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Review

Gut Microbiota—*Campylobacter jejuni* Crosstalk in Broiler Chickens: A Comprehensive Review

Bereket Dessalegn, Motuma Debelo, Michael Hess † and Wageha A. Awad *

Clinic for Poultry and Fish Medicine, Department for Farm Animals and Food System Science, University of Veterinary Medicine Vienna, 1210 Vienna, Austria; bereket.awoke@vetmeduni.ac.at (B.D.); motuma.dibaba@vetmeduni.ac.at (M.D.); michael.hess@vetmeduni.ac.at (M.H.)

* Correspondence: wageha.awad@vetmeduni.ac.at

† Current address: Histovac GmbH, Magdeburggasse 10, 3400 Klosterneuburg, Austria.

Abstract

The interaction between gut microbiota and *C. jejuni* in the guts of broiler chickens is essential for the bacterium's growth and potential pathogenicity. Recent findings highlighted the significance of modifying gut microbiota in relation to higher *C. jejuni* colonization rates and improved immune responses. This study suggested that a varied and balanced microbiota aids in decreasing and preventing *C. jejuni* proliferation via mechanisms including competitive exclusion, the synthesis of antimicrobial peptides, and the modulation of the chicken immune response. *C. jejuni* demonstrates adaptability in the gut environment by encouraging the growth of beneficial bacteria while inhibiting others, improving the way it acquires nutrients, and modifying the transcriptional response of its virulence factors. The dynamic nature of these microbiota communities has caused differences in the results of how gut microbiota and *C. jejuni* proliferation interact. Understanding the relationships between gut microbiota and *C. jejuni* is critical for developing strategies to mitigate the impact of *C. jejuni* in broiler chickens. This review compiles information on the relationships between gut microbiota and *C. jejuni* proliferation in broiler chickens and offers commentary on how the findings could improve gut health and food safety.

Keywords: broiler chickens; *Campylobacter jejuni*; colonization resistance; gut microbiota; short-chain fatty acids

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1. Introduction

Chicken gut microbiota is essential for host physiology, metabolism, and immune development [1]. Gut microbiota ferment complex polysaccharides, leading to the production of short-chain fatty acids (SCFAs), such as propionate, acetate, and butyrate. SCFAs serve as a crucial energy source for the host and demonstrate multiple beneficial effects [2]. The alteration in SCFA profile affects epithelial integrity, as SCFAs are recognized for their role in preserving gut barrier function [3]. Diverse microbiota that produces balanced levels of SCFAs may contribute to protection against pathogen-induced disruptions of the barrier. Furthermore, microbiota contributes to the synthesis of essential nutrients, such as amino acids and vitamins, necessary for the host. It also aids in the development of the host's immune system, maintains intestinal homeostasis, and offers protection against pathogens [4].

Broiler chickens serve as a significant source of animal protein for humans, with demand projected to rise considerably in the forthcoming decades [5]. Conversely, chickens

serve as a major reservoir for foodborne pathogens, notably *Campylobacter jejuni* (*C. jejuni*) [6]. The relationship between gut microbiota and *C. jejuni* in broilers plays an essential role for proliferation and potential pathogenicity [7]. Research demonstrated that commensal gut microbiota members, including *Lactobacillus*, *Enterococcus*, *Bifidobacterium*, and *Bacillus*, inhibit *C. jejuni* colonization [8]. *Lactobacillus* species such as *L. reuteri*, *L. salivarius*, *L. agilis*, and *L. plantarum* have been demonstrated to synthesize antimicrobial peptides or organic acids, thereby significantly decreasing *C. jejuni* proliferation in broiler chickens [9]. *Bacillus subtilis* PS-216 was also reported as having significant anti-*Campylobacter* activity and markedly reduced *C. jejuni* proliferation in the cecum of broiler when administered via drinking water [10].

Chickens with a conventional microbiota exhibited lower proliferation rates of *C. jejuni* in comparison to germ-free (GF) and antibiotic-treated chickens [11]. Chickens colonized by microbiota could not develop gut lesions following infection with *C. jejuni*. The findings highlighted that gut microbiota may play a role in regulating *C. jejuni* proliferation and inhibiting disease formation. Furthermore, deoxycholic acid (DCA), a microbial metabolite, significantly reduces *C. jejuni* proliferation in broiler chickens [12].

C. jejuni proliferation affects the microbiota composition of chickens by enhancing the growth of specific bacteria while diminishing others [13]. *C. jejuni* may act as a hydrogen sink, facilitating the proliferation of specific *Clostridium* species and augmenting their competitive edge through enhanced fermentation. This subsequently leads to enhanced synthesis of organic acids that may be used by *C. jejuni* [14]. In vitro studies demonstrated that the coculture of *C. jejuni* and *C. perfringens* promotes the proliferation and survivability of *C. jejuni* [15]. On the contrary, a decrease in *Corynebacterium* was observed after *C. jejuni* colonization in broiler chickens, as *Corynebacterium* metabolites have the potential to disrupt pathogenic biofilms in various environments [16].

C. jejuni upregulates mechanisms to acquire iron and sulfur from low-iron environments [17]. Bacteria synthesize and secrete siderophores to chelate iron, utilizing specific transporters for reabsorption [15]. *C. jejuni* lacks the ability to synthesize its siderophores for iron metabolism but can utilize those released by other bacteria [18]. *Escherichia coli* produces a siderophore called enterobactin to enhance iron acquisition. However, *C. jejuni* lacks the ability to synthesize enterobactin; rather, it utilizes the siderophore produced by *E. coli* for iron acquisition [19]. *C. jejuni* secretes cysteine-containing peptides from host epithelial tissue to obtain sulfur [17]. It also alters the transcriptional response of flagella, potentially enhancing adhesion, invasion, and persistence [20]. Results consistently indicated that *C. jejuni* exerts multifaceted effects on the gut microbiome, encompassing alterations in microbial community composition and changes in gene expression of both commensal bacteria and host cells [21]. Investigating the relationship between gut microbiota and *C. jejuni* may yield insights into strategies for managing *C. jejuni* proliferation, including the manipulation of key metabolic pathways or targeted modulation of specific bacterial groups. This review presents an overview of the interaction between gut microbiota and *C. jejuni* proliferation in chickens, along with the role of microbiota in enhancing gut health and food safety in broiler chickens.

2. Chicken Gut Microbiota and Its Role in Gastrointestinal Health

With its dense population of intricate microbial inhabitants, the chicken gut microbiota is an extremely complex and diversified environment [22]. It is dominated by Firmicutes, which make up almost 70% of the population, followed by Bacteroidetes (12.3%) and Proteobacteria (9.3%) [23]. Numerous scientific teams have thoroughly examined and evaluated the dynamics of the interaction between the chicken and the gut microbiota, and

these interactions are currently recognized as critical determinants in the contexts of gut health (Figure 1) [24].

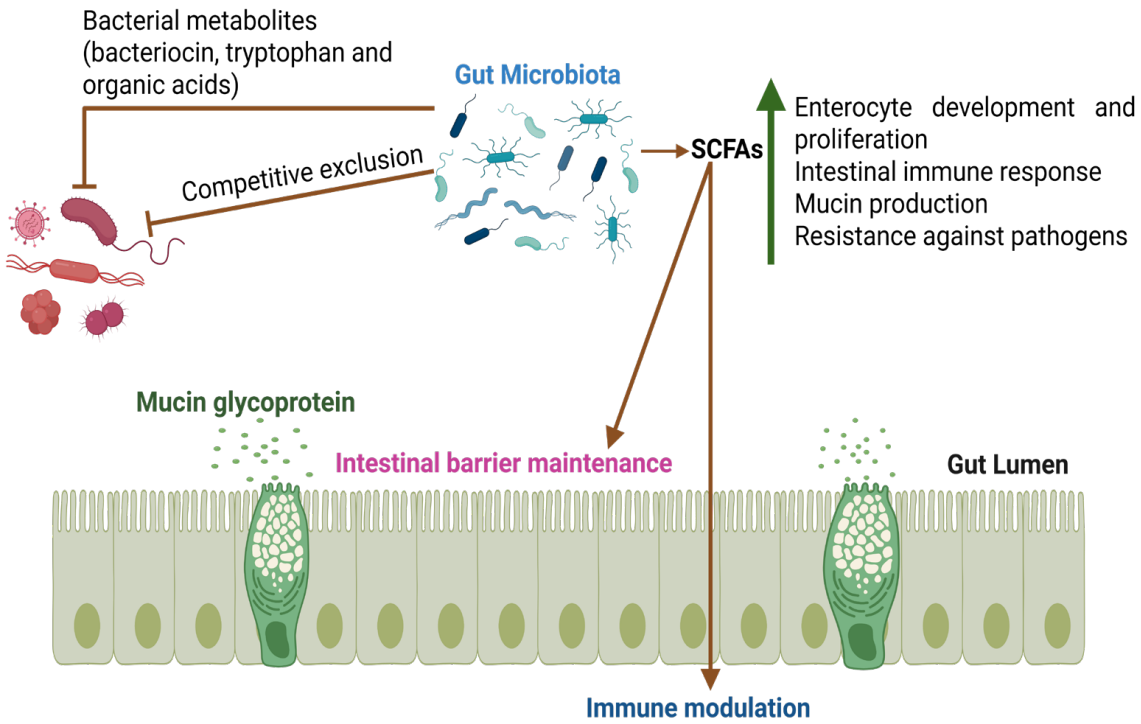

Figure 1. Mechanisms through which microbiota contribute to intestinal health. Microbial fermentation of non-digestible saccharides produces SCFAs, enhancing gut function and overall health. Created with BioRender.com (accessed on 30 August 2024).

Chicken gut microbiota plays a crucial role in extracting vital nutrients from the feed and making them available to chickens [25]. Numerous biochemicals with growth promoting properties are extracted, absorbed, and synthesized during this process, such as SCFAs like butyric acid, acetic acid, and propionic acid; vitamins that are soluble in water and lipids (like vitamin B and vitamin K); organic acids (like lactic acid); complementary enzymes; and antimicrobial substances (like bacteriocins) [26]. Furthermore, the gut microbiome stimulates non-pathogenic immune responses and lowers triglyceride levels [27]. Additionally, they contribute to the supplementation of amino acids like lysine and glutamine [28]. Moreover, the cloacal digestion of uric acid, which produces amino acids, is largely dependent on microbial communities [25]. The breakdown of accessible cell wall mucin by bacteria such as *Bacteroides*, *Akkermansia muciniphila* [29], and *Bifidobacterium* [30] serves as a crucial source of carbon and nitrogen in the gastrointestinal tracts of chickens. As a result, a two-way nutrition exchange between the bacterium and the host has developed [31].

Metabolites mediated by the gut microbiota have a tight association with the host defense system and are significant modulators of host–microbiota communication. The immune system components, like the mucus layer, epithelial monolayer, lamina propria, and gut immune cells, including helper and cytotoxic T cells, immunoglobulin-producing cells, and phagocytic cells, are encouraged to develop by metabolites [32,33]; this strengthens the protection against unwanted gut pathogens and creates barriers between the microbes and host [34].

Regardless of the steady state or length of the disease, immune function is determined by the type, concentration, and content of metabolites linked to the chicken sensor molecules [35]. Thus, immunological homeostasis, intestinal health, and chicken growth are

all impacted by balanced metabolites. Furthermore, the experimental studies indicated that the chicken fed formulated with growth-promoter antibiotics or phytochemicals changes the composition of metabolites, which are linked to host immunity and gut integrity [36].

The gut microbiota not only supplies nutrients but also helps to protect the chicken intestinal barrier by adhering to the epithelial walls of the enterocytes, which enhance gut health [37]. Furthermore, the growth of mucosal epithelia, particularly immune cells, which are primarily responsible for protecting the gut barrier against pathogens, is concurrently supported by the microbiota. It also investigated that more mucous cells were found in the GF and antibiotic-treated birds of *C. jejuni* than in the corresponding control chickens. This result showed that the pathogenesis of *C. jejuni* is modulated by a decreased variety and population number of the gut microbiota [38].

2.1. Gut Microbiota Interaction with the Immune System

The relationships between gut microbiota and the chicken immune system are essential for sustaining gut health [39]. Microbiota play a significant role in innate and adaptive immunity by facilitating T cell differentiation and regulating cytokine levels and intestinal IgA+ cell populations. These immune system effector components work together to create a signalling network between various immune cell types and preserve gut homeostasis [40].

To date, many studies have described detailed the connections between poultry immune response and gut flora. Additionally, research has shown that GF chickens treated with antibiotics are appropriate in vivo models for investigating the role of the intestinal microbiota on the development of host immunity [38]. The impact of gut microbial colonization on mucin gene expression was assessed by comparing germ-free chickens with conventional chickens [41]. It highlighted that the density of acidic and neutral goblet cells was decreased in the absence of gut microbiota, downregulate the expression of MUC2 in the intestine; to disappear sialylated goblet cells and to increase sulfated mucin. Another experimental study demonstrated a decrease in the number of macrophage-like (KUL01+) cells in broiler chickens treated with 0.8 mg of amoxicillin compared to the control group (Table 1) [42]. Therefore, a lack of gut microbiota causes a decrease in mucin secretion and synthesis, which in turn causes the small intestine mucosa to become less mature [43].

Table 1. The effect of gut microbiota on chicken immune system development.

Component	Breed Type	Bacteriological Status	Immune Response	References
Innate	Broiler (Aviagen phylogenetically distinct lines)	Hygiene	Decreased expression of AvBD in the duodenum and caecum observed in high hygiene compared to low hygiene at day 7	[44]
	Broiler (Ross 308)	Germ-free	A decrease in the number and density of neutral and acidic goblet cells, an increase in sulfated mucin, the absence of sialylated goblet cells, and a reduction in mucin 2 mRNA expression were observed in the small intestine of GF compared to conventional broilers	[41]
	Broiler (Cobb 500)	24 h antibiotic (amoxicillin) treatment via drinking water	Decreased expression of immune-related genes in the jejunum at 5 days and macrophage-like cells at 14 days	[42]

Table 1. *Cont.*

Component	Breed Type	Bacteriological Status	Immune Response	References
Adaptive	Layer	Germ-free	T cells, specifically CD4+ and CD8+ subsets, are not present in gut tissues. B cells are absent from the lamina propria, and there are no germinal centers in the cecal tonsil. Absence of intestinal and serum IgA was observed for 28 days	[45]
		Gnotobiotic (strains of *E. coli*, *Lactobacillus*, *Enterococcus*, *Clostridium*)	Reduction in caecal tonsil germinal centers and IgA production over a 28-day period	[32]
	Layer (Rhode Island Red)	Gnotobiotic (single *Bacillus* species)	Biased TCRαβ population of T cells in gut at 21 days	[46]
	Broiler (Ross308)	Conventional (72 h feed and water withholding)	Delayed gut colonisation by B and T cells and modified cytokine expression. Decreased bursa mass and intestinal immunoglobulin responses to rectal antigens	[47]
	Cobb500 male broilers		Increased expression of TLR2 and TLR4 at 21 days of age, TLR2 at 42 days of age and CD3+, CD4+ and CD8+ T cells in the jejunum	[48]

Around hatching, T cells move in waves from the thymus, but significant quantities do not appear in the gut tissue until 14 days of age [49]. At this stage, lymphoid aggregates form and there is substantial colonization. On the contrary, GF chickens lack T lymphocytes in the intestinal tissues until 4 weeks of age [44]. Additionally, Meijerink et al., 2020 [50], indicated that, at 14 and 21 days of age, broiler chickens injected with adult-derived microbiota exhibited a higher relative number of intestine cytotoxic CD8αα+ T cells than control birds. As compared to conventional birds, GF birds showed a polyclonal non-selected population of T cells, whereas the mono-colonized gnotobiotic broilers (*Bacillus* species) showed a biased repertoire in the gut at 21 days of age [51]. In comparison to the control broiler, the chicks that received probiotics containing *L. fermentum* and *Saccharomyces cerevisiae* exhibited a higher proportion of CD4+, CD8+ and CD3+T cells, but a reduction in CD8+ T cells was observed in broiler chickens that received antibiotics at 21 and 42 days [48]. Overall, these results demonstrated that the intestinal microbiota also affects the ratio of CD4+ to CD8+ T cells. The effect of the intestinal microbiota on the CD4+/CD8+ T cell ratio should be investigated further in future studies since it helps to balance inflammation and antibody production.

Pro- and anti-inflammatory cytokines are crucial for controlling the chicken immunological reaction to fluctuations in the composition of microbiota and thus maintaining intestinal balance. It has been demonstrated that *Lactobacillus rhamnosus* and *Lactobacillus reuteri* induce T regulatory cells (Tregs) to produce IL-10, which is necessary for preserving intestinal homeostasis [52]. In addition, signals from gut bacteria, which are impacted by the microbiota's composition, are necessary to maintain the balance between pro-inflammatory interleukin-17-producing effector T helper 17 cells and Forkhead box P3 (Foxp3+) Tregs in the intestine [53]. The formation of polysaccharide A was reported to facilitate the restoration of the balance between Th1 and Th2 cells in GF mice colonized with *Bacteroides fragilis* [54]. Bacterial polysaccharide A interacts with Toll-like Receptor 2 (TLR2) to affect

T cell activation (Figure 2). TLR2 enhances immunological tolerance by promoting Treg activity and suppressing Th17 differentiation [55].

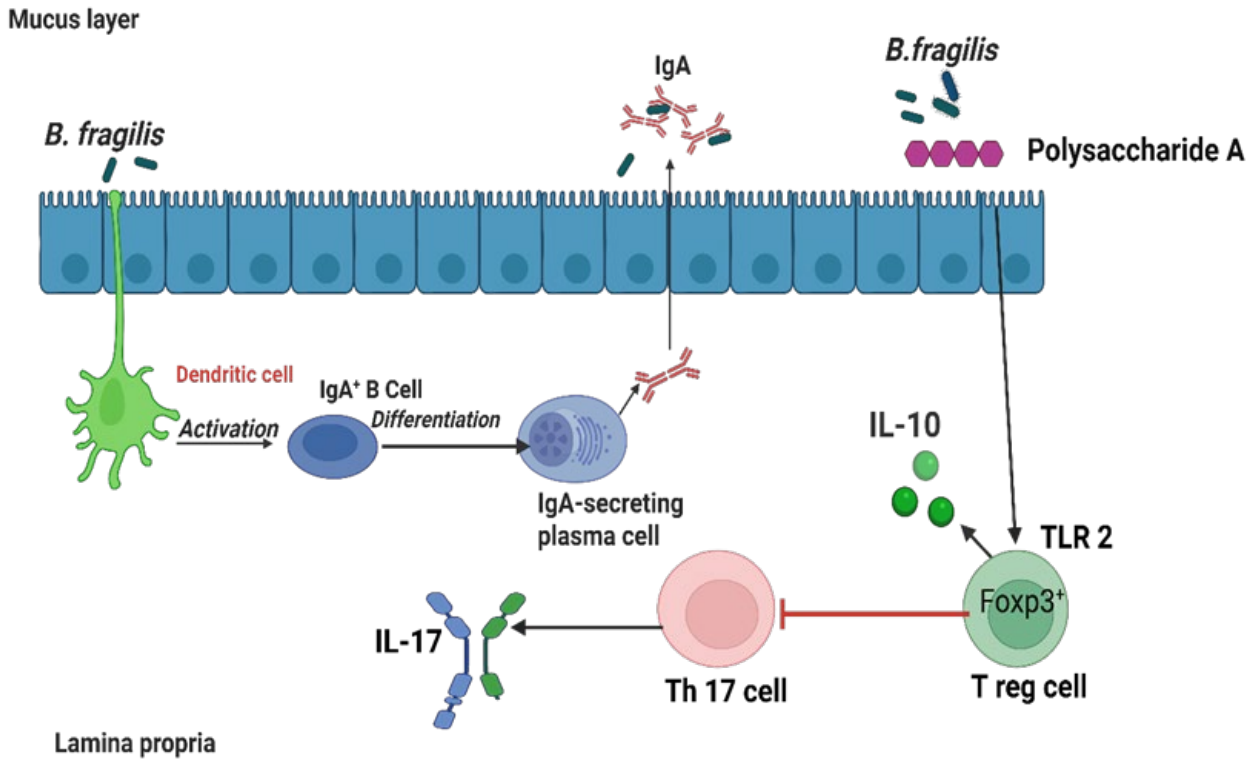

Figure 2. Signals from the gut microbiota, conveyed by dendritic cells (DCs), contribute to the activation of B cells, leading to their differentiation into plasma cells and the production of protective secretory immunoglobulin A (sIgA). *B. fragilis* promotes the differentiation of CD4+ T cells into Treg cells, resulting in increased production of IL-10 and the suppression of Th17 cells. TLR2 facilitates the differentiation into Treg by recognizing bacterial polysaccharide A and initiating a signalling cascade. Created with BioRender.com (accessed on 5 September 2024).

Furthermore, by boosting Foxp3 lymphocyte expression and encouraging the development of regulatory T cells. *B. longum* and *B. infantis* have demonstrated the ability to raise blood IL-10 levels while lowering pro-inflammatory cytokines (IL-17, IL-23, and IL-12) [56]. T cells, macrophages, and dendritic cells also produced more IFN-γ when different *Lactobacillus* species were added to the diet [57,58]. Several *Lactobacillus* strains can also influence IL-12, a critical factor for the polarization of CD4+ T cells towards the Th1 phenotype [54].

Besides the impact on T cells and cytokines, the chicken intestinal microbiota regulates B-cell responses and IgA synthesis. It has been explored by IgA and B lymphocytes were not found in the serum and lamina propria of GF chickens up to 28 days of age [11]. This contributes to underdeveloped B-cell areas and a deficiency of germinal centres in the caecal tonsils, essential for the generation of immunoglobulin. Moreover, GF chickens have reduced expression of genes crucial for immunoglobulin class switching and B-cell maturation [25]. Extracellular signals from the local microbiota influenced gut immunoglobulin repertoires and controlled early B cell maturation in the lamina propria [59]. The host protein cell death 1, which is produced on T follicular helper cells, is partially responsible for the microbiome alteration of immunoglobin A homeostasis [60]. The gut microbial communities showed higher levels of *Enterobacteriaceae* and lower levels of *Bifidobacterium* and *Bacteroides* in mice with cell death 1 deficiency and modified IgA repertoires [35].

The development of immune effector cells (IECs), which comprise defensins including ribonucleases, C type lectins, angiopoietin 4, and S100 proteins that rapidly kill or inactivate bacteria, is similarly regulated by the gut microbiota [61]. Certain antimicrobial peptides are triggered by microbes, while others, like α-defensins and β-defensin 1, are constitutively produced [62]. Therefore, there is a clear correlation between the immunological homeostasis of chickens and the homeostasis of the gut microbial community. Along with the constitutive expression of IECs, the gut microbiota of chickens grown in conventional or GF settings also exhibits a considerably increased expression pattern [27].

Metabolites from the chicken intestinal microbiome support gut health and regulate the immune system [63]. Specifically, SCFAs interact with host cells and penetrate the epithelial tissue to prevent the synthesis of pro-inflammatory cytokines [64]. They are also responsible as ligands for G protein-coupled receptors (GPCRs) and inhibitors of histone deacetylases (HDACs). Immune homeostasis depends on a tolerogenic and anti-inflammatory cell phenotype, which is often promoted by SCFA-driven inhibition of HDACs [65]. Contrary, amino acids and amino acid derivatives from intestinal microbiome promote epithelial tissue health and protection against pathogens by improving the synthesis of goblet cells and antimicrobial peptide [55]. Thus, the gut microbiota can both modulate and be modulated by immune cells generated in the intestine. However, further study is required to discover how the compositions of the intestinal microbiome affect the chicken immune system's regulation.

2.2. Gut Microbiota Interaction with the Intestinal Barrier

The interruption of the intestinal barrier can ultimately result in the development of disease [66]. The experimental finding demonstrated that the microbiota, *L. reuteri* ATCC PTA 4659, can preserve the integrity of the gut and safeguard the mucosa through upregulation of epithelial heat shock proteins 25 and 70 [67]. Furthermore, the *L. reuteri* D8 strain can promote intestinal mucosa repair by stimulating the regeneration of intestinal stem cells (ISCs) [68].

Multiprotein complexes called tight junctions (TJ) regulate ion flow and prevent harmful germs from moving between gut epithelial cells [69]. Pathogens can cross the epithelial tissue when the intestinal mucosal barrier is disrupted by changes in multiprotein junctional complexes [70]. Microbiota can restore the health of gut barrier function through directly inhibiting pathogens, regulating the synthesis of junctional proteins, or rearranging the conformation of tight junction proteins [71]. Various studies demonstrated the positive effects of microbiota on the regulation of tight junction proteins. *Bifidobacterium infantis* strengthened TJs in mice with necrotizing enterocolitis through enhancing the expression of occludin and claudin 2, 4, and 7 [72]. The expression level of JAM2, occludin, ZO-1, and MUC2 were elevated in broiler chickens injected with lipopolysaccharide (LPS) from *Escherichia coli* and *Limosilactobacillus ingluviei* C37 [73]. Additionally, through bile salt hydrolase activity, gut bacteria can raise taurine levels in the gut. Elevated taurine levels decrease gut permeability, stop gut leakage, and upregulate the expression of TJ proteins [74].

Intestinal microbiota enhance the integrity of the intestinal barrier's mucus layer, which is essential for protecting against bacterial incursions. Mucin acts as a substrate for bacterial adherence, resulting in competition between non-pathogenic and pathogenic microorganisms [75]. The intestinal microbiota engages with mucin on various ways, influencing the proliferation of mucosal cells, mucin production, and breakdown [76]. *Lactobacillus*, *Bifidobacterium*, and *Enterococcus* in chickens augment the goblet cell cup area in the gut, dramatically upregulating MUC expression and boosting mucin glycoprotein production [77].

3. Mechanism of Gut Microbiota Supporting Colonization Resistance

Colonization resistance (CR) denotes the capacity of the gut microbiota to inhibit the invasion of pathogens and the overgrowth of indigenous, potentially pathogenic organisms [78]. The microbiota has evolved numerous strategies to defend against infections in the gut [79].

3.1. Resource-Based Colonization Resistance

Gut microorganisms effectively utilize most available nutrients, maintaining them at low levels in equilibrium, which in turn restricts the proliferation of pathogens. This holds significant importance for bacterial strains within the same species, as they frequently necessitate comparable nutrients [78]. Moreover, the competition for essential metal cofactors like iron, zinc, and manganese significantly influences resistance to pathogenic bacteria. For instance, gut microbiota engages in competition for zinc, rendering it inaccessible for *C. jejuni* [80]. *C. jejuni* engages in nutrient competition with commensals such as *Bacteroides vulgatus*, which can utilize analogous substrates. The results highlighted the role of colonization resistance against pathogens, emphasizing the competition for resources within the intestine [81]. A comprehensive exploration of the variety of nutrient sources utilized by pathogens and gut microbiota, along with the metabolites generated from the metabolism of these nutrients, is essential for grasping how we can reinstate colonization resistance. This understanding can inform the development of innovative microbiome therapeutics [82].

Moreover, gut microbiota strains exhibit strong adhesion capabilities, effectively obstructing pathogen adherence by competing for binding sites on host cells through proteinaceous factors that promote adhesion. *L. salivarius* CTC2197 significantly reduced the colonization of *S. enteritidis* in laying chickens by competing for available nutrients [83]. The resource-based competitive behaviours of microbiota have been explored and examined in vitro; however, their effectiveness and applicability in providing resistance against pathogens in chicken models still need to be determined. The competitive exclusion exerted by microbiota positively influences not just the intestine, but also other regions of the host where microbiota significantly contribute to health [84]. The ability of commensal bacteria to adhere to host tissue and combat pathogens represents traditional screening methods for selecting microbiota candidates; however, clinical studies in this area remain infrequent and often yield conflicting results. Enhanced in vitro and in vivo studies are essential to clarify the mechanisms and clinical effectiveness of microbota in addressing pathogenesis [85].

3.2. Metabolites-Based Colonization Resistance

Gut microbial communities generate various metabolites, such as SCFAs including acetate, propionate, and butyrate, as well as bile acids, bacteriocins, and vitamins [86]. The SCFAs serve as the main source of energy for intestinal enterocytes, contributing to the functionality of the gut barrier system. Additionally, they play a role in preventing pathogen colonization [87]. Acetic, propionic, and butyric acids, produced by anaerobic symbiotic bacteria such as *Bacteroides* and *Clostridia*, have been identified as significant factors in inhibiting the growth of *S. Typhimurium* in mice [88] and are also effective against pathogenic *E. coli* [89] and *C. jejuni* [90]. Butyrate negatively affected the motility and attachment of *C. jejuni*, which are essential for infection [91]. Furthermore, butyrate administration during *C. jejuni* induced enterocolitis in mice decreased the severity of diarrhoea and attenuated pro-inflammatory cytokines responses, leading to improved clinical outcomes [92]. Lactate decreases the expression of genes essential for virulence in *C. jejuni* [93]. SCFAs have been utilized in the management of foodborne pathogens, including *Salmonella* and *C. jejuni*, though outcomes have shown considerable variability [94]. Understanding the impact of

microbiota on SCFA production may yield important insights into the pathogenesis of *C. jejuni* and the interaction between host and microbiota in poultry.

Bile acids are significant compounds that directly influence CR, as bacteria convert them into secondary bile acids through 7-α-dehydroxylation [95]. It has been demonstrated that bile acids alter *C. jejuni* protein metabolism, specifically through the downregulation of fundamental biosynthetic pathways [96]. Additionally, deoxycholic acid, a secondary bile acid, has demonstrated efficacy in decreasing *C. jejuni* colonization in broiler chickens, likely through the accumulation of reactive oxygen species (ROS) and DNA damage [12].

Bacteriocin is a protein compound produced by certain bacteria that target and diminishe the viability of closely related bacterial species [97]. The microbiotas that have been studied for their potential to inhibit *C. jejuni* proliferation include *Lactobacillus*, *Bacillus*, and *Enterococcus* [98]. A prior study demonstrated that a bacteriocin (OR-7) produced by *L. salivarius* significantly inhibit *C. jejuni* proliferation in the cecum of chickens when added to their feed [99]. Another bacteriocin, SMXD51, derived from cecum-isolated *L. salivarius* SMXD51 strain, showed anti-*C. jejuni* activity when administered to broilers [100]. Similarly, the bacteriocin E 50-52, synthesized by *E. faecium*, demonstrated a significant capacity to nearly eliminate *C. jejuni* from the ceca of infected chickens [101]. Studies also indicated the effectiveness of *Saccharomyces cerevisiae* and *Bifidobacterium* spp. in preventing the colonization and proliferation of *C. jejuni* [102].

4. *Campylobacter jejuni* and Its Impact on the Gut Microbiota

C. jejuni is a thermophilic, obligately microaerophilic bacteria that is a primary pathogen associated with food poisoning in Europe [103]. Poultry represents a significant source of *C. jejuni* infections in humans [104]. *C. jejuni* has historically been recognized as non-pathogenic bacterium in the gut of chickens. However, numerous studies highlighted the influence of *C. jejuni* colonization on intestinal permeability and pro-inflammatory immune responses, characterizing it as a pathogen within the broiler chicken intestine [90,105]. The cecum exhibits extensive colonization, with bacterial populations reaching up to 10^9 per g, which increases the risk of horizontal transmission [106]. It has been reported that a single control strategy is inadequate for preventing *C. jejuni* in chickens [107]. Understanding the modulation of gut microbiota composition by *C. jejuni* is essential for the development of new interventions aimed at reducing its impact in chickens.

The age of the host, the type of bacterial strain, and the infection dose all affect *C. jejuni* colonization in broiler chickens. Rarely found in younger chickens, *C. jejuni* spontaneously colonizes birds between the ages of two and three weeks [108]. Investigating the metabolic pathways of *C. jejuni* may indicate insights into its interactions with gut commensal bacteria [109]. The genomic analysis of *C. jejuni* indicates an incomplete glycolysis pathway, potentially explaining its inability to utilize carbohydrates [110]. *C. jejuni* predominantly utilizes the citric acid cycle for energy production, employing various intermediates to facilitate this process. Among the various SCFAs present in the gut, only lactate and acetate are used by *C. jejuni* [111]. In addition, *C. jejuni* has the capability to utilize a range of amino acids, including glutamate, serine, asparagine, aspartate, and proline, to enhance its growth in the gut [15].

Metals like sulfur and iron are key elements for numerous enzymes in bacterial metabolism. *C. jejuni* can produce peptides that contain cystine derived from host epithelial cells in the gut, allowing it to acquire sulfur for its metabolic processes [17]. The main sources of iron are bound contained in complexes and are not accessible as free iron. In iron-deficient environments, many bacteria synthesize and secrete siderophores to chelate iron, utilizing specific transporters for their reabsorption [15]. *C. jejuni* does not synthesize its own siderophores; rather, it utilizes exogenous siderophores generated by the other

bacteria [18]. *E. coli* synthesizes a siderophore called enterobactin to facilitate iron uptake. *C. jejuni* lacks the ability to synthesize enterobactin; however, it can utilize the siderophore generated by *E. coli* [19].

Recent studies indicate that *C. jejuni* colonization affects the microbiota composition of commercial broiler flocks by enhancing the growth of specific bacteria while diminishing others (Figure 3) [13]. This association indicated that a lower abundance of *Proteobacteria* and an increased abundance of *Firmicutes* [112]. Firmicutes are recognized for their capacity to generate SCFAs from complex carbohydrates. The ability of *C. jejuni* to utilize organic acids generated by *Firmicutes* for energy and carbon suggests that the high abundance of *Firmicutes* in birds colonized by *C. jejuni* aligns with increased energy demands and may contribute to a reduction in the presence of *Proteobacteria* [113]. In newly hatched chickens, the abundance of *Proteobacteria* was significantly elevated and reduced with age, whereas *Firmicutes* became predominant as the birds matured [114]. The rise in *Firmicutes* and the decline in maternal antibodies may elucidate the broiler's vulnerability to *C. jejuni* during the second to third weeks of life.

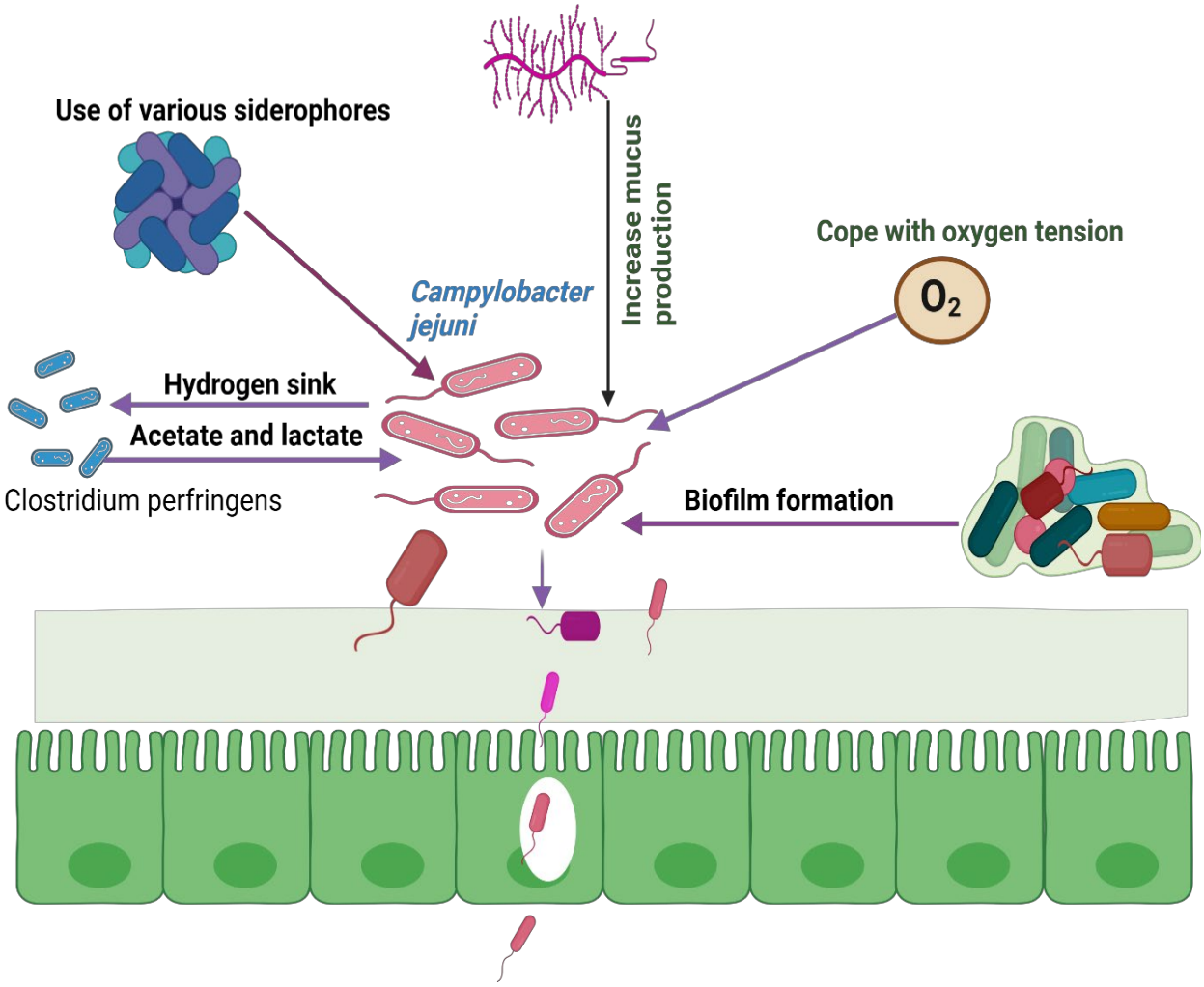

Figure 3. *Campylobacter jejuni* interaction with gut microbiota. Created in BioRender.com (accessed on 10 March 2025).

Broiler chickens with high *C. jejuni* colonization have higher *Streptococcus* and reduced *Lactobacillus* in their cecal microbiota [115]. *Streptococcus* generates lactate, a metabolite that can be metabolised by *C. jejuni* [116]. *Lactobacillus* spp. producing antimicrobial peptides that reduce *C. jejuni* colonization [94]. Reducing the quantity of *Lactobacillus* spp. may

enhance the proliferation potential of *C. jejuni* in colonized broilers [108]. Studies demonstrated the link between *C. jejuni* and *Clostridium* [117]. Specifically, *C. jejuni* may function as a hydrogen sink, facilitating the growth of certain *Clostridium* species and enhancing their competitive advantage via increased fermentation. This leads to a heightened generation of organic acids that can be utilized by *C. jejuni* [118]. The infection caused by *C. jejuni* increases mucin production in the gut, facilitating the proliferation of *Clostridium* spp. In vitro studies highlighted that the coculture of *C. jejuni* with *C. perfringens*, known for biofilm production, increases their proliferation and survivability [15]. The biofilms formed by *Pseudomonas* spp. also increase the survivability of *C. jejuni* on different surfaces [119]. A decrease in *Corynebacterium* was observed after *C. jejuni* colonization in chickens [19]. *Corynebacterium* metabolites have the potential to eliminate pathogenic biofilms in various environments and maintain mucus-associated lymphoid tissue integrity (Figure 3) [16].

F. prausnitzii plays a role in influencing the production of mucin synthesis by goblet cells [120]. Mucus serves as a protective niche for *C. jejuni* that enables resistance to intestinal peristalsis and organic acids [121]. *Bifidobacterium* produces carboxylic acid and succinate that are utilized *C. jejuni*, in low O_2 conditions (below 5%) [122]. It also possesses fucosidase, an enzyme that degrades mucin glycans, facilitating the breakdown of mucus to release fucose, which serves as an intermediate in the citric acid cycle of *C. jejuni* [123].

5. Outlook and Perspectives

The current understanding of the broiler chicken microbiota and its interaction with *C. jejuni* is largely derived from taxonomic profiling and comprehensive bacterial inventories [7]. These studies strengthen our knowledge of microbiota composition. In vitro models provide controlled settings for examining microbiota interactions; however, they cannot completely mimic the intricacies of host physiology, necessitating concurrent validation with in vivo models. In contrast, in vivo experiments illustrate the impact of microbiota in dynamic physiological states, control *C. jejuni* infection, and prevent lesion development [124]. Nevertheless, the principal components of the microbiome and the mechanisms underlying their protective roles remain unidentified. The integration of both techniques addresses individual limitations and offers a more comprehensive understanding of how variations in the poultry microbiome's communities relate to pathogens, growth conditions, environmental factors, and specific feed formulations [125]. Future research should prioritize functional and longitudinal analyses employing multi-omics techniques, including transcriptomics, metabolomics, and proteomics. Standardized experimental models and targeted manipulation of microbiota via probiotics or dietary fiber present potential strategies for sustainably controlling *C. jejuni* colonization in poultry. The application of artificial intelligence and machine learning facilitates the extraction of significant biomarkers and pathways from extensive datasets, thereby enhancing the investigation of enteric diseases and offering a comprehensive insight into the relationship between the gut microbiome and health.

6. Conclusions

The gut microbiota in broiler chickens serves as a crucial barrier to *C. jejuni* proliferation by means of immune modulation, competitive exclusion, and metabolite production. *C. jejuni* can utilize changes in microbiota and host factors to persist and induce infection. Understanding the interaction between gut microbiota and *C. jejuni*, particularly the pathogenic driving factors, is essential for reducing the load of *C. jejuni* in broiler chickens. Further research is necessary to obtain a comprehensive understanding of the molecular mechanisms underlying the interactions between gut microbiota, *C. jejuni*, and the chicken

immune system. This may facilitate the development of preventive or therapeutic strategies for controlling this zoonotic pathogen in poultry industry.

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