071498

[15] Wang X, Chen Z, Geng B, Cai J. The Bidirectional Signal Communication of Microbiota-Gut-Brain Axis in Hypertension. *Int J Hypertens*. 2021;2021:8174789. doi: 10.1155/2021/

[16] Adamu A, Li S, Gao F, Xue G. The role of neuroinflammation in neurodegenerative diseases: current understanding and future therapeutic targets. *Front Aging Neurosci*. 2024;16:1347987. doi: 10.3389/fnagi.2024

[17] Faraji N, Payami B, Ebadpour N, Gorji A. Vagus nerve stimulation and gut microbiota interactions: A novel therapeutic avenue for neuropsychiatric disorders. *Neurosci Biobehav Rev*. 2025;169:105990.

doi: 10.1016/j.neubiorev.2024

[18] Bocchio F, Mancabelli L, Milani C, Lugli GA, Tarracchini C, Longhi G, et al. Compendium of *Bifidobacterium*-based probiotics: characteristics and therapeutic impact on human diseases. *Microbiome Res Rep*. 2024;4(1):2. doi: 10.20517/mrr.2024.52

[19] Piqué N, Berlanga M, Miñana-Galbis D. Health benefits of heat-killed (Tyndallized) probiotics: an overview. *Int J Mol Sci*. 2019;20(10):2534. doi: 10.3390/ijms20102534

[20] Cukrowska B, Bierła JB, Zakrzewska M, Klukowski M, Maciorkowska E. The relationship between the infant gut microbiota and allergy. The role of *Bifidobacterium* breve and prebiotic oligosaccharides in the activation of anti-allergic mechanisms in early life. *Nutrients*. 2020;12(4):946. doi: 10.3390/nu12040946

[21] Turroni F, Duranti S, Bottacini F, Guglielmetti S, Van Sinderen D, Ventura M. *Bifidobacterium bifidum* as an example of a specialized human gut commensal. *Front Microbiol*. 2014;5:437. doi: 10.3389/fmicb.2014.00437

[22] Sovran B, Hugenholtz F, Elderman M, Van Beek AA, Graversen K, Huijskes M, et al. Age-associated impairment of the mucus barrier function is associated with profound changes in microbiota and immunity. *Sci Rep*. 2019;9:1437. doi: 10.038/s41598-018-35228-3

[23] Martin AJ, Serebrinsky-Duek K, Riquelme E, Saa PA, Garrido D. Microbial interactions and the homeostasis of the gut microbiome: the role of Bifidobacterium. *Microbiome Res Rep*. 2023;2(3):17. doi: 0.20517/mrr.2023.10

[24] Azad MAK, Sarker M, Li T, Yin J. Probiotic species in the modulation of gut microbiota: an overview. *BioMed Res Int*. 2018;2018(1):9478630. doi: 10.1155/2018/

[25] Tarracchini C, Lugli GA, Mancabelli L, van Sinderen D, Turroni F, Ventura M, et al. Exploring the vitamin biosynthesis landscape of the human gut microbiota. *msystems*. 2024;9:e00929-24. doi: 10.1128/msystems.-24

[26] Alessandri G, Ossiprandi MC, MacSharry J, van Sinderen D, Ventura M. Bifidobacterial dialogue with its human host and consequent modulation of the immune system. *Front Immunol*. 2019;10:2348. doi: 10.3389/fimmu.2019.02348

[27] Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Nat Acad Sci*. 2010;107(26):11971-5. doi: 10.1073/pnas.1002601107

[28] Hougee S, Vriesema A, Wijering S, Knippels L, Folkerts G, Nijkamp F, et al. Oral treatment with probiotics reduces allergic symptoms in ovalbumin-sensitized mice: a bacterial strain comparative study. *Int Arch Allergy Immunol*. 2010;151(2):107-17. doi: 10.1159/000236000

[29] Inoue Y, Iwabuchi N, Xiao J-z, Yaeshima T, Iwatsuki K. Suppressive effects of Bifidobacterium breve strain M-16V on T-helper type 2 immune responses in a murine model. *Biol Pharm Bull*. 2009;32(4):760-3. doi: 10.1248/bpb.32.760

[30] Akdis CA, Akdis M. Mechanisms of immune tolerance to allergens: role of IL-10 and Tregs. *J Clin Invest*. 2014;124(11):4678-80. doi: 10.1172/JCI78891

[31] Satoh T, Izumi H, Iwabuchi N, Odamaki T, Namba K, Abe F, et al. *Bifidobacterium breve* prevents necrotising enterocolitis by suppressing inflammatory responses in a preterm rat model. *Benef Microbes*. 2016;7(1):75-82. doi: 10.3920/BM2015.0035

[32] Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell*. 2004;118(2):229-41. doi: 10.1016/j.cell.2004.07.002

[33] Sánchez B, González-Rodríguez I, Arboleya S, López P, Suárez A, Ruas-Madiedo P, et al. The effects of *Bifidobacterium breve* on immune mediators and proteome of HT29 cells monolayers. *BioMed Res Int*. 2015;2015:479140. doi: 10.1155/2015/479140

[34] Birchenough GM, Johansson ME, Gustafsson JK, Bergström JH, Hansson G. New developments in goblet cell mucus secretion and function. *Mucosal Immunol*. 2015;8(4):712-9. doi: 10.1038/mi.2015.32

[35] Abdelhamid M, Counts SE, Zhou C, Hida H, Kim J-I, Michikawa M, et al. Protective effects of Bifidobacterium breve MCC1274 as a novel therapy for Alzheimer's disease. *Nutrients*. 2025;17(3):558. doi: 10.3390/nu17030558

[36] Di Vincenzo F, Del Gaudio A, Petito V, Lopetuso LR, Scaldaferri F. Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. *Intern Emerg Med*. 2024;19(2):275-93. doi: 10.1007/s11739-023-03374-w

[37] Hughes KR, Harnisch LC, Alcon-Giner C, Mitra S, Wright CJ, Ketskemety J, et al. *Bifidobacterium breve* reduces apoptotic epithelial cell shedding in an exopolysaccharide and MyD88-dependent manner. *Open Biol*. 2017;7(1):160155. doi: 10.1098/rsob

[38] Du X, Liu M, Li J, Liu Y, Ge S, Gao H, et al. *Bifidobacterium animalis* Supplementation Improves Intestinal Barrier Function and Alleviates Antibiotic-Associated Diarrhea in Mice. *Foods*. 2025;14(10):1704. doi: 10.3390/foods14101704

[39] Abdulqadir R, Engers J, Al-Sadi R. Role of

Bifidobacterium in modulating the intestinal epithelial tight junction barrier: current knowledge and perspectives. *Curr Dev Nutr*. 2023;7(12):102026. doi: 10.1016/j.cdnut.2023

[40] Abdelhamid M, Counts SE, Zhou C, Hida H, Kim J-I, Michikawa M, et al. Protective effects of Bifidobacterium breve MCC1274 as a novel therapy for Alzheimer's disease. *Nutrients*. 2025;17(3):558. doi: 10.3390/nu17030558

[41] Aleman RS, Moncada M, Aryana KJ. Leaky gut and the ingredients that help treat it: a review. *Molecules*. 2023;28(2):619. doi: 10.3390/molecules28020619

[42] Sun M, Wu W, Liu Z, Cong Y. Microbiota metabolite short chain fatty acids, GPCR, and inflammatory bowel diseases. *J Gastroenterol*. 2017;52(1):1-8. doi: 10.1007/s00535-016-1242-9

[43] Li Y, Xu H, Zhou L, Zhang Y, Yu W, Li S, et al. *Bifidobacterium breve* protects the intestinal epithelium and mitigates inflammation in colitis via regulating the gut microbiota–cholic acid pathway. *J Agric Food Chem*. 2024;72(7):3572-83. doi: 10.1021/acs.jafc.3c08527

[44] Yoshii K, Hosomi K, Sawane K, Kunisawa J. Metabolism of dietary and microbial vitamin B family in the regulation of host immunity. *Front Nutr*. 2019;6:434971. doi: 10.3389/fnut.2019.00048

[45] Nogal A, Valdes AM, Menni C. The role of short-chain fatty acids in the interplay between gut microbiota and diet in cardio-metabolic health. *Gut Microbes*. 2021;13(1):1897212. doi: 10.1080/19490976.2021.1897212

[46] Lugli GA, Milani C, Duranti S, Alessandri G, Turroni F, Mancabelli L, et al. Isolation of novel gut bifidobacteria using a combination of metagenomic and cultivation approaches. *Genome Biol*. 2019;20:96. doi: 10.1186/s13059-019-1711-6

[47] Gavzy SJ, Kensiski A, Lee ZL, Mongodin EF, Ma B, Bromberg JS. *Bifidobacterium* mechanisms of immune modulation and tolerance. *Gut Microbes*. 2023;15(2):2291164. doi: 10.1080/19490976.2023.2291164

[48] Guo S, Gillingham T, Guo Y, Meng D, Zhu W, Walker WA, et al. Secretions of *Bifidobacterium infantis* and Lactobacillus acidophilus protect intestinal epithelial barrier function. *J Pediatr Gastroenterol Nutr*. 2017;64(3):404-12. doi: 10.1097/MPG.0000000000001310

[49] Gevers D, Kugathasan S, Denson LA, Vázquez-Baeza Y, Van Treuren W, Ren B, et al. The treatment-naive microbiome in new-onset Crohn's disease. *Cell Host Microbe*. 2014;15(3):382-92. doi: 10.1016/j.chom.2014.02.005

[50] Shin N-R, Whon TW, Bae J-W. Proteobacteria: microbial signature of dysbiosis in gut microbiota. *Trends Biotechnol*. 2015;33(9):496-503. doi: 10.1016/j.tibtech.2015.06.011

[51] Henrick BM, Rodriguez L, Lakshmikanth T, Pou C, Henckel E, Arzoomand A, et al. Bifidobacteria-mediated immune system imprinting early in life. *Cell*. 2021;184(15):3884-98. E11. doi: 10.1016/j.cell.2021.05.030

[52] Davis MM, Brodin P. Rebooting human immunology. *Annu Rev Immunol*. 2018;36:843-64. doi: 10.1146/annurev-immunol-042617-53206

[53] Renz H, Skevaki C. Early life microbial exposures and allergy risks: opportunities for prevention. *Nat Rev Immunol*. 2021;21:177-91. doi: 10.1038/s41577-020-00420-y

[54] Vatanen T, Kostic AD, d'Hennezel E, Siljander H, Franzosa EA, Yassour M, et al. Variation in microbiome LPS immunogenicity contributes to autoimmunity in humans. *Cell*. 2016;165(4):842-53. doi: 10.1016/j.cell.2016.04.007

[55] O'Neill I, Schofield Z, Hall LJ. Exploring the role of the microbiota member *Bifidobacterium* in modulating immune-linked diseases. *Emerg Top Life Sci*. 2017;1(4):333-49. doi: 10.1042/ETLS20170058

[56] Mukherjee S, Karmakar S, Babu SPS. TLR2 and TLR4 mediated host immune responses in major infectious diseases: a review. *Braz J Infect Dis*. 2016;20(2):193-204. doi: 10.1016/j.bjid.2015.10.011

[57] Rodríguez-Gómez JA, Kavanagh E, Engskog-Vlachos P, Engskog MK, Herrera AJ, Espinosa-Oliva AM, et al. Microglia: agents of the CNS pro-inflammatory response. *Cells*. 2020;9(7):1717, doi: 10.3390/cells9071717

[58] Chen L, Yu J. Modulation of Toll-like receptor signaling in innate immunity by natural products. *Int Immunopharmacol*. 2016;37:65-70. doi: 10.1016/j.intimp.2016.02.005

[59] Ruíz García L, Delgado S, Ruas-Madiedo P, Sánchez García B, Margolles Barros A. Bifidobacteria and their molecular communication with the immune system. *Front Microbiol*. 2017;2017:8. doi: 10.3389/fmicb.2017.02345

[60] Inturri R, Stivala A, Furneri P, Blandino G. Growth and adhesion to HT-29 cells inhibition of Gram-negatives by *Bifidobacterium longum* BB536 e *Lactobacillus rhamnosus* HN001 alone and in combination. *Eur Rev Med Pharmacol Sci*. 2016;20:4943-9.

[61] Macpherson AJ, Slack E, Geuking MB, McCoy KD. The mucosal firewalls against commensal intestinal microbes. *Semin Immunopathol*. 2009;31:145-9. doi: 10.1007/s00281-009-0174-3

[62] Owaga E, Hsieh R-H, Mugendi B, Masuku S, Shih C-K, Chang J-S. Th17 cells as potential probiotic therapeutic targets in inflammatory bowel diseases. *Int J Mol Sci*. 2015;16(9):20841-58. doi:

10.3390/ijms160920841

[63] Lee A, Lee YJ, Yoo HJ, Kim M, Chang Y, Lee DS, et al. Consumption of dairy yogurt containing Lactobacillus paracasei ssp. paracasei, Bifidobacterium animalis ssp. lactis and heat-treated Lactobacillus plantarum improves immune function including natural killer cell activity. *Nutrients*. 2017;9(6):558. doi: 10.3390/nu9060558

[64] Ren J, Zhao Y, Huang S, Lv D, Yang F, Lou L, et al. Immunomodulatory effect of *Bifidobacterium breve* on experimental allergic rhinitis in BALB/c mice. *Exp Ther Med*. 2018;16(5):3996-4004. doi: 10.3892/etm.2018.6704

[65] Narayanan KB, Park HH. Toll/interleukin-1 receptor (TIR) domain-mediated cellular signaling pathways. *Apoptosis*. 2015;20:196-209. doi: 10.1007/s10495-014-1073-1

[66] Dąbek J, Kułach A, Gąsior Z. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB): a new potential therapeutic target in atherosclerosis? *Pharmacol Rep*. 2010;62(5):778-83. doi: 10.1016/S734-140(10)70338-8

[67] Ganguli K, Meng D, Rautava S, Lu L, Walker WA, Nanthakumar N. Probiotics prevent necrotizing enterocolitis by modulating enterocyte genes that regulate innate immune-mediated inflammation. *Am J Physiol Gastrointest Liver Physiol*. 2013;304(2):G132-G41. doi: 10.1152/ajpgi.00142.2012

[68] Baffoni L, Gaggìa F, Di Gioia D. Therapeutic Microbiology: The Role of *Bifidobacterium breve* as Food Supplement for the Prevention/Treatment of Paediatric Diseases. *Nutrients*. 2018;10(11):E1723. doi: 10.3390/nu10111723

[69] Verma R, Lee C, Jeun E-J, Yi J, Kim KS, Ghosh A, et al. Cell surface polysaccharides of *Bifidobacterium bifidum* induce the generation of Foxp3+ regulatory T cells. *Sci Immunol*. 2018;3(28):eaat6975. doi: 10.1126/sciimmunol.aat6975

[70] Nicola S, Amoruso A, Deidda F, Pane M, Allesina S, Mogna L, et al. Searching for the perfect homeostasis: five strains of Bifidobacterium longum from centenarians have a similar behavior in the production of cytokines. *J Clin Gastroenterol*. 2016;50:S126-S30. doi: 10.1097/MCG.0000000000000678

[71] Geva-Zatorsky N, Sefik E, Kua L, Pasman L, Tan TG, Ortiz-Lopez A, et al. Mining the human gut microbiota for immunomodulatory organisms. *Cell*. 2017;168(5):928-43. E11. doi: 10.1016/j.cell.2017.01.022

[72] Rivière A, Gagnon M, Weckx S, Roy D, De Vuyst L. Mutual cross-feeding interactions between *Bifidobacterium longum* subsp. *longum* NCC2705 and Eubacterium rectale ATCC 33656 explain the bifidogenic and butyrogenic effects of arabinoxylan oligosaccharides. *Appl Environ Microbiol*. 2015;81(22):7767-81. doi: 10.1128/AEM.02089-15

[73] Zamora-Pineda J, Kalinina O, Osborne BA, Knight KL. Probiotic molecules that inhibit inflammatory diseases. *Appl Sci*. 2022;12(3):1147. doi: 10.3390/app12031147

[74] An D, Oh SF, Olszak T, Neves JF, Avci FY, Erturk-Hasdemir D, et al. Sphingolipids from a symbiotic microbe regulate homeostasis of host intestinal natural killer T cells. *Cell*. 2014;156(1):123-33. doi: 10.1016/j.cell.2013.11.042

[75] Stefan KL, Kim MV, Iwasaki A, Kasper DL. Commensal microbiota modulation of natural resistance to virus infection. *Cell*. 2020;183(5):1312-24. E10. doi: 10.016/j.cell.2020.10.047

[76] Moreau JM, Velegraki M, Bolyard C, Rosenblum MD, Li Z. Transforming growth factor–β1 in regulatory T cell biology. *Sci Immunol*. 2022;7(69):eabi4613. doi: 10.1126/sciimmunol.abi4613

[77] Conrad ML, Barrientos G, Cai X, Mukherjee S, Das M, Stephen-Victor E, et al. Regulatory T cells and their role in allergic disease. *Allergy*. 2025;80(1):77-93. doi: 10.1111/all.16326

[78] Liu M, Lu Y, Xue G, Han L, Jia H, Wang Z, et al. Role of short-chain fatty acids in host physiology. *Anim Model Exp Med*. 2024;7(5):641-52. doi: 10.1002/ame2.12464

[79] Ney L-M, Wipplinger M, Grossmann M, Engert N, Wegner VD, Mosig AS. Short chain fatty acids: key regulators of the local and systemic immune response in inflammatory diseases and infections. *Open Biol*. 2023;13(3):230014. doi: 10.1098/rsob

[80] Hodgkinson K, El Abbar F, Dobranowski P, Manoogian J, Butcher J, Figeys D, et al. Butyrate's role in human health and the current progress towards its clinical application to treat gastrointestinal disease. *Clin Nutr*. 2023;42(2):61-75. doi: 10.1016/j.clnu.2022.10.024

[81] Sen A, Nishimura T, Yoshimoto S, Yoshida K, Gotoh A, Katoh T, et al. Comprehensive analysis of metabolites produced by co-cultivation of *Bifidobacterium breve* MCC1274 with human iPS-derived intestinal epithelial cells. *Front Microbiol*. 2023;14:1155438. doi: 10.3389/fmicb.2023

[82] Naoki M. GPR31-dependent dendrite protrusion of intestinal CX3CR1+ cells by bacterial metabolites: Doctoral Dissertation, Osaka University, Japan; 2019.

[83] Sakurai T, Horigome A, Odamaki T, Shimizu T, Xiao J-Z. Production of hydroxycarboxylic acid receptor 3 (HCA3) ligands by *bifidobacterium*. *Microorganisms*. 2021;9(11):2397. doi: 10.3390/microorganisms9112397

[84] Meng D, Sommella E, Salviati E, Campiglia P, Ganguli K, Djebali K, et al. Indole-3-lactic acid, a metabolite of tryptophan, secreted by *Bifidobacterium longum* subspecies *infantis* is anti-inflammatory in the immature intestine. *Pediatr Res*. 2020;88:209-17. doi: 10.1038/s41390-019-0740-x

[85] Mei Y, Chen H, Yang B, Zhao J, Zhang H, Chen W. Research progress on conjugated linoleic acid bio-conversion in *Bifidobacterium*. *Int J Food Microbiol*. 2022;369:109593. doi: 10.1016/j.ijfoodmicro.2022

[86] Vonaesch P, Araújo JR, Gody J-C, Mbecko J-R, Sanke H, Andrianonimiadana L, et al. Stunted children display ectopic small intestinal colonization by oral bacteria, which cause lipid malabsorption in experimental models. *Proc Nat Acad Sci*. 2022;119(41):e2209589119. doi: 10.1073/pnas

[87] Tindjau R, Chua J-Y, Liu S-Q. Growth, substrate, and metabolite changes of probiotic Bifidobacterium animalis subsp. Lactis in soy (tofu) whey. *Fermentation*. 2023;9(12):1024. doi: 10.3390/fermentation9121024

[88] Lee J-H, O'Sullivan DJ. Genomic insights into bifidobacteria. *Microbiol Mol Biol Rev*. 2010;74(3):378-416. doi: 10.1128/mmbr.00004-10

[89] Lu L, Lu J, Yu Y, Claud E. Necrotizing enterocolitis intestinal barrier function protection by antenatal dexamethasone and surfactant-D in a rat model. *Pediatr Res*. 2021;90:768-75. doi: 10.1038/s41390-020-01334-0

[90] Bozzi Cionci N, Baffoni L, Gaggìa F, Di Gioia D. Therapeutic microbiology: the role of *Bifidobacterium breve* as food supplement for the prevention/treatment of paediatric diseases. *Nutrients*. 2018;10(11):1723. doi: 10.3390/nu10111723

[91] Diez-Martin E, Hernandez-Suarez L, Munoz-Villafranca C, Martin-Souto L, Astigarraga E, Ramirez-Garcia A, et al. Inflammatory bowel disease: a comprehensive analysis of molecular bases, predictive biomarkers, diagnostic methods, and therapeutic options. *Int J Mol Sci*. 2024;25(13):7062. doi: 10.3390/ijms25137062

[92] Patole SK, Keil AD, Nathan E, Doherty D, Esvaran M, Simmer KN, et al. Effect of *Bifidobacterium breve* M-16V supplementation on faecal bifidobacteria in growth restricted very preterm infants–analysis from a randomised trial. *J Mater Fetal Neonatal Med*. 2016;29(23):3751-5. doi: 10.109/14767058.2016.1147554

[93] Ishizeki S, Sugita M, Takata M, Yaeshima T. Effect of administration of bifidobacteria on intestinal microbiota in low-birth-weight infants and transition of administered bifidobacteria: a comparison between one-species and three-species administration. *Anaerobe*. 2013;23:38-44. doi: 1016/j.anaerobe.2013.08.002

How to cite this article

Mohammed Z.S.; Hasan A.D.; Immunomodulatory Effects of Bifidobacterium Breve: Mechanism and Therapeutic Potential. Trends in Pharmaceutical Biotechnology (TPB). 2025;3(2):1-12. doi: 10.57238/tpb.2025.153196.1031