Review



# Interplay between Bile Acids and Intestinal Microbiota: Regulatory Mechanisms and Strategic Interventions for Infections

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# Interplay Between Bile Acids and Intestinal microbiota: Regulatory Mechanisms and Strategic Interventions for Infections

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**Abstract:** Bile acids (BAs) play a crucial role in the human body's defense against infections caused by bacteria, fungi, and viruses. BAs counteract infections not only through interactions with intestinal bacteria exhibiting bile salt hydrolases (BSHs) activity but also directly combat infections. Building upon our research group's previous discoveries highlighting the role of BAs in combating infections, we have initiated an in-depth investigation into the interactions between BAs and microbiota. Leveraging existing literature, we offer a comprehensive analysis of the relationships between BAs and 16 key microbiota. This investigation encompasses bacteria (e.g., *Clostridioides difficile, Staphylococcus aureus, Escherichia coli, Enterococcus, Pseudomonas aeruginosa, Mycobacterium tuberculosis, Bacteroides, Clostridium scindens, Streptococcus thermophilus, Saccharomyces boulardii, Clostridium butyricum, Lactic Acid Bacteria*), fungi (e.g., *Candida albicans*), and viruses (e.g., Coronavirus SARS-CoV-2, influenza virus, norovirus). Our research underscores the critical role of the interplay between BAs and intestinal microbiota, including *Bacteroides, Clostridium scindens, Streptococcus thermophilus, Saccharomyces boulardii, Clostridium butyricum,* and *Lactic Acid Bacteria*, in maintaining intestinal homeostasis and combating infections. It is imperative to note that Primary bile acid (PBA) and Secondary bile acid (SBA) often exhibit distinct roles in the anti-infection process. In the antimicrobial action of BAs, SBA demonstrate antagonistic properties against a wide range of microbiota, with the exception of Norovirus. Given the intricate interplay between BAs and intestinal microbiota, and their regulatory effects on infections, we assert that BAs hold significant potential as a novel approach for preventing and treating intestinal microbial infections.

**Keywords:** bile acid; infection; microbiota

## 1. Introduction

The modulation of BAs in mammalian systems constitutes an intricate procedure, jointly orchestrated by the liver, intestines, and some intestinal microbiota [1]. PBA, predominantly comprised of cholic acid and chenodeoxycholic acid (CDCA) [2], are largely reabsorbed within the enterohepatic circulation. These are subsequently converted by the intestinal microbiota, yielding SBA, largely comprised of lithocholic acid (LCA) and ursodeoxycholic acid (UDCA) [3,4]. In this metabolic cascading, enzymes engendered by the intestinal microbiota, particularly BSHs mediated by the bile salt hydrolase (BSH) gene and 7$\alpha$ hydroxylase facilitated by the bai operon, assume a pivotal role [5–10].

Both BAs and intestinal microbiota emerge as keystones in host metabolism, wherein their synthesized or regulated metabolites frequently function as signaling molecules, precluding the colonization of pathogens within the host [5,11].

The changes in the concentration and composition of intestinal BAs are not only pivotal in affecting the growth and colonization of various pathogens but also play a significant role in the mechanisms of disease prevention and pathogenesis [11,12].Some studies have found the vital roles of PBA and SBA in maintaining intestinal homeostasis and combating infections [13–15]. For example, PBA have been shown to facilitate the germination of *Clostridioides difficile* spores, while SBA play a role in inhibiting its proliferation [16]. Interestingly, alterations in the intestinal microbiota significantly affect the host's health and disease progression by profoundly influencing BAs conversion dynamics [17,18]. A wide array of intestinal microbiota with BSHs activity, plays a crucial

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role in maintaining the balance of bile acid pools [9,10,19–23]. Moreover, the association between BSHs activity and various health conditions, such as obesity, cancer, and inflammatory bowel disease, has become a burgeoning research hotspot [24–30], and BSHs are emerging as potential therapeutic targets for metabolic diseases [31–35]. Recent studies have highlighted the critical role of the bai operon-mediated 7$\alpha$-dehydroxylation reaction in the intestinal microbiota, predominantly carried out by members of Clostridium cluster XIVa, particularly *Clostridium hiranonis* and *Clostridium scindens* [36], which not only increases the hydrophobicity of bile acids but also triggers a range of significant biological effects, including alterations in intestinal permeability, antibiotic biosynthesis, and activation of the Farnesoid X Receptor (FXR) [37–39]. The bai operon has shown effectiveness in reducing intestinal inflammation [40]. Furthermore, *Clostridium scindens*, equipped with the bai operon, has shown promise in combatting *Clostridioides difficile* infections [41].

The dynamic interaction between BAs and the intestinal microbiota not only leads to changes in bile acid pools but also allows BAs to influence the structural composition of the intestinal microbiota [42]. Although earlier research focused on the interactions of PBA or SBA with specific intestinal microbiota, BAs transformation is an ongoing process facilitated by intestinal microbiota exhibiting BSHs activity [43]. Increasing evidence suggests that the structure and function of the intestinal microbiota can exert long-lasting impacts on the host [44,45]. This review aims to offer a comprehensive exploration of the interactions between BAs and key intestinal microbes from the perspective of the intestinal microbiota. In the current era of widespread antibiotic use and rising microbial resistance [46], the role of BAs as preventive and therapeutic agents is becoming increasingly important.

## 2. Regulatory Mechanisms of Bile Acids in Maintaining Intestinal Homeostasis and Counteracting Infections

BAs play a pivotal role in regulating intestinal homeostasis[47]. Some studies have shown that BAs can enhance intestinal epithelial permeability, thereby increasing susceptibility to infections [48]. Interestingly, natural BAs have demonstrated significant antimicrobial properties against a variety of organisms including bacteria, parasites, and fungi [49–52]. That is becasue the roles of PBA and SBA are different. For instance, PBA like taurocholic acid (TCA), can promotes *Clostridioides difficile* proliferation and facilitates *Candida albicans* colonization [12,28,53–55]. In contrast, SBA such as taurodeoxycholic acid, can mitigate sepsis-induced intestinal inflammation, and deoxycholic acid and LCA encourage *Clostridium scindens* proliferation and inhibit *Clostridioides difficile* spore germination [56–59]. These diverse effects could be attributed to specific bile acid species, the unique receptors they activate and their interactions with intestinal microbiota.

BAs interact with various cellular receptors, including FXR, TGR5 (Takeda G Protein-Coupled Receptor 5), Pregnane X Receptor, Sphingosine-1-Phosphate Receptor 2, and Vitamin D Receptor. FXR is activated primarily by CDCA. FXR activation strengthens the intestinal barrier, influences microbial community composition, and modulates inflammatory responses [60–62]. Moreover, FXR promotes the proliferation of regulatory T cells, enhancing their antiviral capabilities [63–65]. Taurodeoxycholic acid-induced TGR5 activation, which can reduce cAMP levels, inhibit the Myosin Light Chain Kinase pathway and thus mitigate *Escherichia coli* epithelial barrier damage [66,67]. Other receptors such as Sphingosine-1-Phosphate Receptor 2, Pregnane X Receptor, and Vitamin D Receptor also play important roles in inflammatory response modulation when activated by BAs [68,69].

### *2.1. BAs and Fungal*

Interactions Between BAs and *Candida albicans*

*Candida albicans* (*C.albicans*), an opportunistic fungus, primarily originates from its endogenous populations in the gastrointestinal tract [70–76]. *C.albicans* frequently causes invasive infections, particularly in immunocompromised individuals or in those with dysbiosis of the intestinal microbiota [53,73,77–80].

TCA, a primary bile acid, can modulate immune responses and microbial balance within the intestine, influencing the colonization and spread of fungi like *C.albicans* [81]. Specifically, TCA has been shown to suppress key immune molecules, such as angiogenin-4 and CX3CR1, which are crucial for maintaining intestinal barrier integrity [82–84]. Additionally, TCA is associated with reduced

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expression of tight junction proteins [85–87]. This may promote the growth of harmful microbes like *C. difficile* and facilitate *C.albicans* over-colonization [28,88–91]. In contrast, SBA, specifically LCA and deoxycholic acid, can prevent the *C.albicans*'s morphological transformation and restricting its proliferation in the intestine [92].

During the mouse experiments investigations into intestinal microbiota composition following *C.albicans* infection, there's an increase in *Bacteroides*, *Proteobacteria, Pseudomonas*, and *Enterococcus*, while *Firmicutes* levels decrease [93,94]. These changes may facilitate enhanced *C.albicans* colonization by altering BSHs activity and SBA concentrations in the intestine. Moreover, TCA supplementation can heighten *C.albicans* 's invasiveness and virulence by increasing specific bacterial populations, like enterohemorrhagic *Escherichia col* [88](Figure 1).

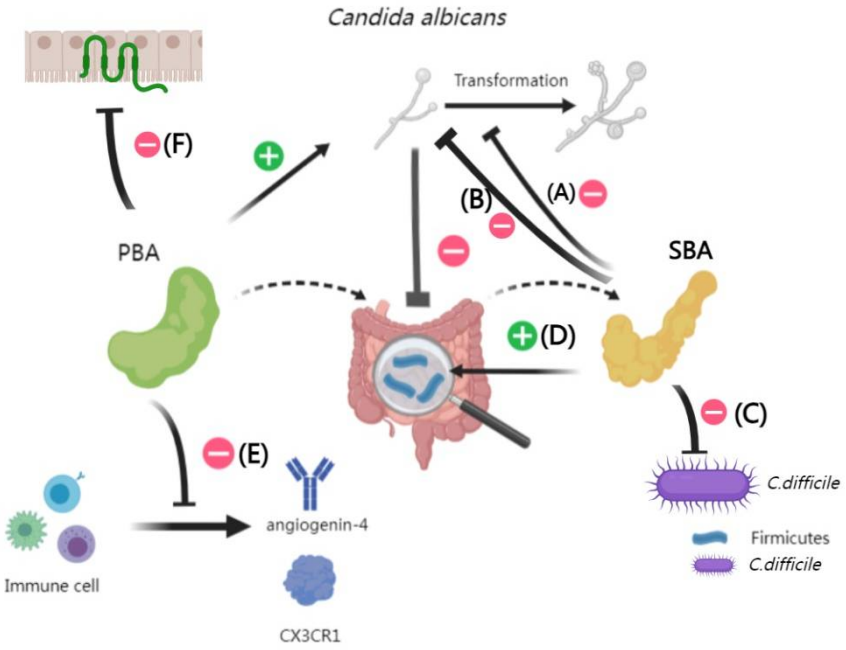


**Figure 1.** Interactions Between BAs and *Candida albicans*.SBA:(A) Inhibit the morphological transformation of *Candida albicans*; (B) Direct antimicrobial activity against *Candida albicans*; (C) Inhibit the growth of *Clostridioides difficile*; (D) Increased the abundance of *Firmicutes*. PBA:(E) Inhibit the production of immune active substances angiogenin-4 and CX3CR1; (F) Reduce the tight junction proteins in the intestine. PBA: Primary bile acid; SBA: Secondary bile acid.

### *2.2. BAs and Bacteria*

#### 2.2.1. Interactions Between BAs and *Clostridioides difficile*

*Clostridioides difficile* (*C. difficile*), is a gram-positive bacterium. Its spores can detect specific environmental cues in the gastrointestinal tract and initiat germination processes [95,96]. *C. difficile* can produce two major protein toxins, TcdA and TcdB, which can disrupt host cell signaling pathways and lead to apoptosis [97]. In clinical settings, *C. difficile* infections can range from mild diarrhea to severe pseudomembranous colitis [98]..

In the lifecycle of *C. difficile*, BAs play a regulatory role [99,100]. Some studies have identified that BAs can affect the proliferation of *C. difficile* by influencing both the structural and functional aspects of the TcdB toxin [93,101]. In addition, BAs also can cause disruptions in the equilibrium of intestinal microbiota. Specifically, TCA, a primary bile acid, has been implicated in facilitating the in vitro germination of *C. difficile* spores, which can promote the subsequent release of toxins [102]. Conversely, SBA like LCA and deoxycholic acid are known to inhibit the growth and toxic effects of *C. difficile* [99,103,104]. This inhibition includes: 1) The activation of bile acid receptors such as FXR and TGR5 by SBA, which enhances the innate immune response and inhibits *C. difficile* proliferation through signaling pathways, notably NF-κB [105]; 2) The direct interaction of SBA with the C-terminal region of TcdB, leading to conformational changes in the toxin and preventing its binding and toxic effects on host cells [106] (Figure 2).

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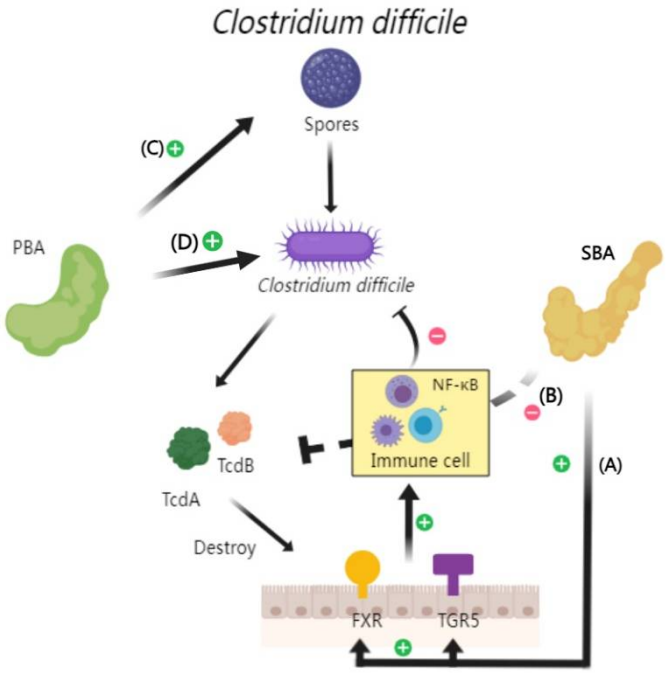


**Figure 2. Interactions Between BAs and *Clostridioides difficile*.** SBA: (A) Binding to FXR and TGR5 receptors, activating NF-κB and other signaling pathways, enhancing innate immunity, and inhibiting the growth of *Clostridioides difficile*; (B) Directly interacting with the C-terminus of toxin TcdB, inducing toxin structural changes, and preventing toxin binding with host cells. PBA: (C) Promote the spore germination of *Clostridioides difficile*; (D) Promote the release of *Clostridioides difficile* toxins TcdA and TcdB. PBA: Primary bile acid; SBA: Secondary bile acid; FXR: Farnesoid X Receptor; TGR5: Takeda G Protein-Coupled Receptor 5.

### 2.2.2. Interactions Between BAs and *Staphylococcus aureus*

*Staphylococcus aureus (S. aureus)*, a Gram-positive bacterium, presents significant clinical management challenges exacerbated by indiscriminate antibiotic use [107]. Recent research, though limited in number with only two studies identified so far, has begun to elucidate the significant role of SBA in the response to *S. aureus* infections.

Deoxycholic acids, a secondary bile acid, has been observed to promote the repair of tight junction proteins and substantially reduces the expression of inflammation-associated markers in mouse experiments [8]. Furthermore, deoxycholic acids can also alleviat *S. aureus*-induced endometritis discovered in Hu, J's studies [108]. Its protective effects are thought to stem from deoxycholic acid's influence on the TGR5/PKA-NF-κB-NLRP3 signaling axis [109]. However, deoxycholic acid does not directly suppress the proliferation of *S. aureus* [8].

Studies indicate that an imbalance in intestinal microbiota leads to an exacerbated response to mastitis in mouse experiments challenged with *S. aureus*, thereby intensifying the clinical symptoms [110,111]. Remarkably, supplementing the intestinal microbiota of infected mouse with BSHs-active organisms, such as *Clostridium scindens*, significantly reduces the inflammatory response to mastitis [8] (Figure 3).

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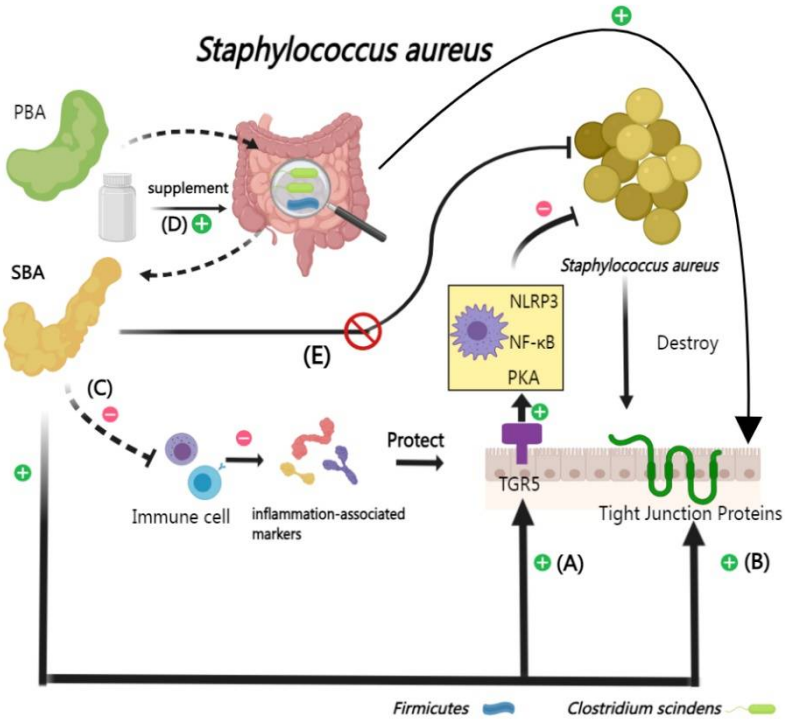


**Figure 3. Interactions Between BAs and *Staphylococcus aureus*.** SBA:(A) Inhibit infection through the TGR5/PKA—NF-κB and NLRP3 signaling pathways; (B) Repair tight junction proteins in the intestinal epithelium; (C) Reduce the expression of inflammatory markers; (D) Promote the release of *Clostridioides difficile* toxins TcdA and TcdB; (E) Cannot directly inhibit the growth of *Staphylococcus aureus*. SBA: Secondary bile acid; TGR5: Takeda G Protein-Coupled Receptor 5.

### 2.2.3. Interactions Between BAs and Extended-Spectrum Beta-Lactamase-Resistant *Escherichia coli*

The overuse of antibiotics has led to a widespread increase in the prevalence of extended-spectrum beta-lactamase-resistant *Escherichia coli* (ESBL-EAEC). This particular *E. coli* strain is highly pathogenic, often resulting in severe diarrheal diseases. The pathological hallmarks of ESBL-EAEC infection include inflammation, epithelial cell exfoliation, and compromised epithelial barrier functionality [112].

UDCA, a secondary bile acid, has shown significant inhibitory effects on ESBL-EAEC in mouse experiments. In the context of ESBL-EAEC infection, a notable reduction in the abundance of key intestinal microbial families with BSHs activity such as *Corbacteriaceae, Ruminococcaceae*, and *Lachnospiraceae* has been observed. However, this change is effectively countered by UDCA treatment by repairing microbial imbalances [113]. Moreover, UDCA enhances tight junction functionality by upregulating TGR5 transcription and inhibiting IκB $\alpha$ phosphorylation[14,114] (Figure 4).

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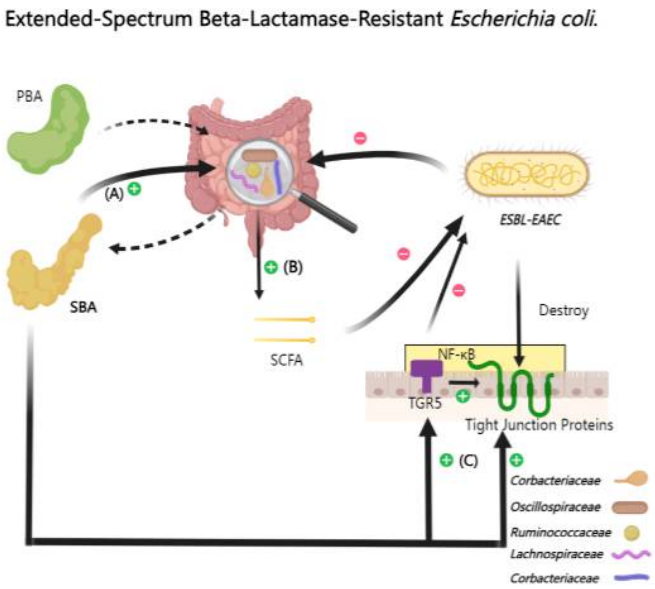


**Figure 4. Interactions Between BAs and Extended-Spectrum Beta-Lactamase-Resistant *Escherichia coli*.** SBA:(A) By optimizing the structure of the intestinal microbiota; (B) Resist infection by promoting the production of SCFA; (C) Increase TGR5 transcription, activate the NF-κB signaling pathway, enhance innate immunity, and strengthen the intestinal barrier. SBA: Secondary bile acid; SCFA: short-chain fatty acids; TGR5: Takeda G Protein-Coupled Receptor 5.

2.2.4. Interactions Between BAs and *Enterococci*

In the gastrointestinal tract, *Enterococcus faecalis*, is a commensal bacterium. However, under conditions of intestinal microbiota dysbiosis, E. faecalis may transition to a pathogenic state, particularly in elderly or immunocompromised individuals [115–117]. Recent clinical studies have elucidated that through the elevation of deoxycholic acid levels or the reduction of TCA, can effectively curtail the proliferation of *Enterococcus faecalis*. Further research suggests that deoxycholic acid 's growth-inhibitory effect on *E. faecalis* could be due to its impact on the expression of various ribosomal protein genes [118].

Vancomycin-resistant *enterococci* (VRE) present significant challenges in clinical settings due to their antibiotic resistance. The formation of biofilms is critical for the colonization of enterococci in various host environments [119]. Rahman's study has revealed that LCA can curtail the growth of VRE by maintain *VRE* in a diplococcal state and inhibiting the morphological transformation of *VRE*. Additionally, LCA exposure induces genetic mutations in VRE that result in persistent diplococcal morphology, reduced biofilm production [120] (Figure 5).

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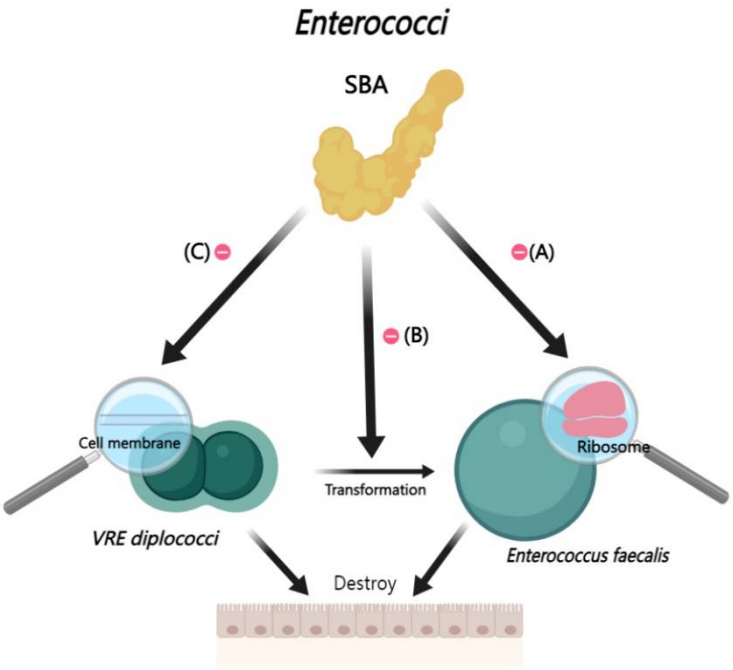


**Figure 5. Interactions Between BAs and *Enterococci*.** SBA:(A) Inhibit the expression of ribosomal protein genes, suppress the growth of *Enterococcus faecium*; (B) Maintain *VRE* in a diplococcal state, and inhibit the morphological transformation of *VRE*; (C) Inhibit the formation of *VRE* biofilms. SBA: Secondary bile acid; *VRE: Vancomycin-resistant enterococci.*

2.2.5. Interactions Between BAs and Other Bacteria (*Pseudomonas aeruginosa, Mycobacterium tuberculosis*, etc.)

*Pseudomonas aeruginosa* is known for its diverse infection profiles [121]. Surprisingly, TCA as a primary bile acid, demonstrates a significant inhibitory effect on *Pseudomonas aeruginosa*. In detail, TCA is particularly effective in inhibiting biofilm formation and dispersing existing biofilms [122,123]. This effect is believed to originate from TCA's modulation of *Pseudomonas aeruginosa* 's virulence factors, including its impact on metabolites like the siderophore pyochelin, thereby altering its toxicity and biofilm dynamics [124].

*Mycobacterium tuberculosis*, the causative agent of tuberculosis, shows a unique susceptibility pattern in the gastrointestinal tract [125]. Regions with lower bile acid concentrations, such as the terminal ileum and cecum, are more susceptible to intestinal tuberculosis [126]. BAs like CDCA, deoxycholic acid, and cholic acid have demonstrated inhibitory effects on the proliferation of *Mycobacterium tuberculosis*. This inhibition could be due to the detrimental impact of BAs on the distinctive lipid-rich cell wall of *Mycobacterium tuberculosis* [127].

Moreover, BAs influence various other pathogenic bacteria. For example, deoxycholic acid has been shown to induce the transcription of genes involved in DNA repair and recombination in response to infections by bacteria such as *Escherichia coli*, *Salmonella enterica* serovar Typhimurium, *Bacillus cereus*, and *Listeria monocytogenes* [128]. However, BAs also have a dual role; their presence has been linked to increased virulence in *Shigella dysenteriae*, promoting infection [129] (Figure 6).

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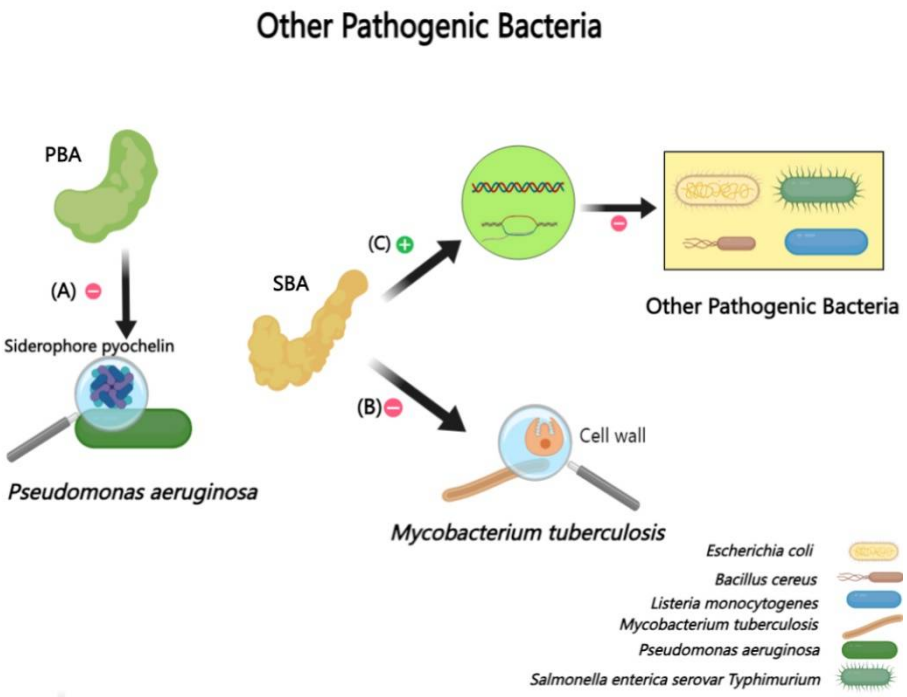


**Figure 6.** Interactions Between BAs and Other Pathogenic Bacteria. PBA:(A) Regulate the synthesis of virulence-related metabolites, such as the iron chelator pyochelin, thereby affecting *Pseudomonas aeruginosa*'s toxicity and inhibit its biofilm formation. SBA:(B) Disrupt the cell wall of lipid-rich *Mycobacterium tuberculosis*.; (C) Suppression of Infections by *Escherichia coli, Salmonella enterica* serovar Typhimurium, *Bacillus cereus*, and *Listeria monocytogenes* through the Induction of DNA Repair Damage and Transcription of Recombination-Related Genes. PBA: Primary bile acid; SBA: Secondary bile acid.

2.2.6. Interactions Between BAs and *Bacteroidetes*

The Bacteroidetes phylum significantly contributes to gastrointestinal health and the prevention of infections [130]. It has reported that *Bacteroides thetaiotaomicron* (*B. thetaiotaomicron*), *Bacteroides ovatus* and *Bacteroides fragilis* can alleviate colitis in mouse experiments by regulating BA metabolism to inhibit the proliferation of *C .difficile* [131–134].

In related research, *Bacteroides dorei* strain (BDX-01) and its therapeutic effects in a colitis mouse model by regulating BA metabolism, indicated by changes in total fecal bile acid levels and bile acid ratios, and by affecting the FXR-NLRP3 signaling pathway which lead to reduced proinflammatory cytokine expression and diminished IL-1β secretion in the colon, thereby mitigating DSS-induced experimental colitis [9,135–139].

However, it has revealed a potential adverse role of *Bacteroides fragilis* NCTC9343 in gastrointestinal health, particularly concerning their BSHs activity [140]. Elevated BSH gene expression in colonizing Bacteroidetes strains can lead to an increased influx of bile acids, which may activate signaling pathways like WNT/β-catenin and NF-κB resulting in oxidative DNA damage and enhanced cellular proliferation, eventually exacerbating colorectal cancer progression in mouse experiments [9,34,141](Figure 7).

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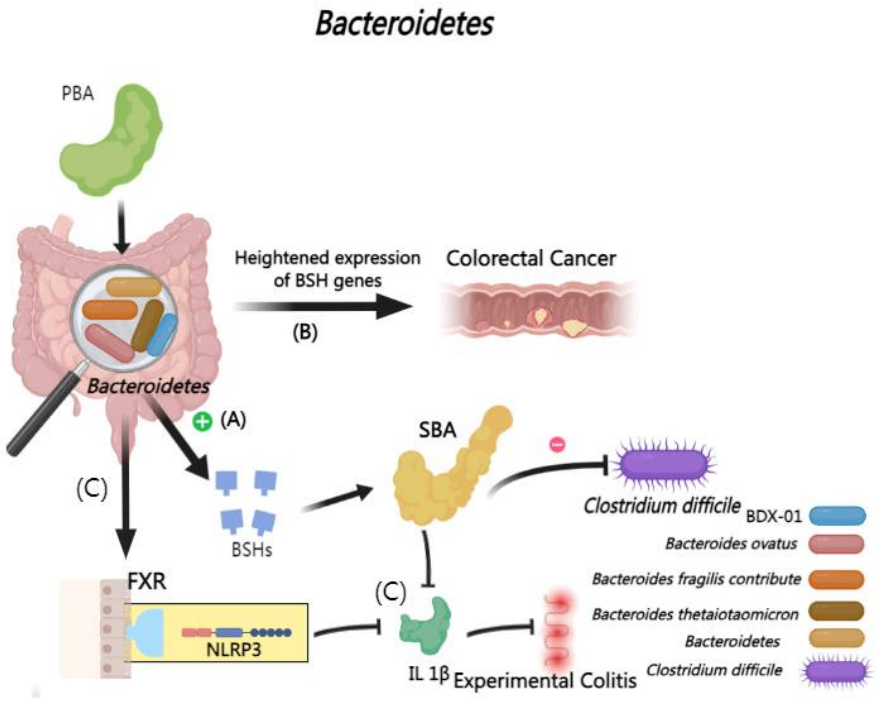


**Figure 7. Interactions Between BAs and *Bacteroidetes*.** (A) *Bacteroidetes* exhibit BSHs activity, facilitate SBA production, and inhibit *Clostridioides difficile* infection; (B) *Bacteroides* with high BSH gene expression will promote the massive production of SBA, which can induce colorectal cancer; (C) BDX-01 enhances intestinal health by modulating bile acid metabolism and the FXR-NLRP3 signaling pathway, leading to lower proinflammatory cytokine levels and reduced IL-1β in the colon, thus mitigating experimental colitis. SBA: Secondary bile acid; BSHs: Bile salt hydrolases; FXR: Farnesoid X Receptor;.

2.2.7. Interactions Between BAs and *Clostridium scindens*

*Clostridium scindens* (*C. scindens*) harbors a bile acid-inducible operon, bai [56]. This operon is essential for the synthesis of SBA by regulating the expression of 7α-dehydroxylase [7,57]. Some studies have discovered that *C. scindens* plays a crucial role in preventing the colonization and proliferation of *Clostridioides difficile* (*C. difficile*) [40]. In cases of acute *C. difficile* Infection, a marked decrease in both BSHs and 7α-dehydroxylase expression is observed in the cecal contents of mouse, aligning with reduced gene expressions in the *Lachnospiraceae* and *Clostridiaceae* families [142].However, introducing *C. scindens* into the gut of mouse with acute *C. difficile* Infection significantly enhances intestinal health. Particularly, *C. scindens* has been shown to suppress TcdA/TcdB toxin production by *C. difficile* and reduce its overall cellular count [40,99,143,144]. Therefore, the synergistic action of SBA and *C. scindens* is increasingly recognized as a critical strategy in countering intestinal colonization by this pathogenic bacterium [145] (Figure 8).

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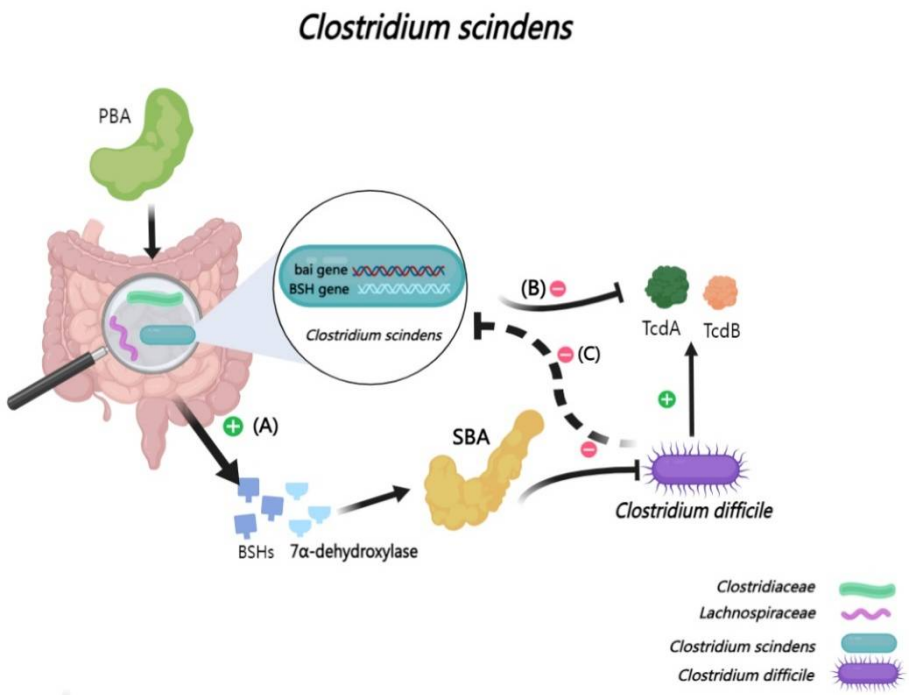


**Figure 8. Interactions Between BAs and *Clostridium scindens*.** (A) *Clostridium scindens* exhibit BSHs and 7α-dehydroxylase activity, facilitate SBA production, and inhibit *Clostridium difficile* infection; (B) *Clostridium scindens* inhibit the toxin production of *Clostridium difficile*; (C) *Clostridium difficile* also inhibits the formation of *Clostridium scindens* biofilms. SBA: Secondary bile acids; BSHs: Bile salt hydrolases.

2.2.8. Interactions Between BAs and *Streptococcus thermophilus*

*Streptococcus thermophilus* MN002 *(S. thermophilus),* acknowledged as an efficacious probiotic [146,147], has shown promising potential in mitigating the risks associated with metabolic syndrome and colorectal tumors [148–150], as well as reducing the incidence of obesity, neonatal bacteremia, and meningitis caused by *Escherichia coli* K1 [151]. The consumption of a high-fat diet is known to disrupt the intestinal microbial equilibrium, leading to both intestinal and systemic inflammation [152–154].Intriguingly, deoxycholic acid can reduce the inflammatory symptoms in high-fat diet mouse experiments. Specifically, *S. thermophilus* is capable of optimizing BAs configurations and fostering a balanced intestinal microbiota [155,156]. This is achieved by augmenting the relative abundance of bacteria proficient in producing SBA, including members of the *Ruminococcaceae, Bacteroides, Clostridium*, and *Blautia* families[157] (Figure 9).

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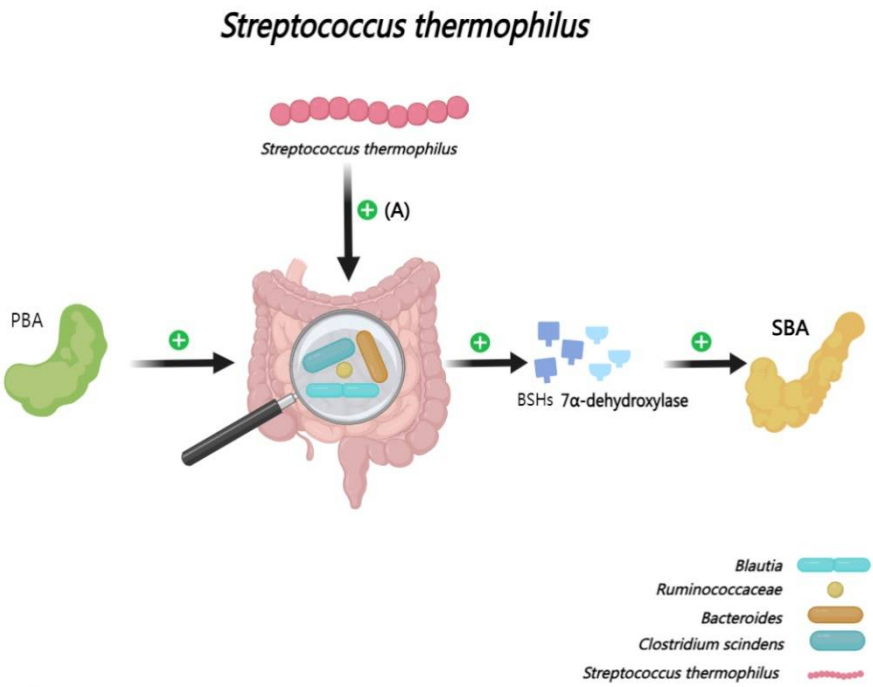


**Figure 9. Interactions Between BAs and *Streptococcus thermophilus*.** (A) *Streptococcus thermophilus* can regulate the structure of the intestinal microbiota, increase the bacterial populations that produce SBA, and modulate the bile acid spectrum. SBA Secondary bile acid.

### 2.2.9. Interactions Between BAs and *Saccharomyces boulardii*

*Saccharomyces boulardii* CNCM I-745 *(SB)* has been shown to effectively mitigate the risk of *Clostridioides difficile* enteritis following antibiotic therapy in a clinical randomized controlled trial [158,159]. Central to the protective mechanism of SB is its ability to inhibit bacterial proliferation while rapidly restoring the balance of the intestinal microbiota [160]. In detail, SB not only can thwart bacterial adhesion,but also can accelerate the neutralization of enteric toxins and bolster the immune response within the intestinal mucosa [161–163]. Furthermore, research involving healthy volunteer cohorts has illuminated SB can safeguard the health of intestine by promoting the proliferation of microbiota with BSHs activity [28]. Complementing this, vitro studies also have discovered that SB can hinder the germination of *Clostridioides difficile* spores [164–166] (Figure 10).

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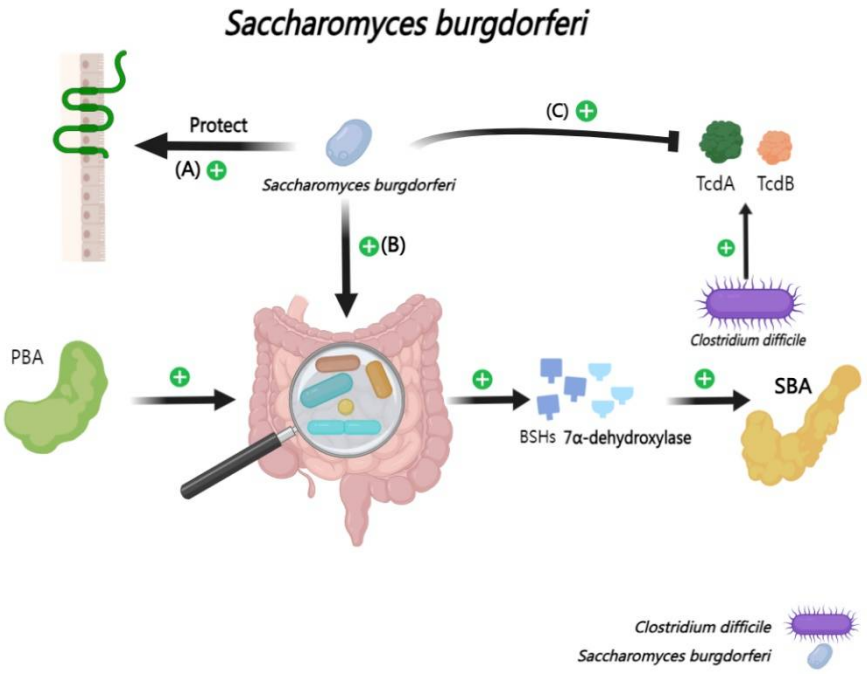


**Figure 10. Interactions Between BAs and *Saccharomyces boulardii.*** (A) *Saccharomyces boulardii* can protect the intestinal barrier; (B) *Saccharomyces boulardii* can facilitate the proliferation of intestinal microbiota endowed with BSHs activity; (C) *Saccharomyces boulardii* aids in the neutralization of enteric toxins. BSHs: Bile salt hydrolases.

2.2.10. Interactions Between BAs and *Clostridium butyricum*

*Clostridium butyricum* (*C. butyricum*) can modulate lipid metabolism by influencing the bile acid profile within the liver and ileum [167,168]. Research has been shown that *C. butyricum* supplementation can reshape the gut microbiota composition and BA distribution of intrauterine growth restricted piglets, thereby optimizing their lipid metabolism. At the same time, it significantly reduces the abundance of specific gut microbiota *Streptococcus* and *Enterococcus* in the ileum of these piglets, leading to an increase in conjugated BAs, thereby activating key liver receptors like liver X receptor $\alpha$ and FXR, that is crucial for reducing inflammatory response and protecting normal liver function [166,169–176].

*Clostridium butyricum* strain CCFM1299 administration significantly leads to an increase in UDCA levels in feces and taurocholic acid levels in serum, thereby activating TGR5 and inhibiting FXR, subsequently enhancing GLP-1 production in the intestine, which helps regulate blood sugar and reduce obesity [177–180]. Furthermore, *C. butyricum* reshapes the microbiota by increasing butyric acid levels, maintaining secondary bile acid balance, and attenuating the inhibitory effects of the FXR/SHP pathway on lipid synthesis [181]. And it also activates the butyrate/GPR43 pathway, reducing damage to the intestinal barrier and restoring the intestinal immune microenvironment in CP rabbits [182] (Figure 11).

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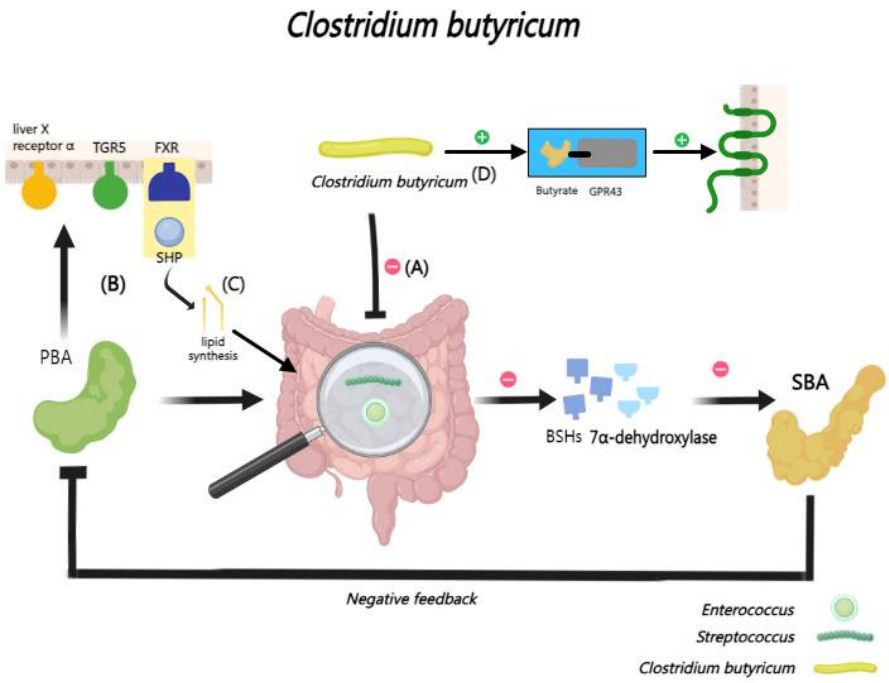


**Figure 11. Interactions Between BAs and *Clostridium butyricum*.** (A) *Clostridium butyricum* can decrease the abundance of intestinal bacterial populations with BSHs activity, leading to an increase in conjugated bile acid levels; (B) Conjugated bile acids stimulate LXRα and FXR receptors, maintaining intestinal health; (C) *Clostridium butyricum* reshapes the microbiota by attenuating the inhibitory effects of the FXR/SHP pathway on lipid synthesis; (D) *Clostridium butyricum* activates the butyrate/GPR43 pathway, reducing damage to the intestinal barrier and restoring the intestinal immune microenvironment. BSHs: Bile salt hydrolases; LXRα: liver X receptor alpha; FXR: Farnesoid X Receptor.

### 2.2.11. Interactions Between BAs and Lactic Acid Bacteria

*Pediococcus pentosaceus* Li05 belong to the *Pediococcus* genus of the *Lactobacillaceae* family. Li05 can improve tight junction proteins and downregulates inflammatory responses in mouse experiments by modulating intestinal microbiota and bile acid metabolism [183]. And it can promote the growth of beneficial microbial taxa such as *Lactobacillus*, *Prevotella*, and *Paraprevotella*, while inhibiting opportunistic pathogens, thereby altering the BAs composition and influencing liver injury processes [54,184]. It has reported that Li05 treatment notably reduced weight loss, liver damage, and bile stasis in DDC-induced cholestasis mouse experiments[185,186], which is likely linked to Li05's modulation of the intestinal microbiota, particularly enhancing propionate and butyrate-producing bacteria like *Anaerostipes* and *Eubacterium*. *Anaerostipes* and *Eubacterium* that all of them known for metabolizing inositol into propionic and butyric acids and converting PBA into SBA via 7α-dehydroxylation [19,187,188].

Liu L et al also revealed *Lactiplantibacillus plantarum* LPJZ-658 modulates intestinal microbiota and BA metabolism in mouse model which reveals the potential for treating non-alcoholic fatty liver [189]. Furthermore, *Lactiplantibacillus plantarum* LPJZ-658 increased the abundance of *Firmicutes* and *Actinobacteria*, suggesting a healthier intestinal environment conducive to non-alcoholic steatohepatitis mitigation [190–192] (Figure 12).

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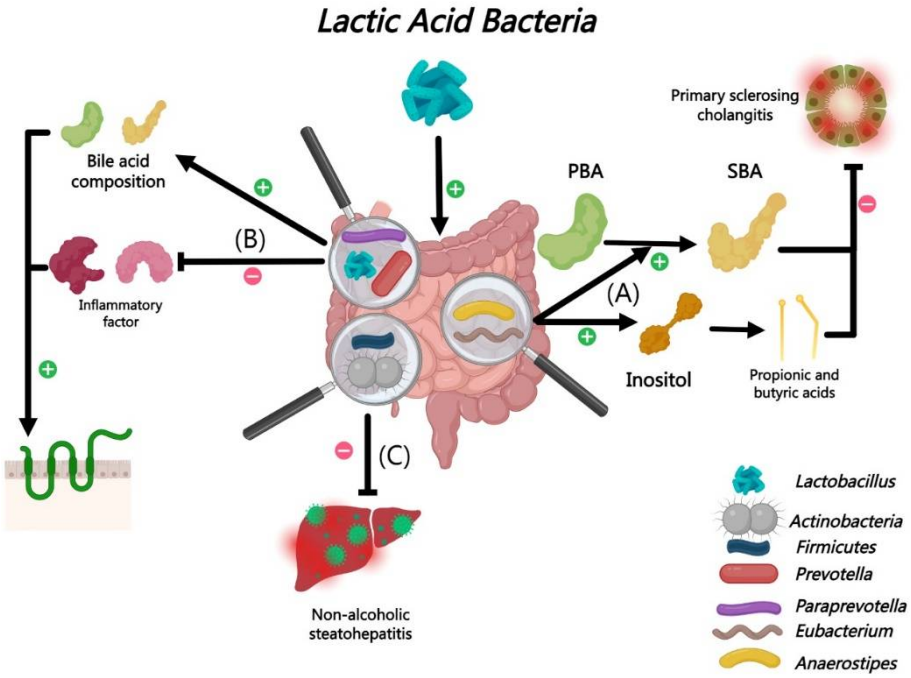


**Figure 12.** Interactions Between BAs and *Lactic Acid Bacteria*. (A) *Lactic Acid Bacteria* enhances intestinal microbiota, particularly increasing *Anaerostipes* and *Eubacterium*, which metabolize inositol into propionic and butyric acids and convert PBA into SBA via 7α-dehydroxylation, potentially inhibiting primary sclerosing cholangitis; (B) *Lactic Acid Bacteria* improves tight junction proteins ,downregulates inflammatory responses by promoting the growth of beneficial microbial taxa such as *Lactobacillus*, *Prevotella*, and *Paraprevotella* during *Clostridioides difficile* infection ,thereby altering the bile acid composition and influencing liver injury processe; (C) *Lactic Acid Bacteria* increased the abundance of *Firmicutes* and *Actinobacteria*, thereby conducting to non-alcoholic steatohepatitis mitigation. PBA: Primary bile acid; SBA: Secondary bile acid.

### *2.3. BAs and Viruses*

#### 2.3.1. Interactions Between BAs and Coronavirus SARS-CoV-2

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) utilizes the receptor binding domain within its spike protein to engage the host's angiotensin-converting enzyme 2 (ACE2) receptor, facilitating cellular entry [193–195]. Recent investigations have revealed the potential of BAs, particularly UDCA and CDCA, in disrupting this critical virus-host interaction.

Some studies have identified that UDCA can directly bind the receptor binding domain of SARS-CoV-2, thereby diminishing its affinity for ACE2 and potentially mitigating cellular damage [196–198]. Specifically, UDCA appear to alter the virus's structural integrity, allowing the penetration of polar inhibitors and solvents into the viral cells, which could impede replication [198,199].

Beyond direct antiviral effects, UDCA also can modulate the host's immune response. The cytokine storm, a critical factor in severe COVID-19 cases, can be mitigated by UDCA's anti-inflammatory, antioxidant, immunomodulatory, and anti-apoptotic properties [200–205]. Notably, UDCA can also reduce ACE2 expression in various human and animal tissues by regulating ACE2 transcription [206–208] [209,210]. In addition, retrospective studies have indicated that UDCA can improve clinical outcomes in patients [211]. However, UDCA did not demonstrate a reduction in susceptibility to SARS-CoV-2 infection in pediatric populations [212].

Emerging research suggests a correlation between the intestinal microbiome, particularly the *Collinsella* genus, and COVID-19 outcomes. Hirayama M. et al. employed machine learning to uncover a potential link between intestinal *Collinsella* and reduced COVID-19 severity [213]. UDCA produced by *Collinsella* may prevent COVID-19 infection and ameliorate acute respiratory distress syndrome in COVID-19 by suppressing cytokine storm syndrome in clinical setting [214] (Figure 13).

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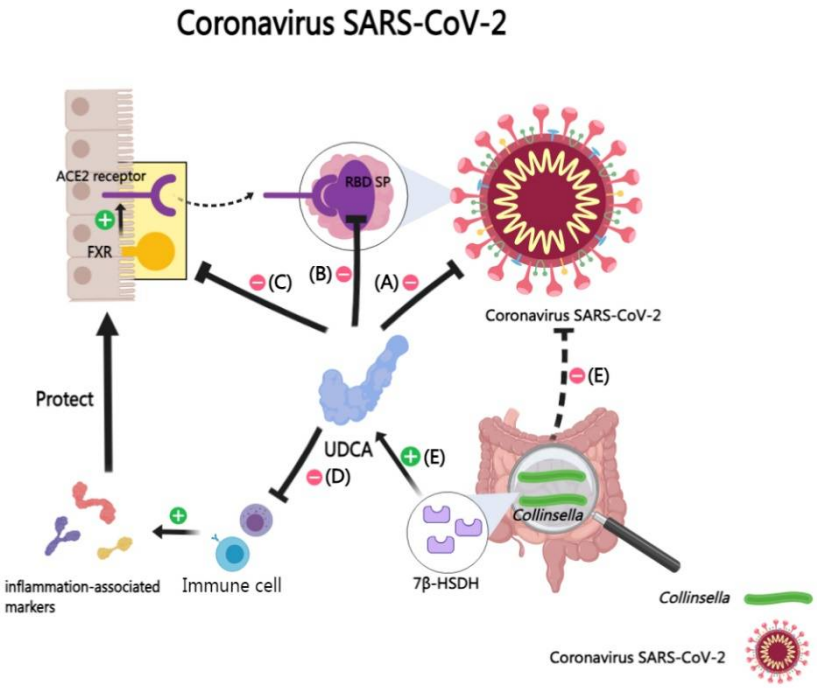


**Figure 13. Interactions Between BAs and Coronavirus SARS-CoV-2.** UDCA directly damages the virus structure, inhibiting its replication; (B) UDCA reduces the affinity between the receptor binding domain of Coronavirus SARS-CoV-2 and the host ACE2; (C) UDCA can inhibit FXR gene expression, thereby suppressing ACE2 expression; (D) UDCA possesses anti-inflammatory, antioxidative, immunomodulatory, and anti-apoptotic properties; (E) Increasing the abundance of *Collinsella* promotes the synthesis of 7β-Hydroxysteroid dehydrogenase, enhancing SBA synthesis and protecting the intestinal barrier. UDCA: Ursodeoxycholic acid; SARS-CoV-2: Severe Acute Respiratory; FXR: Farnesoid X Receptor; ACE2: Angiotensin-converting enzyme 2; SBA: Secondary bile acid.

2.3.2. Interactions Between BAs and Other Viruses (Influenza Virus, Norovirus, etc.)

Influenza A virus (IAV), a significant respiratory pathogen. Recent studies have uncovered the antiviral potential of CDCA and sodium taurocholate against IAV. They attenuate IAV infection by inhibiting the nuclear export of viral ribonucleoproteins and modulating the Toll-like receptor 4/NF-κB signaling pathway [215,216]. Specifically, CDCA, a secondary bile acid, shows promise in inhibiting IAV subtypes, including H5N1, H9N2, and H1N1, by interfering with viral ribonucleoproteins nuclear export and inhibiting viral replication [215]. Sodium taurocholate, a primary bile acid derivative , surprisingly exhibits antiviral efficacy against various influenza strains, including H5N6 and H3N2, by targeting the early stages of viral transcription and replication via the TLR4/NF-κB pathway [217].

BAs play a interesting role in norovirus infection [218,219]. Glycine deoxycholic acid, a secondary BA, could enhance murine noroviruses infectivity [220]. In addition, The intestinal microbiota distinctly modulates norovirus infection dynamics in different intestinal regions, with BAs mediating their inhibitory effect in the proximal small intestine, while bile acid receptors regulate infection in the distal small intestine [221,222].

Moreover, CDCA has shown inhibitory effects against digestive system viruses, including rotavirus, hepatitis B, and hepatitis D viruses [63,223]. Specifically, CDCA activates FXR and TGR5 receptors in HBV infections in mouse experimets [64,216] (Figure 14).

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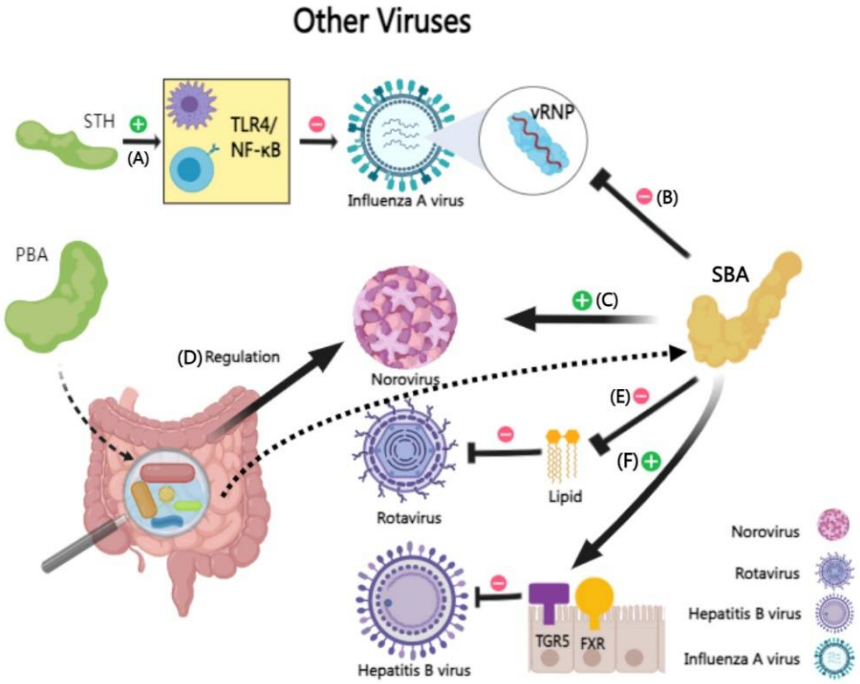


**Figure 14.** Interactions Between BAs and Other Viruses. (A) STH manifests antiviral activity against IVA infections through the modulation of signaling pathways, including TLR4, NF-κB, and MAPK; (B) CDCA demonstrates the capacity to attenuate IAV infections by inhibiting the nuclear export of vRNPs; (C) GCDCA enhances the virulence of Norovirus through a mechanism that is not yet clarified; (D) The intestinal microbiota modulates Norovirus-induced infections; (E) CDCA can reduce virus-induced lipid synthesis, inhibiting the replication of Rotavirus; (F) CDCA activates FXR and TGR5 receptors to counteract HBV infection. STH: Sodium taurocholate; TLR4: Toll-like receptor 4; CDCA Chenodeoxycholic acid; vRNPs: Viral ribonucleoproteins; IAV: Influenza A virus; GCDCA: Glycine deoxycholic acid; FXR: Farnesoid X Receptor; TGR5: Takeda G Protein-Coupled Receptor 5; HBV: Hepatitis B virus.

## 3. In Conclusion

The regulation of BA is a complex process in mammalian systems. Intestinal microbiota play a crucial role in converting PBA to SBA by regulating the metabolic activities of BSHs and 7$\alpha$-hydroxylase. Here, we explored the interactions between BAs and a comprehensive array of 16 key intestinal microbiota. We reveal that SBA demonstrate a robust resistance against infections induced by these microbiota, with the notable exception of norovirus. Furthermore, the interplay between BAs and specific intestinal microbiota, including *Bacteroides, Clostridium scindens, Streptococcus thermophilus, Saccharomyces boulardii, Clostridium butyricum*, and *Lactic Acid Bacteria*, plays a crucial role in maintaining intestinal homeostasis and combating infections.

SBA combat infections in several ways. First, SBA slow down the growth of harmful microbiota, inhibit the transformation of *Candida albicans*, reduce *Clostridioides difficile* spore sprouting, disrupt VRE biofilms, and weaken *Mycobacterium tuberculosis* cell walls. SBA also reduce SARS-CoV-2's binding to ACE2 receptors and inhibit influenza virus replication. Second, SBA modify the structure of *Clostridioides difficile*'s TcdB toxin and trigger the NF-κB signaling pathway via bile acid receptors like FXR and TGR5. This interaction boosts the body's immune defenses, enhancing responses against pathogens like *Clostridioides difficile* and SARS-CoV-2. Last, the synergy between SBA and some specific intestinal microbiota is crucial, particularly in enhancing their anti-infective potential. *Clostridium butyricum*, for example, promotes intestinal health through enterohepatic circulation, reducing BSH-active microbiota and increasing conjugated BAs production. However, certain *Bacteroidetes* strains with high BSH gene expression may inadvertently increase BAs entry into the colon, potentially triggering colorectal cancer.

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The interaction between viruses and BAs is complex. Most SBA preserving intestinal mucosal health, but glycine deoxycholic acid, a secondary bile acid potentially exacerbating norovirus infections. In addition, sodium taurocholate, a primary bile acid derivative, surprisingly shows efficacy against the influenza virus.

BAs are diverse in type, each with unique physical structures and biological properties. The dynamic metabolism of BAs in the human body results in fluctuations in types and concentrations along the intestinal tract. Current research, often utilizing fixed BAs formulations, may not fully capture these variations. Nonetheless, it is evident that SBA generally exert a favorable anti-infectious influence against most intestinal microorganism-induced infections. Given the intricate interplay between BAs and intestinal microbiota, and their regulatory effects on infections, we assert that BAs hold significant potential as a novel approach for preventing and treating intestinal microbial infections.

**Abbreviations**

BAs: Bile acids
BSHs: Bile salt hydrolases
BSH: Bile salt hydrolase
PBA: Primary bile acid
CDCA: Chenodeoxycholic acid
TCA: Taurocholic acid
SBA: Secondary bile acid
LCA: Lithocholic acid
UDCA: Ursodeoxycholic acid
FXR: Farnesoid X Receptor
TGR5: Takeda G Protein-Coupled Receptor 5
ACE2: Angiotensin-converting enzyme 2
*C. albicans*: *Candida albicans*
*C. difficile: Clostridioides difficile*
*C. scindens: Clostridium scindens*
*E. coli*: *Escherichia coli*
*S. aureus*: *Staphylococcus aureus*
*ESBL-EAEC*: Extended-spectrum beta-lactamase-resistant *Escherichia coli*
*VRE*: *Vancomycin-resistant enterococci*
*M. tuberculosis*: *Mycobacterium tuberculosis*
*S. thermophilus*: *Streptococcus thermophilus*
*SB*: *Saccharomyces boulardii*
*C. butyricum*: *Clostridium butyricum*
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
IAV: Influenza A virus
COVID-19: Coronavirus Disease 2019
PBA: Cholic acid, Chenodeoxycholic acid, Taurocholic acid, Sodium.taurocholate.
SBA: Lithocholic acid, Deoxycholic acid, Ursodeoxycholic acid, Taurodeoxycholic acid, Glycine deoxycholic acid.

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