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Review

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Enhancing the intestinal barrier with Bacteroides uniformis: a potential preventive strategy against swine enteric coronaviruses

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Abstract: Swine enteric coronaviruses (SECoVs) are major pathogens that cause acute, lethal diarrhea in neonatal piglets. To invade intestinal epithelial cells, SECoVs must first breach the intestinal barrier. Intestinal barrier function is relatively fragile in neonatal piglets due to their immature intestinal microecology and underdeveloped mucosal immunity. Furthermore, SECoVs can disrupt this barrier through multiple mechanisms, thereby accelerating infection. Consequently, maintaining intestinal barrier homeostasis represents a crucial strategic direction for the prevention and control of SECoVs infection. Intestinal probiotics and their metabolites play a critical role in maintaining intestinal barrier function, exerting protective effects by modulating the intestinal microecology, fortifying the mucus layer, enhancing tight junctions, and maintaining immune homeostasis. *Bacteroides uniformis* (*B. uniformis*), an important intestinal commensal bacterium, has demonstrated potential probiotic effects, including improvements in intestinal microecology and enhanced barrier function across various models of intestinal inflammation and metabolic disorder. However, direct evidence of its efficacy against SECoVs remains limited. This review therefore summarizes the mechanisms by which SECoVs disrupt the host intestinal barrier from microbial, chemical, physical, and immunological perspectives, and systematically outlines the potential roles of *B. uniformis* in barrier maintenance. The review thus provides a theoretical basis and identifies future research directions for the application of *B. uniformis* as a candidate probiotic for SECoVs prevention and control.

Key words: Swine enteric coronaviruses (SECoVs); Porcine epidemic diarrhea virus (PEDV); Porcine deltacoronavirus (PDCoV); Intestinal barrier; Antiviral strategy; *B. uniformis*

1 Introduction

Swine enteric coronaviruses (SECoVs), including porcine epidemic diarrhea virus (PEDV), transmissible gastroenteritis virus (TGEV), porcine deltacoronavirus (PDCoV), and swine acute diarrhea syndrome coronavirus (SADS-CoV), are enteric pathogens that cause severe watery diarrhea in neonatal piglets (Pan et al. 2017, Zhou et al. 2018, Yuan et al. 2021, Zhang et al. 2022, Su et al. 2024). Due to their high mutation rates and

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emerging or re-emerging epidemics, SECoVs pose a persistent threat to the global swine industry, causing substantial economic losses (Janetanakit et al. 2016, Su et al. 2020, Hu et al. 2023, Sun et al. 2025). As coronaviruses, SECoVs undergo continuous genetic variation during endemic circulation, significantly diminishing the efficacy of antigen-specific vaccines (Guo et al. 2024). The development of non-vaccine antiviral strategies is therefore urgently needed.

SECoVs primarily infect epithelial cells in the small intestinal villi. Infection is established when the virus crosses the intestinal mucosal barrier and enters target cells (Turlewicz-Podbielska and Pomorska-Mól 2021, Xu et al. 2024). In neonatal piglets, intestinal microecology is not yet stable, and the mucosal immune system is underdeveloped, resulting in relatively weak barrier functions, including a thin mucus layer, fragile epithelial tight junctions, and inadequate local immune defenses (Lu et al. 2026). This makes them highly susceptible to SECoV invasion (Smith et al. 2010). Upon infection, SECoVs further damage intestinal epithelial cells, impair tight junction integrity, and destroy intestinal villus structures, thereby increasing intestinal permeability (Wang et al. 2019). This promotes continuous viral replication and local dissemination within the intestine, ultimately inducing clinical and pathological changes, including severe watery diarrhea, dehydration, and villus damage (Wang et al. 2019, Yang et al. 2020). Antiviral strategies focused on enhancing the intestinal mucosal barrier function of piglets may therefore reduce the efficiency of SECoV invasion of intestinal epithelial cells and provide a valuable complementary approach to viral prevention and control.

The intestinal probiotic community is essential for maintaining intestinal mucosal barrier homeostasis and defending against pathogen invasion (Madhogaria et al. 2022, Hao Z et al. 2024, Song MZ et al. 2024). Its composition, colonization status, and metabolic activity directly influence the occurrence and progression of intestinal diseases (Chen et al. 2021, Xing et al. 2024, Zhang et al. 2025). During enteric viral infections, probiotics and their metabolites contribute to host defense through multi-layered barrier regulation. These mechanisms include such as the competitive exclusion of pathogen colonization, the upregulation of tight junction protein expression, the promotion of mucin and antimicrobial peptide production, and the modulation of mucosal immune responses, through which probiotics can ameliorate SECoV infection-associated intestinal barrier damage and inflammatory responses (Wang et al. 2024, Xing et al. 2024, Liu et al. 2025, Sun et al. 2025, Xing et al. 2025). *Bacteroides uniformis* (*B. uniformis*) is an important intestinal probiotic with a proven role in maintaining intestinal homeostasis and repairing barrier function in models of inflammatory bowel disease, metabolic disorders, antibiotic-associated diarrhea, and other intestinal barrier dysfunctions (Fabersani et al. 2021, Dai et al. 2023, Guo et al. 2024). It achieves this by remodeling the structure of intestinal microbiota, promoting metabolic pathways (such as short-chain fatty acids and bile acids), fortifying the mucus layer and tight junction integrity, and modulating inflammatory and mucosal immune responses (Fabersani et al. 2021, Yan et al. 2023, Wu et al. 2024, Zhang et al. 2024, Liu et al. 2025, Weis et al. 2025). Given its reported intestinal barrier-protective and immunomodulatory properties, a systematic evaluation of the potential value of *B. uniformis* in the prevention and control of SECoVs is of theoretical significance.

The present review therefore summarizes the primary mechanisms by which SECoVs disrupt the host intestinal barrier—from microbial, chemical, physical, and immunological perspectives—and outlines the potential role of *B. uniformis* in maintaining intestinal microecological homeostasis, enhancing mucosal barrier function, and modulating mucosal immune responses. The objective is to provide a reference for assessing the theoretical feasibility of using *B. uniformis* to mitigate SECoV-associated intestinal barrier damage and to support the development of prevention and control strategies based on intestinal microecological modulation.

2 The intestinal barrier is a crucial line of defense against pathogen invasion

As a vital organ for maintaining systemic homeostasis, the intestine is critical not only for the digestion, absorption, and metabolism of nutrients but also for the homeostatic regulation of the host defense system. The intestinal barrier comprises multiple interconnected defense tiers, including the microbial barrier formed by

commensal microorganisms; the chemical barrier primarily composed of the mucus layer, antimicrobial molecules, and metabolites; the physical barrier formed by the intestinal mucosal epithelium and intercellular junctions; and the immune barrier maintained by immune effector cells, immune molecules, and gut-associated lymphoid tissues (**Fig.1**).

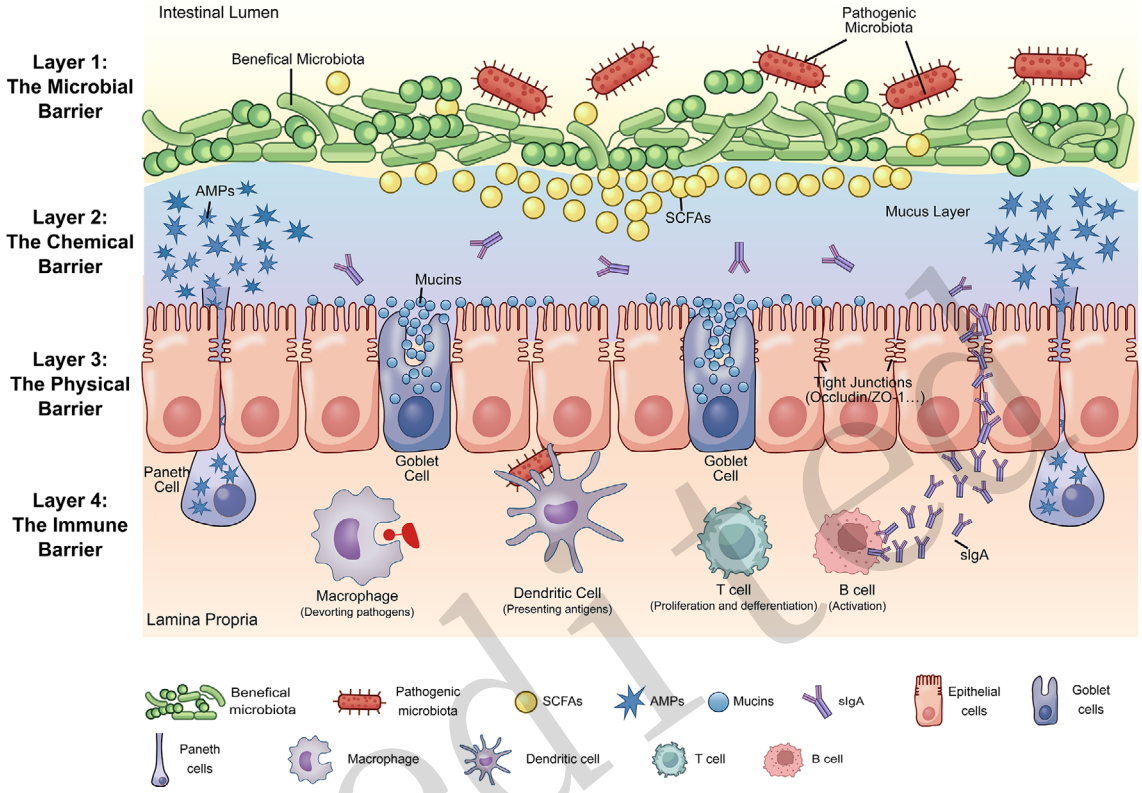

Fig.1 Schematic diagram of the four barriers that maintain intestinal health in the host. (Layer 1) Microbial Barrier: as the first line of defense, commensal microbiota and probiotics inhibit pathogen colonization through competitive exclusion; (Layer 2) Chemical Barrier: a chemical defense line composed of the mucus layer secreted by goblet cells, AMPs, SCFAs, and sIgA; (Layer 3) Physical Barrier: comprising intestinal epithelial cells, goblet cells, and Paneth cells, it relies on intercellular tight junctions to prevent the penetration of harmful substances, serving as the structural core of the intestine; (Layer 4) Immune Barrier: Located in the lamina propria, it includes macrophages, dendritic cells, T cells, and plasma cells that produce sIgA, responsible for recognizing pathogens and initiating immune responses.

2.1 Microbial barrier

The intestinal microbial barrier is primarily composed of bacterial, viral, and fungal communities that colonize the intestinal lumen, serving as the first line of defense against exogenous pathogen invasion (Fig.1, Layer 1) (Di Vincenzo et al. 2024). By interacting with viral particles or the host cellular microenvironment, the intestinal microbiota can reduce pathogen adhesion and invasion. Simultaneously, it maintains intestinal homeostasis through synergistic mechanisms, including preserving the integrity of the intestinal epithelial barrier and promoting the maturation of the intestinal immune system (Beaumont et al. 2020, Mahmud et al. 2023).

During the early postnatal period, the intestinal microbiota of neonatal piglets is still in the initial colonization stage. The abundance, diversity, and colonization stability of commensal microbes in the intestinal lumen remain relatively low, indicating that the microbial barrier is not yet fully established (Larsen et al. 2023, Lv et al. 2025). Due to incomplete occupation of mucosal niches, piglets exhibit a weak capacity for competitive exclusion against exogenous pathogens, making it difficult to effectively restrict SECoV adhesion and colonization on the intestinal mucosal surface (Yang et al. 2021, Zhang et al. 2025). Sow colostrum provides neo-

natal piglets with nutrients, immunoglobulins, and multiple immunomodulatory signals, which play a significant role in establishing the early intestinal microbiota (Li et al. 2022, Le Bourgot et al. 2026). However, during the early postnatal period, particularly within the first 10 days of life, the structure of the intestinal microbiota remains highly unstable. Deficiencies in microbe-derived metabolites and microbiota-mediated immune maturation signals can further impair mucus layer formation, epithelial barrier maintenance, and local immune development, thereby increasing the overall fragility of the neonatal piglet's intestinal barrier (Tang et al. 2024, Liu et al. 2025, Lv et al. 2025). This characteristic creates favorable conditions for SECoVs to invade intestinal epithelial cells and disseminate within the gut, suggesting that strengthening the early intestinal microbial barrier could represent a critical intervention strategy to reduce the risk of SECoV infection.

2.2 Chemical barrier

The intestinal chemical barrier is formed by the mucus layer, antimicrobial substances, and microbial metabolites (Fig.1, Layer 2) and plays a pivotal role in restricting pathogens from accessing the intestinal epithelium while protecting intestinal tissues from injury (Mazmanian et al. 2008, Paone and Cani 2020). Mucins secreted by goblet cells are the core molecular components of the mucus layer, forming a mucous gel that covers the surface of the intestinal epithelium, thereby establishing a vital spatial isolation barrier between the luminal contents and the epithelial cells (Layunta et al. 2021, Bergstrom and Xia 2022, López-Cauce et al. 2022, Fu et al. 2023). In addition, antimicrobial peptides (AMPs) secreted by Paneth cells and microbial metabolites, such as short-chain fatty acids (SCFAs), can further enhance intestinal chemical defense by modulating the intestinal microenvironment and maintaining epithelial homeostasis (Lee and Gulati 2022). When this chemical barrier is compromised—for example, under pathological conditions such as ulcerative colitis and Crohn's disease—host susceptibility to enteric pathogens increases significantly (McCole 2014, Tajik et al. 2020). For enteric pathogens such as SECoVs, an intact mucus layer can restrict direct contact between viral particles and intestinal epithelial cells, thereby reducing the likelihood of viral adhesion and invasion into target cells (Yang et al. 2024). Regarding intervention strategies, existing studies show that supplementation with certain probiotics (such as *Bacteroides vulgatus*, *Bacteroides thetaiotaomicron*, and *Akkermansia muciniphila*) can modulate the composition of the intestinal microbiota, increase beneficial metabolites such as SCFAs, and promote the production of defense molecules such as mucins and AMPs (Lee et al. 2020, Ghosh et al. 2021, Chen et al. 2024). Therefore, probiotic interventions can consolidate intestinal chemical barrier function by enhancing mucus layer stability and stimulating the secretion of antimicrobial molecules, providing a theoretical basis for restricting the early invasion of SECoVs into intestinal epithelial cells.

2.3 Physical barrier

The intestinal physical barrier is built on a continuously arranged layer of intestinal epithelial cells and their intercellular junctional complexes (Fig. 1, Layer 3), serving as a crucial structural line of defense that prevents luminal pathogens and harmful substances from crossing the epithelium into mucosal tissues. This barrier comprises various epithelial cell populations, including absorptive enterocytes, goblet cells, and Paneth cells (Chelakkot et al. 2018). Adjacent epithelial cells anchor to one another via intercellular junctional complexes, such as tight junctions and adherens junctions, thereby maintaining epithelial continuity, polarity, and selective permeability. Tight junctions are key determinants of the integrity of the intestinal physical barrier and are primarily assembled by core molecules such as Occludin, Claudins, and Zonula occludens-1 (ZO-1) (Chelakkot et al. 2018). The downregulation or abnormal spatial distribution of these tight junction proteins can disrupt the intercellular junctional architecture, directly increasing intestinal permeability. This facilitates pathogen invasion, prompting intestinal pathological processes such as diarrhea and inflammation (Schulzke et al. 2005, Zeissig et al. 2007, Wang et al. 2024). During SECoV infection, the virus primarily infects small intestinal villus epithelial cells, inducing epithelial cell injury, necrosis, or shedding. This disrupts the tight junction structure, weakens the integrity of the intestinal physical barrier, and increases intestinal permeability, thereby exacerbating malabsorption of water and electrolytes and promoting malabsorptive diarrhea (Wang et al.

2019). Targeting the damage to this structural barrier, certain probiotics and their metabolites can support the restoration of intestinal epithelial structural integrity by modulating epithelium-repair-related signaling pathways, promoting tight junction protein expression, and improving intestinal villus morphology (Laval et al. 2015, Ruiz et al. 2017, Han et al. 2024). Therefore, enhancing the stability of intercellular junctions and maintaining the structural integrity of villi can mitigate abnormal intestinal permeability and tissue damage caused by the destruction of the physical barrier during SECoV infection.

2.4 Immune barrier

The intestinal immune barrier comprises gut-associated lymphoid tissue (GALT), immune cells (such as macrophages, dendritic cells, and T/B lymphocytes), and immune molecules (such as cytokines, chemokines, and secretory immunoglobulin A) (Fig.1-Layer 4). It constitutes an essential defense system that recognizes enteric pathogens, initiates mucosal immune responses, and maintains inflammatory homeostasis (Rivera and Lennon-Duménil 2023). The maturation of the immune barrier and the efficiency of the immune response directly affect the susceptibility of piglets to enteric viral infections. Specifically, sIgA can bind to viral particles and restrict their adhesion to intestinal epithelial cells, thereby inhibiting viral entry into target cells during the early stages of infection (Cai et al. 2025). The GALT-mediated innate and adaptive immune responses play critical roles in viral recognition, antigen presentation, effector cell activation, and viral clearance (Zhang et al. 2020, Lin et al. 2022, Huang et al. 2023, He et al. 2025, Yang et al. 2025, Zhang et al. 2026). However, the immune barrier in neonatal piglets is not yet fully developed; sIgA secretion levels are low, antigen presentation capabilities are limited, and immune cell response coordination is insufficient. This incomplete immune development can weaken piglets' early restriction of SECoVs, creating conditions for viral replication and the expansion of inflammatory damage (Langel et al. 2019). In this context, the interaction between the intestinal microbiota and the immune barrier is of profound importance. A healthy intestinal microbiota can enhance the host's defensive capacity against enteric pathogens by regulating immune cell development, promoting mucosal immune maturation, and maintaining cytokine balance (Xing et al. 2024, Sun et al. 2025). Concurrently, host immune molecules can reverse-regulate the structure of the microbial community, thereby participating in the regulation of intestinal inflammatory responses (Zeissig and Blumberg 2014, Kashiwagi et al. 2015). Probiotic interventions can therefore support intestinal immune barrier homeostasis by promoting sIgA-related mucosal immunity, modulating immune cell function, and limiting excessive inflammatory responses, thereby establishing a potential theoretical basis for alleviating SECoV-associated intestinal immune injury.

In summary, a healthy and stable intestinal microbiota is crucial for maintaining the intestinal barrier function in piglets. It promotes the establishment and maintenance of intestinal homeostasis by regulating interactions among the microbial, chemical, physical, and immune barriers. During the early developmental stage of neonatal piglets, in particular, a stable intestinal microecology helps enhance the host's resistance to exogenous pathogen invasion and reduces the risk of intestinal diseases such as diarrhea, thereby providing vital support for piglet intestinal health and early growth.

3 Swine enteric coronavirus infection compromises the intestinal barrier in piglets

Intestinal barrier function is of paramount importance to piglet health; its impairment can lead to nutrient malabsorption, growth retardation, declined immune function, and increased disease susceptibility (Tang et al. 2022, Hu et al. 2024). The intestinal barrier of neonatal piglets is still developing, and insufficient colonization of the intestinal microecology, immature mucosal immune development, and relatively fragile epithelial barrier function make them highly sensitive to enteric pathogen invasion (Zhang et al. 2025). Subsequent to SECoV infection, this fragile barrier system is further compromised, resulting in damage to intestinal epithelial cells, the destruction of villus structures, increased intestinal permeability, and local immune dysregulation. This impairs

the capacity for nutrient absorption and water-electrolyte balance regulation, inducing severe watery diarrhea, dehydration, and even death (Fig.2).

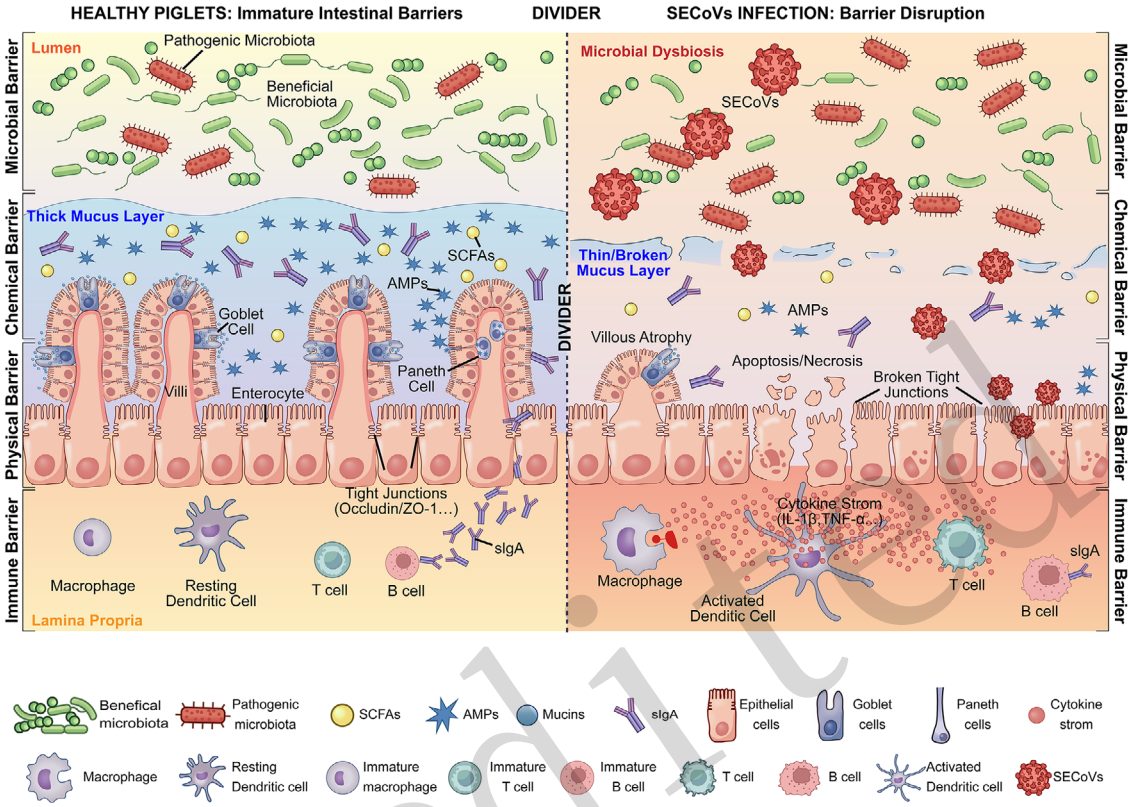

Fig.2 Schematic diagram of the mechanism by which SECoV infection disrupts the weak intestinal barrier in piglets. In the healthy state (left), the four intestinal barriers of piglets are intact but are weaker than those of adult pigs and more susceptible to virus attacks. Following SECoV infection (right), the barrier system is severely damaged: (1) Microbial Barrier: Viral infection causes severe dysbiosis, characterized by decreased abundance of beneficial bacteria, reduced SCFAs, and enrichment of pathogenic bacteria; (2) Chemical Barrier: Reduced number and impaired function of goblet cells lead to thinning or rupture of the mucus layer; meanwhile, the secretion of mucins, AMPs, and sIgA is significantly decreased; (3) Physical Barrier: Viral replication induces villous atrophy, apoptosis/necrosis of intestinal epithelial cells, and disruption of tight junction proteins (e.g., ZO-1, Occludin), resulting in increased intestinal permeability; (4) Immune Barrier: Viral invasion triggers a severe inflammatory response, leading to abnormal activation of dendritic cells and macrophage aggregation, and inducing the release of pro-inflammatory cytokines such as IL-1β and TNF-α to form a "cytokine storm," which further exacerbates intestinal tissue damage.

3.1 SECoV infection disrupts the intestinal microbial barrier in piglets

Research indicates that SECoV infection significantly disrupts piglets' intestinal microecological homeostasis and alters their intestinal microbial community structure. This microecological perturbation exhibits certain virus-type specificities and is also influenced by host age and infectious dose. Following PEDV infection, the α-diversity of the piglet intestinal microbiota decreases significantly (by over 50%), characterized by a reduction in probiotics such as *Lactobacillales* and an increase in opportunistic pathogens such as *Escherichia-Shigella* (Koh et al. 2015). Furthermore, the impact of PEDV infection on the core intestinal microbiota is not entirely consistent across piglets of different ages, displaying distinct microbial shift patterns in 1-, 2-, and 4-week-olds (Yang et al. 2020). The dysbiosis induced by PDCoV infection exhibits age- and dose-dependent characteristics; the microbial perturbation is more severe in 8-day-old piglets than in 90-day-old pigs, and high-dose infections can elevate the abundance of potentially pathogenic bacteria, such as *Enterococcus*, to up to three times that of the control group (Li et al. 2022). Following TGEV infection, the intestinal microbiota

undergoes changes both at the phylum level and in metabolic functions, characterized by an increase in Proteobacteria and Actinobacteria, coupled with a sharp decline in SCFA-producing bacteria and a concurrent reduction in intestinal butyrate concentration by approximately 60% (Liang et al. 2022, Yin et al. 2024). Under co-infection with PEDV and PDCoV, changes in the intestinal microbiota may be even more complex, presenting as elevated *Actinobacteria* levels alongside decreases in *Firmicutes* and *Fusobacteria* (Shu et al. 2022).

The dysregulation of the microbial barrier caused by SECoV infection is not an isolated event; it is closely linked to virus-induced alterations in the local intestinal microenvironment. SECoVs primarily infect intestinal epithelial cells, inducing villus atrophy and crypt hyperplasia and inhibiting the secretion of barrier-related molecules such as mucin 2 (MUC2) and the antimicrobial peptide Reg3γ (Zhang et al. 2025). These changes can destroy the local ecological environment commensal bacteria rely on for colonization and homeostasis. Simultaneously, viral infection can promote the release of pro-inflammatory cytokines by activating inflammation-related signals such as NF-κB and interfere with the normal immune cross-talk between the host and the microbiota (e.g., PEDV can affect aryl hydrocarbon receptor-related ligand metabolism; (Wang et al. 2024). The resulting epithelial tissue damage, inflammatory responses, and microbial dysbiosis create a vicious cycle that further exacerbates intestinal microecological imbalance (Shu et al. 2022, Wang et al. 2024). Notably, fecal microbiota transplantation (FMT) can alleviate clinical symptoms in piglets by promoting the restoration of beneficial bacteria, further supporting the close relationship between the state of the intestinal microecology and the outcomes of infection with enteric pathogens such as SECoVs (Zhang et al. 2025).

In conclusion, SECoV infection weakens the intestinal microbial barrier function by altering the composition of the piglet intestinal microbiota, reducing the abundance of beneficial bacteria, and promoting the expansion of potential pathogens. This microecological imbalance can further impact local intestinal metabolism, inflammatory responses, and barrier homeostasis, thereby contributing to the development of SECoV-associated diarrhea and intestinal damage.

3.2 SECoV infection impairs the intestinal chemical barrier in piglets

The intestinal chemical barrier comprises the mucus layer, antimicrobial molecules, and metabolites and is a critical line of defense that restricts enteric viruses from approaching epithelial cells, maintains local microenvironmental homeostasis, and protects intestinal tissues from injury. Studies have demonstrated that SECoV infection impairs intestinal chemical barrier function, which may be a critical pathological link leading to intestinal damage and diarrhea in piglets (Curry et al. 2017, Jung and Saif 2017, Yang et al. 2024).

Mucus layer damage is a primary manifestation of the impact of SECoVs on the intestinal chemical barrier. Infections with PEDV, TGEV, and PDCoV can significantly decrease the number of goblet cells in the small intestine or colon, accompanied by a significant downregulation in the transcription and protein expression of MUC2, the core mucus component, thereby weakening the barrier protective effect of the mucus layer (Li et al. 2022, Liu et al. 2024). In the PEDV infection model, the virus can also interfere with the O-glycosylation of MUC2, reducing the binding capacity between MUC2 and the viral S protein, thereby diminishing the ability of the mucus layer to capture and sequester viral particles (Yang et al. 2024). Additionally, FMT can increase goblet cell numbers, thicken the mucus layer, and restore MUC2 expression, thereby mitigating intestinal epithelial damage caused by PDCoV infection (Zhang et al. 2025). Aside from the mucus layer, SECoV infection also affects the homeostasis of local intestinal antimicrobial molecules, metabolites, and digestion-related factors. Regarding antimicrobial molecules, TGEV infection downregulates the expression of key antimicrobial peptides like pBD-1 and Reg3γ, weakening their ability to restrict viruses and regulate the microbiota; exogenous supplementation of related antimicrobial peptides can effectively restore barrier defense functions to a certain extent (Liang et al. 2020, Bai et al. 2021, Liang et al. 2022). In terms of metabolites, PEDV infection is accompanied by a decline in SCFA-producing bacteria (Huang et al. 2019). Meanwhile, SECoV infection may indirectly perturb bile acid metabolism by affecting the host's immune status and intestinal microecology (Xing et al. 2024, He et al. 2026). These changes can compromise the direct inactivating effects of bile acids and digestive factors on the virus, as well as their regulatory role in the local microenvironment, further exacer-

bating chemical barrier dysfunction. Notably, similar chemical barrier dysfunctions are observed during other coronavirus infections. For instance, goblet cell damage, decreased expression of Paneth cell-derived defensin 5 (HD5), and bile acid metabolic disorders have been reported in SARS-CoV-2 infection (Niv 2020, Wang et al. 2020, Xu et al. 2021, Jiang et al. 2025).

In summary, SECoV infection weakens the piglet intestinal chemical barrier function through pathways affecting mucus layer integrity, mucin expression and glycosylation, antimicrobial peptide secretion, SCFA levels, and bile acid metabolism. These changes diminish the capacity within the intestinal lumen to restrict viral contact with epithelial cells and contribute to the progression of SECoV-associated diarrhea and intestinal injury.

3.3 SECoV infection damages the intestinal physical barrier in piglets

The intestinal physical barrier primarily comprises a continuous monolayer of intestinal epithelial cells and their intercellular tight junction structures, serving as an essential structural line of defense that prevents luminal pathogens and harmful substances from entering mucosal tissues. Unlike the microbial barrier (which emphasizes bacterial colonization and competitive exclusion) and the chemical barrier (which emphasizes the mucus layer and soluble defense factors), physical barrier damage is primarily characterized by the destruction of intestinal epithelial cell integrity, the loosening of intercellular junctions, the impairment of intestinal villus structure, and elevated intestinal permeability. SECoVs exhibit clear tropism for intestinal epithelial cells, and their infection directly affects epithelial architecture and barrier integrity, thereby providing an important pathological basis for malabsorptive diarrhea in piglets (Jung and Saif 2017, Chen et al. 2022).

At the tissue and cellular levels, SECoV infection induces injury to intestinal epithelial cells and structural changes in intestinal villi. Taking PEDV as an example, when the virus replicates in intestinal epithelial cells, it causes host-cell necrosis and shedding, leading to severe villus atrophy, blunting, and crypt hyperplasia (Zong et al. 2019). Simultaneously, PEDV infection can accelerate programmed cell death in epithelial cells by activating apoptotic pathways involving caspase-3, Bax, and P53 (Zhang et al. 2019, Li et al. 2024). Furthermore, during the later stages of infection, absorptive epithelial cells at the apex of jejunal villi undergo epithelial-mesenchymal transition (EMT), suggesting that epithelial structural stability and absorptive functions may be persistently affected; a sharp decline in the number of M cells in ileal Peyer's patches may also weaken local transmucosal antigen transport and mucosal immune surveillance functions (Chen et al. 2021). At the intercellular junction level, SECoV infection disrupts the expression and distribution of tight junction proteins, thereby affecting the selective permeability of the epithelial barrier. Studies have confirmed that PEDV, TGEV, and PDCoV can significantly downregulate the expression of tight junction-related proteins, such as ZO-1, Occludin, and Claudins, and perturb their localization on the cell membrane (Zhao et al. 2014, Jung et al. 2015, Wang et al. 2022). In the case of co-infection with PEDV and TGEV, the virus can also influence the dynamic regulation of tight junctions by activating MAPK-related signaling pathways (Zhao et al. 2014). Furthermore, the impact of coronavirus infection on the intestinal physical barrier may be similar across different hosts. Research indicates that SARS-CoV-2 variants, such as Delta and Omicron, can also induce degradation of tight junction proteins, such as ZO-1 and Occludin, in the intestine, accompanied by increased intestinal permeability (Assimakopoulos et al. 2021, Volcic et al. 2024). Additionally, compromised physical barriers may facilitate the transmembrane translocation of harmful substances like bacterial endotoxins, which in turn triggers intense systemic inflammatory responses, a phenomenon reported in both SARS-CoV-2-infected patients and PEDV-infected piglets (Assimakopoulos et al. 2021, Chen et al. 2021).

The aforementioned studies indicate that SECoVs can destroy the piglet intestinal physical barrier function by damaging intestinal epithelial cells, inducing cell necrosis and apoptosis, destroying villus structures, and downregulating tight junction proteins. This structural barrier damage leads to elevated intestinal permeability, water and electrolyte malabsorption, and exacerbated local inflammation, ultimately triggering acute watery diarrhea.

3.4 SECoV infection dysregulates the intestinal immune barrier in piglets

The intestinal immune barrier is a vital defense system that enables the host to recognize enteric pathogens, initiate mucosal immune responses, and maintain inflammatory homeostasis. SECoV infection not only damages the intestinal epithelial structure but also weakens the local defensive capabilities of the piglet intestine by affecting mucosal antibody responses, innate immune signaling, and immune cell functions.

Mucosal immunity mediated by sIgA and maternal passive immunity are essential protective mechanisms against enteric viral infections for neonatal piglets (Langel et al. 2016, Langel et al. 2019). GALT and the secretory sIgA it induces can bind to viral particles in the intestinal lumen, restricting their adhesion to intestinal epithelial cells and reducing the likelihood that the virus enters target cells (Crouch 1985, Jung et al. 2018). Studies have shown that PEDV infection in late-gestation sows results in a failure to accumulate adequate levels of specific sIgA in both colostrum and mature milk. This delayed and insufficient maternal passive immunity significantly compromises the lactogenic immune protection conferred to neonatal piglets (Langel et al. 2019, Langel et al. 2020). Because the mucosal immunity of neonatal piglets is not yet fully mature, insufficient maternal IgA protection further increases their susceptibility to SECoV infection. At the level of innate immunity, SECoVs can create an innate immune imbalance characterized by enhanced pro-inflammatory responses concurrent with suppressed antiviral interferon responses. Following SECoV infection of intestinal epithelial cells, viral replication and cellular damage release damage-associated molecular patterns and pathogen-associated molecular patterns, which subsequently activate innate immune cells such as macrophages and dendritic cells (Li et al. 2017, Yu et al. 2023, Zhong et al. 2025). Subsequently, inflammation- and antiviral-related signaling pathways (such as NF-κB, RIG-I, and JAK/STAT) are activated or modulated, triggering a cascade release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α (Luo et al. 2016, Zhu et al. 2017, Wu et al. 2024, Jiang et al. 2025, Zhang et al. 2025). Excessive inflammatory responses can exacerbate intestinal tissue injury, which in turn downregulates the production of type I and type III interferons, suppressing the host's antiviral immune response (Saif 1996, Langel et al. 2016, Zhang et al. 2018).

SECoV infection also impacts the quantity and function of intestinal immune cells. Research shows that PEDV infection significantly reduces the number of intestinal dendritic cells and impairs their function, thereby affecting viral recognition, antigen presentation, and the subsequent adaptive immune response (Saif et al. 1994, Charley et al. 2006, Xing et al. 2024). In parallel, PEDV infection can interfere with the proliferation and differentiation of T cells and natural killer (NK) cells, weakening cell-mediated viral clearance capacities (Saif 1996, de Arriba et al. 2002, Jung et al. 2018, Langel et al. 2020). Furthermore, there is a mutual interplay between immune barrier damage and microecological dysbiosis. The microbial perturbation and decreased SCFA levels caused by SECoV infection can further impair innate immune defense, tight junction homeostasis, and inflammatory cytokine expression, thus exacerbating the imbalance of intestinal immune homeostasis (Chen et al. 2022, He et al. 2023, Sun et al. 2025). Conversely, antiviral immune responses can be augmented by increasing sIgA levels or restoring dendritic cell function, which helps to alleviate virus-associated intestinal damage and promote tissue repair (Wang et al. 2022, Huang et al. 2023, Amimo et al. 2024).

In conclusion, SECoV infection impairs the piglet intestinal immune barrier by affecting sIgA-mediated mucosal immunity and maternal passive immunity, perturbing innate immune signaling, inducing the abnormal release of pro-inflammatory cytokines, suppressing interferon-related antiviral responses, and damaging the functions of dendritic cells, T cells, and NK cells.

4 *B. uniformis* fortifies the intestinal barrier: a potential probiotic candidate against SECoV infection

B. uniformis is an intestinal commensal bacterium with probiotic properties. Existing studies demonstrate that in models of various inflammations, metabolic disorders, and antibiotic-associated diarrhea, *B. uniformis* contributes to the maintenance of intestinal homeostasis and tissue injury repair by improving the intestinal microecology, modulating the metabolic environment, and supporting mucosal barrier function (López-Almela

et al. 2021, Wang et al. 2024, Liu et al. 2025). Given that SECoV infection disrupts the piglet intestinal barrier on multiple levels—including the microbial, chemical, physical, and immune barriers—*B. uniformis* may alleviate SECoV-mediated intestinal barrier destruction by remodeling the microbial barrier, supporting chemical defense mediated by mucus and metabolites, enhancing the physical barrier through epithelial integrity, and regulating the immune barrier to balance mucosal immunity. Therefore, this section theoretically evaluates the potential value of *B. uniformis* as a candidate probiotic to intervene in SECoV-associated intestinal damage, based on these four categories of barrier functions (**Fig. 3**).

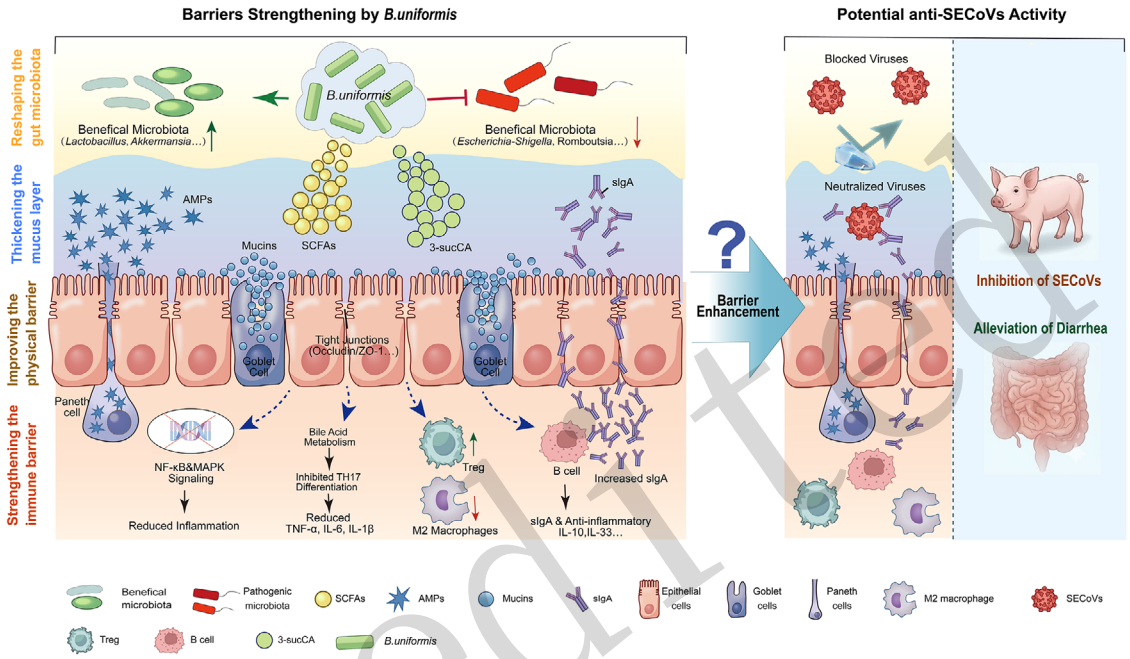

Fig.3 The proposed potential mechanistic model of *B. uniformis* in strengthening the four-layered intestinal barrier and antagonizing SECoV infection. (A) *B. uniformis* systematically reinforces the four gut barriers: reshaping the microbial barrier (promoting beneficial commensals and inhibiting pathogens), thickening the chemical shield (enhancing mucins, SCFAs, and AMPs secretion), improving the physical barrier (upregulating tight junctions), and strengthening the immune barrier (promoting sIgA and Tregs while suppressing inflammation); (B) Antiviral Outcome & Symptom Relief. These barrier-supporting effects may collectively restrict viral access to epithelial cells, reduce SECoV-associated epithelial injury, and alleviate diarrhea. Note: This model is proposed based on existing literature rather than mechanisms directly confirmed by SECoV-infected models.

4.1 *B. uniformis* stabilizes the microbial barrier

The intestinal microecological dysbiosis triggered by SECoV infection is a key factor in the development of intestinal barrier damage and diarrhea in piglets. As summarized above, beneficial bacteria in the piglet intestine plummet following SECoV infection, while potential or opportunistic pathogens increase. When the microbial barrier is impaired, the ability of commensal microbiota to occupy mucosal niches and competitively restrict exogenous pathogens declines, further exacerbating local intestinal inflammation and barrier dysfunction. Therefore, maintaining or restoring intestinal microecological homeostasis represents a potential intervention strategy to mitigate SECoV-induced disruption of the intestinal barrier.

Research on the impact of probiotics and their metabolites on viral infections is currently growing. Certain probiotics have been proven to exert inhibitory effects against infections caused by the Hepatitis B virus, Influenza virus, Human papillomavirus, SARS-CoV-2, and Zika virus (Ceccarelli et al. 2020, Huang et al. 2024, Low et al. 2024, Sun et al. 2025, Xu et al. 2025). In SECoV-related research, the metabolites of *Lactobacillus rhamnosus* promote intestinal stem cell regeneration by activating the AhR-ILC3-IL-22 signaling axis, which

improves the survival rate of PEDV-infected piglets (Wang et al. 2024); extracellular vesicles derived from *Faecalibacterium prausnitzii* can alleviate PEDV-induced intestinal damage by regulating microecological metabolism and increasing phosphatidylcholine levels (Xing et al. 2025); the intestinal microbiota metabolite lithocholic acid (LCA) can also inhibit PEDV replication and reduce viral loads by activating the bile acid receptor TGR5 (Xing et al. 2024). These findings indicate that the intestinal microbiota and their metabolites participate in the host defense process against SECoV infection by modulating microecological homeostasis and the local metabolic environment.

As an important intestinal probiotic, *B. uniformis* has been reported to improve intestinal microbiota structure in various disease models, increasing the relative abundance of beneficial bacteria such as *Bacteroides* and *Bifidobacterium*, while reducing the colonization levels of potential pathogens such as *Helicobacter pylori* and *Escherichia-Shigella* (Dai et al. 2023, Yan et al. 2023). Furthermore, *B. uniformis* regulates the intestinal metabolic environment through pathways such as influencing SCFA production and bile acid metabolism, thereby participating in the amelioration of inflammatory bowel disease, irritable bowel syndrome, and other intestinal diseases associated with microecological dysbiosis (Fabersani et al. 2021, Dai et al. 2023, Yan et al. 2023). *B. uniformis* is also associated with virus-related microecological alterations. In HIV-1 high-risk-related studies, a decline in the abundance of *B. uniformis* was significantly negatively correlated with microbiota changes such as the pathogenic *Dehalobacterium spp.*; following exogenous supplementation with *B. uniformis*, the abundance of *Dehalobacterium spp*. significantly reduced (Lin et al. 2024). In conclusion, given that SECoV infection disrupts the piglet intestinal microbial barrier and that *B. uniformis* is capable of improving microbiota structure, promoting beneficial bacteria recovery, inhibiting potential pathogen expansion, and regulating the microecological metabolic environment in other disease models, this provides a theoretical basis for the potential of *B. uniformis* to indirectly alleviate the intestinal barrier damage caused by SECoV infection by stabilizing the intestinal microbial barrier.

4.2 *B. uniformis* fortifies the chemical barrier

The intestinal chemical barrier is an important interface that restricts luminal viruses from approaching susceptible intestinal epithelial cells, relying primarily on the synergistic defense of the mucus layer, AMPs, and microbial metabolites. Research has demonstrated that certain probiotics and their metabolites, such as SCFAs, can enhance intestinal mucosal barrier function by thickening the mucus layer, promoting AMP secretion, and improving the local immune and metabolic environment (Paone and Cani 2020, Paparo et al. 2020, Luo et al. 2024, Ioannou et al. 2025). This alleviates intestinal inflammation and barrier damage to some extent, defending against viral invasion.

B. uniformis contributes to the maintenance of intestinal chemical barrier homeostasis by regulating mucus layer-related molecules, antimicrobial factors, and metabolite levels. Regarding the mucus layer, *B. uniformis* has been reported to stimulate goblet cells to secrete MUC2 (Benítez-Páez et al. 2017). MUC2 is the core structural component of the mucus layer, and the mucous overlay it forms can physically prevent direct contact between pathogenic microbes and intestinal epithelial cells, thereby supporting the barrier protective function on the intestinal surface. Regarding antimicrobial molecules, *B. uniformis* has also been reported to enhance the release of antimicrobial peptides from intestinal epithelial cells, thereby heightening intestinal resistance to pathogens (Liu et al. 2025). In metabolic regulation, *B. uniformis* participates in ameliorating intestinal inflammation and maintaining chemical barrier function by increasing SCFA production, improving intestinal microbiota homeostasis, and regulating bile acid-related metabolic pathways, such as hyodeoxycholic acid and isolithocholic acid (López-Almela et al. 2021, Yan et al. 2023, Nie et al. 2024, Zhang et al. 2024). Correspondingly, SECoVs inhibit MUC2 synthesis and reduce AMP secretion, leading to severe damage and thinning of the mucus layer, thereby increasing the opportunity for viral particles to approach intestinal epithelial cells (Curry et al. 2017, Zhang et al. 2023, Luo et al. 2024, Saleem et al. 2024, Yang et al. 2024). Therefore, existing research indicates that the mucus layer-supporting, antimicrobial factor-regulating, and metabolic homeostasis-maintaining roles of *B. uniformis, as* demonstrated in other intestinal disease models, correspond to the

chemical barrier elements compromised during SECoV infection, suggesting a potential antiviral role.

4.3 *B. uniformis* consolidates the physical barrier

SECoV infection significantly disrupts the intestinal physical barrier in piglets, primarily manifesting as villus atrophy, crypt hyperplasia, and degradation of tight junction proteins, thereby severely compromising intestinal barrier integrity (Jung et al. 2015). Existing studies indicate that multiple probiotics exert protective effects in models of colitis and viral diarrhea by promoting intestinal epithelial cell repair, enhancing tight junction protein expression, and improving intestinal villus structures (Liu et al. 2013, Mao et al. 2016, Paparo et al. 2020, Wu et al. 2022, Luo et al. 2024, Wang et al. 2024, Guo et al. 2025).

Research on *B. uniformis* shows that its effects on the intestinal physical barrier are primarily reflected in the maintenance of epithelial integrity and the regulation of tight junctions. In an antibiotic-associated diarrhea model, *B. uniformis* improved intestinal epithelial integrity and upregulated the expression of tight junction-related proteins such as Occludin, accompanied by the restoration of intestinal microbiota homeostasis and SCFA levels (Guo et al. 2021). In a mouse model of ulcerative colitis, *B. uniformis* significantly increased Occludin expression in colonic tissue and markedly reduced intestinal epithelial cell permeability (Wang et al. 2024). These studies suggest that *B. uniformis* can defend against SECoV invasion of intestinal epithelial cells by maintaining tight junction protein expression and by reducing abnormal paracellular permeability.

Beyond directly affecting tight junctions, *B. uniformis* may also indirectly support epithelial barrier repair by modulating the local metabolic environment. SCFAs are a crucial energy source for intestinal epithelial cells and participate in epithelial renewal, barrier function maintenance, and inflammatory regulation. Research has demonstrated that *B. uniformis* can elevate intestinal SCFA levels in disease models of colitis and diarrhea (Guo et al. 2021, Nie et al. 2024, Wang et al. 2024, Zhang et al. 2024). Simultaneously, SCFAs such as butyrate have been reported to inhibit PEDV replication through GPR43-mediated interferon-related pathways (He et al. 2023, Chen et al. 2024). By promoting the restoration of SCFA-related metabolic environments, *B. uniformis* may therefore indirectly support intestinal epithelial cell repair and barrier stability. However, this hypothesis requires further validation in SECoV-infected piglet models. Future studies should therefore focus on verifying whether *B. uniformis* can maintain the expression of tight junction proteins such as ZO-1, Occludin, and Claudins, reduce intestinal permeability, improve intestinal villus structure, and ultimately mitigate virus-associated malabsorptive diarrhea and intestinal tissue damage in SECoV-infected piglets.

4.4 *B. uniformis* regulates the immune barrier

SECoV infection disrupts the piglet intestinal immune barrier, characterized by the abnormal expression of inflammatory factors and antiviral-related cytokines, which exacerbates diarrhea and inflammatory injury (Li et al. 2019). During this process, gut probiotics contribute to the host's antiviral defense and the maintenance of immune homeostasis by modulating innate immune recognition, the release of inflammatory cytokines, and mucosal antibody responses. Prior studies have demonstrated that certain probiotics can antagonize viral infections via diverse immune pathways. For instance, exopolysaccharides produced by *Lactobacillus delbrueckii* can upregulate the expression of type I interferons and MxA proteins (Kanmani et al. 2018); *Lactobacillus johnsonii* influences inflammatory responses by modulating Toll-like receptor-related signals (Villena et al. 2012, Du et al. 2018); and *Enterococcus faecium* and *Limosilactobacillus reuteri* can alleviate virus-associated cellular damage and inflammatory responses by binding to viral particles or secreting metabolites such as LRC8-CFS (Chai et al. 2013, Huang et al. 2025). Furthermore, *Lactobacillus rhamnosus* can promote IgA secretion by B cells, enhancing the sIgA axis and cytokine responses induced by PEDV vaccines (Guo et al. 2019, Jin et al. 2021, Su et al. 2023).

B. uniformis has been reported to potentially play a role in regulating intestinal inflammatory damage and mucosal immunity. In a colitis model, *B. uniformis* alleviated intestinal inflammatory damage by modulating bile acid metabolism pathways (e.g., α-muricholic acid, hyodeoxycholic acid, and isolithocholic acid), which blocked NF-κB/MAPK pro-inflammatory signaling and Th17 cell differentiation, thereby reducing the ex-

pression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β (Yan et al. 2023, Ma et al. 2024). In a diet-induced obesity model, *B. uniformis* increased the proportion of regulatory T cells (Tregs) and promoted the secretion of anti-inflammatory cytokines such as IL-10 and IL-33, thereby contributing to intestinal immune tolerance and the regulation of inflammatory homeostasis (Fabersani et al. 2021). Furthermore, *B. uniformis* may support intestinal defense functions through microbial cross-talk and the activation of mucosal immunity-related pathways. Research indicates that *B. uniformis* exerts a cross-feeding effect by degrading β-glucans, which promotes the proliferation of *Lactobacillus johnsonii* and subsequently activates the AhR-IL-22-MUC2-related pathway, supporting intestinal barrier and mucosal immune homeostasis (Zhang et al. 2024). Additionally, *B. uniformis* has been shown to promote high levels of sIgA secretion in the intestines of weaned piglets, thereby alleviating local inflammation (Tang et al. 2024). In vaccine-immunity-related studies, a high abundance of *B. uniformis* is positively correlated with the long-term maintenance of neutralizing antibodies following SARS-CoV-2 vaccination (Ng et al. 2024). In summary, given that SECoV infection triggers mucosal immune dysregulation, intensified inflammatory responses, and antiviral defense imbalance, *B. uniformis* theoretically possesses potential value in mitigating SECoV-associated immunopathological damage.

5 Conclusion and future perspectives

SECoVs are critical pathogens that cause acute diarrhea and high mortality in piglets, resulting in significant economic losses for the swine industry (Zhang et al. 2023). Existing research consistently suggests that their core pathogenic feature is the multi-layered disruption of intestinal barrier homeostasis, including microbial barrier imbalance, weakened chemical defense, physical barrier destruction, and immune response dysregulation. This ultimately creates a pathological process in which inflammation amplification and viral dissemination mutually promote one another. While vaccines remain the core tool of the current prevention and control system, their long-term protective efficacy is limited by continuous viral mutations and antigenic drift. Therefore, microecological intervention strategies focused on maintaining intestinal barrier homeostasis are increasingly recognized as an essential supplementary preventative direction.

In this context, *B. uniformis*, an intestinal commensal bacterium with potential probiotic properties, is believed to contribute to maintaining intestinal homeostasis through multi-layered, synergistic regulation of the barrier. Current evidence indicates that its potential roles manifest primarily in four interconnected ways: first, in maintaining the ecological balance of the microbial barrier by regulating the composition and structural stability of the intestinal microbiota; second, in synergistically supporting chemical barrier function by influencing mucus layer formation, antimicrobial peptide expression, and the levels of metabolites such as SCFAs; third, in participating in the stable maintenance of the physical barrier by regulating tight junction protein expression and epithelial structural integrity; and fourth, in influencing immune barrier functional homeostasis by regulating the Treg/Th17 immune balance and sIgA-related mucosal immune responses. Collectively, these multi-level regulatory roles constitute the potential value of *B. uniformis* in maintaining intestinal barrier integrity. However, current evidence is primarily derived from non-SECoV infection models and correlation studies, lacking direct functional validation against SECoVs. Therefore, the role of *B. uniformis* in the context of SECoV infection still reflects its potential value through intestinal barrier regulatory mechanisms, and its actual protective effects require further systematic evaluation in SECoV-infected animal models.

Based on the comprehensive analysis of the potential value of *B. uniformis* in intestinal barrier regulation, future research should focus on the following: (i) systematically verifying the antiviral efficacy of *B. uniformis* in SECoV-infected piglet models and clarifying the effects of strain type, dosage, and administration route on its preventive and therapeutic efficacy; (ii) utilizing multi-omics technologies (metagenomics, metabolomics, transcriptomics, and single-cell sequencing, etc.) to systematically decipher its key effector molecules and signaling pathways, elucidating its potential mechanisms for regulating SECoVs replication and intestinal

barrier repair at the molecular level; (iii) exploring the combined application of *B. uniformis* and its key metabolic factors with existing vaccine strategies, to evaluate its synergistic potential as an adjuvant in enhancing overall prevention and control efficacy; and (iv) systematically evaluating the toxicity of live *B. uniformis* and its key metabolic factors in neonatal animal models, to develop intervention protocols that balance improved safety and functionality.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

Huihua ZHENG contributed to the study conceptualization, funding acquisition, and wrote, reviewed, and edited the manuscript. Zheyi LIU and Xingyu DONG performed the methodology and formal analysis, and reviewed and edited the manuscript. Jinjia YANG performed the methodology. Junlong BI performed the methodology and contributed to funding acquisition. Xiaodu WANG performed the formal analysis. Guanghong XIE reviewed and edited the manuscript. Dongbo SUN contributed to funding acquisition, and reviewed and edited the manuscript. Houhui SONG supervised the study, conducted investigations, and contributed to funding acquisition. Mingjun SU contributed to the study conceptualization, and reviewed and edited the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

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

Declaration on the use of generative AI tools

No generative AI tools were used in the preparation of this manuscript.

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