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Review Article

Review Article

The involvement of oral bacteria in inflammatory bowel disease

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Abstract

Microorganisms play an important role in the pathogenesis of inflammatory bowel disease (IBD). The oral cavity, the second-largest microbial niche, is connected to the gastro-intestinal tract. Ectopic gut colonization by oral microbes is a signature of IBD. Current studies suggest that patients with IBD often report more oral manifestations and these oral issues are closely linked with disease activity. Murine studies have indicated that several oral microbes exacerbate intestinal inflammation. Moreover, intestinal inflammation can promote oral microbial dysbiosis and the migration of oral microbes to the gastro-intestinal tract. The reciprocal consequences of oral microbial dysbiosis and IBD, specifically through metabolic alterations, have not yet been elucidated. In this review, we summarize the relationship between oral bacteria and IBD from multiple perspectives, including clinical manifestations, microbial dysbiosis, and metabolic alterations, and find that oral pathogens increase anti-inflammatory metabolites and decrease inflammation-related metabolites.

Keywords: inflammatory bowel disease; microbiota; oral bacteria; periodontitis; ectopic colonization

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder affecting the digestive tract, encompassing Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis. Growing evidence indicates that bacterial dysbiosis plays a prominent role in IBD development. The gastro-intestinal tract, extending from the oral cavity to the anus, harbors a variety of bacteria that colonize distinct ecological niches along its length [1]. Oral and intestinal microbes interact structurally and functionally [2]. Under normal physiological conditions, interactions between bacteria in different ecological niches are limited [3]. However, a microbial imbalance exists in pathological states compared with healthy controls (HCs) [4]. Ectopic colonization is more common in pathological states and worsens pathology [3, 5, 6]. A recent study investigated the dynamic alterations in oral bacteria in patients with IBD ($n = 22$) compared with HCs ($n = 8$) and found that there was a notable rise in the levels of Saccharibacteria (TM7) and Absconditabacteria (SR1) in the saliva of patients with IBD [7]. TM7 and SR1 are positively correlated with altered inflammatory cytokines in IBD, indicating that oral microbial dysbiosis is associated with inflammatory immune responses in IBD [7, 8]. These findings imply that the mouth can act as a reservoir for pathogens. The ectopic translation from the mouth to the intestine may contribute to triggering inflammation in individuals with IBD [9].

Recently, several reviews have been published on oral bacteria and gastro-intestinal disease [2, 8, 10–16]. These reviews summarize the oral bacteria contributing to IBD and the related mechanisms; however, these mechanisms mainly focused on the host immune response (Table 1). For example, *Klebsiella* spp., *Fusobacterium nucleatum*, and *Campylobacter concisus* can drive pro-inflammatory cytokine release in the gut [14]. However, systematic summaries exploring the role of oral bacteria in IBD through metabolic alterations are limited.

Thus, a more comprehensive and profound understanding of the oral–intestinal microbial axis will provide better insights into the progression of IBD. Here, we review the relationship between oral bacteria and IBD from multiple perspectives, including clinical manifestation, microbial dysbiosis, and metabolic alteration.

Clinical manifestations

Periodontal diseases, including gingivitis and periodontitis, have been linked to gastro-intestinal disorders. Periodontitis, a type of

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Table 1. The mechanisms of oral bacteria affecting gut inflammation summarized in previous reviews

Oral bacteria	Pathway	References
Veillonella spp.	(i) *Veillonella* spp. correlate with increased levels of circulating lymphocytes (ii) *V. parvula* positively correlates with the inflammatory marker calprotectin (iii) Adhesive bacteria (involving *Veillonella*) increase Th17 cell activation and luminal secretory IgA (iv) *Veillonella* spp. positively coexist with *Clostridioides* in *C. difficile* colonization patients	Read E, 2021 [14] Lu Y, 2023 [15]
Klebsiella spp.	(i) *Klebsiella* spp. interact with macrophages to promote the release of IL-1β via cysteine-11-mediated inflammatory vesicles, activating intestinal inflammasome (ii) *Klebsiella* spp. can activate Th1 cells via IFN-γ and Th17 cells (iii) *K. pneumoniae* invades the colonic mucus layer and intestinal epithelial cell lines, and translocates across the intestinal epithelium through Rho GTPase- and PI3K/Akt-dependent cell invasion (iv) The capsular polysaccharide of *K. pneumoniae* resists the opsonization and phagocytosis of macrophages, DCs, neutrophils, and epithelial cells (v) *K. pneumoniae* downregulates *Lactobacillus reuteri* and *Bifidobacterium pseudolongum*, and alters cecal metabolome (e.g. SCFAs)	Read E, 2021 [14] Lu Y, 2023 [15] Kitamoto S, 2022 [2] Qi Y, 2022 [10] Imai J, 2021 [3]
Streptococcus mutans	(i) *S. mutans* exacerbates colitis though IFN-γ signaling (ii) *S. mutans* positively correlates with the inflammatory marker calprotectin	Read E, 2021 [14]
Streptococcus salivarius	(i) *S. salivarius* downregulates the NF-κB pathway by LPS and inhibits PPARγ activation (ii) *S. salivarius* alters I-FABP and Angptl4 gene products regulating intracellular lipid accumulation (iii) *S. salivarius* reacts upon gastro-intestinal-derived CD4+ T cells and activates monocytes to secrete higher levels of IL-6, IL-12, and TNF (the Th1- and Th17-skewed cytokines) (iv) *S. salivarius* positively correlates with the inflammatory marker calprotectin	Read E, 2021 [14] Lu Y, 2023 [15]
Streptococcus agalactiae	*S. agalactiae* reacts upon gastro-intestinal-derived CD4+ T cells and activates monocytes to secrete higher levels of IL-6, IL-12, and TNF (the Th1- and Th17-skewed cytokines)	Lu Y, 2023 [15]
Haemophilus parainfluenzae	*H. parainfluenzae* correlates with the inflammatory marker calprotectin	Read E, 2021 [14]
Rothia mucilaginosa	*R. mucilaginosa* correlates with the inflammatory marker calprotectin	Read E, 2021 [14]
Campylobacter concisus	*C. concisus* can be classified into adherent toxigenic *C. concisus* (*AToCC*) and adherent invasive *C. concisus* (*AICC*) (i) *AToCC* possess a Zot, upregulate PAR2 expression, and break tight junctions and cytoskeletal remodeling; Zot can stimulate intestinal epithelial cells and macrophages to release pro-inflammatory cytokines and enhance the responses of macrophages to other enteric bacteria (ii) *AICC* can stimulate neutrophil cells by upregulating the neutrophil adherence molecule CD11b and oxidative burst response (iii) *C. concisus* flagellum-mediated attachment to and invasion of the colonic epithelial cell line Caco-2 (iv) *C. concisus* increases intestinal permeability through the downregulation of ZO-1, occludin, and claudin-5, together with apoptotic leaks (v) *C. concisus* impairs sodium (Na+) absorption in HT-29/B6 cells through the dysfunction of the epithelial Na+ channels, dependent on IL-32-regulated extracellular signal, regulated protein kinase (ERK)1/2, and claudin-8-dependent barrier dysfunction (vi) *C. concisus* increases levels of pattern-recognition receptors (e.g. TLR4, but not TLR2 or TLR5) (vii) *C. concisus* reduces autophagy-related genes, such as ATG9B (viii) Virulence factor membrane-bound hemolytic PLA2 exhibits cytolytic effects (ix) *C. concisus* enhances inflammatory response (IL-2, IL-5, IL-18, CCL2, IL-8, COX-2, IL-8 and TNF-α, CREB1, NF-κB, STAT, and interferon regulatory factor, IFI16 inflammasome, TLR3)	Read E, 2021 [14] Qi Y, 2022 [10] Kitamoto S, 2022 [2]
Fusobacterium nucleatum	(i) *F. nucleatum* reduces the killing capacity of macrophages and NK cells (ii) *F. nucleatum* aggravates the progression of DSS-induced colitis by promoting M1 macrophage polarization through the activation of the AKT2 pathway (iii) *F. nucleatum* and its outer membrane vesicles activate the TLR/MyD88/NF-κB pathway, promoting the secretion of a series of pro-inflammatory cytokines, including IL-8, TNF, keratinocyte-derived chemokine (KC), IL-6, IFN-γ, and MCP-1 (iv) *F. nucleatum* activates the STAT3 signaling pathway, promoting Th1 and Th17 responses (v) *F. nucleatum* activates the CARD3/IL-17F/NF-κB cascade in epithelial	Read E, 2021 [14] Lu Y, 2023 [15] Qi Y, 2022 [10] Kitamoto S, 2022 [2]

(continued)

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Table 1. (continued)

Oral bacteria	Pathway	References
	cells (vi) Fap2 protein produced by *F. nucleatum* interacts with TIGIT, mediates NK-cell and T-cell inhibition, while T cell regulates inflammatory factors IL-10, IL-1β, and IL-6 (vii) *F. nucleatum* coexists with *Clostridium* through adhesin RadD, encouraging the bacterial biofilm formation of the intestinal mucus layer (viii) *F. nucleatum* invades human intestinal epithelial cell lines, disrupts the integrity of the epithelial barrier, reducing tight junction proteins such as ZO-1 and occluding, and stimulates the function change of MUC2 (ix) H2S produced by *F. nucleatum* inhibits the effective use of anti-inflammatory butyrate in colon cells	
Porphyromonas gingivalis	(i) *P. gingivalis* disrupts the intestinal barrier by downregulating tjp-1 and Zo-1 (ii) *P. gingivalis* secretes gingipains (iii) *P. gingivalis* LPS activates Th2 response: significantly higher levels of IL-5, IL-10, and IL-13 but a lower level of IFN-γ, and activates Th17 cells (iv) *P. gingivalis* stimulates the overgrowth of commensal microbes in the intestine (generally upregulates Bacteroidetes and Deferribacteres, and downregulates Firmicutes) (v) *P. gingivalis* positively correlates with *Pyricularia pennisetigena* and *Alternaria alternata* (vi) *P. gingivalis* upregulates phenylalanine, tyrosine, and tryptophan in the intestinal microbiota, and alanine, glutamine, histidine, tyrosine, and phenylalanine in serum	Imai J, 2021 [16] Lu Y, 2023 [15] Qi Y, 2022 [10] Kitamoto S, 2022 [2]
Fusobacterium varium	*F. varium* invade the intestinal epithelium and evoke the production of pro-inflammatory cytokines, such as IL-8 and TNF-α	Kitamoto S, 2022 [2]
Atopobium parvulum	*A. parvulum* increases expression of CXCL1 and IL-17 in the gut and induces pro-inflammatory molecules (e.g. COX-2, IL-8, and CEBPB) in epithelial cells and to promote T-cell activation by liberating H2S	Kitamoto S, 2022 [2]
Staphylococcus aureus	(i) *S. aureus* causes epithelial damage in the small, but not the large, intestine by producing SEB (ii) *S. aureus* dampens adheren junction protein expression (iii) *S. aureus* interacts with antigen-presenting cells (e.g. macrophages and dendritic cells)	Kitamoto S, 2022 [2]

IL = interleukin, IFN = interferon, PI3K = phosphatidylinositol 3-kinase, DCs = dendritic cells, SCFA = short-chain fatty acid, NF-κB = nuclear factor-κB, LPS = lipopolysaccharides, PPARγ = peroxisome proliferator-activated receptor γ, Zot = zonula occludens toxin, Zo-1 = zonula occludens-1, TLR = Toll-like receptor, NK = natural killer, MCP-1 = monocyte chemoattractant protein-1, STAT = signal transducer and activator of transcription, CARD = caspase activation and recruitment domain, H2S = hydrogen sulfide, CXCL1 = chemokine (C–X–C motif) ligand 1, COX = cyclooxygenase, CEBPB = CCAAT enhancer-binding protein beta, SEB = staphylococcal enterotoxin B.

periodontal disease, is characterized by progressive destruction of the supporting structure of the teeth, such as the gum and bone surrounding the teeth [17, 18]. Its association with the accumulation of dental plaque and bacterial dysbiosis is well established [19]. Inflammation induced by bacteria present in dental plaque contributes to periodontitis [20]. *Porphyromonas gingivalis* is the major causative agent of periodontitis [4, 21]. A recent study showed that incipient periodontitis contributes to an increased short CD activity index [3]. A notable correlation was observed between periodontitis or tooth loss and increased IBD-related disability over the past 12 months [22]. Animal experiments demonstrate that saliva from patients with periodontitis exacerbates dextran sodium sulfate (DSS)-induced colitis [23] and ligature-induced periodontitis aggravates gut inflammation in a murine model of colitis [24]. IBD is accompanied by an increased incidence of periodontal disease and periodontal disease can affect the disease activity of IBD.

Microbial dysbiosis

The gut bacteria of healthy individuals are dominated by four bacterial phyla: Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, and ∼90% of them belong to Firmicutes and Bacteroidetes [25]. Patients with IBD have shown a significant reduction in microbial biodiversity (especially Firmicutes) and decreased stability. Increased levels of *Ruminococcus gnavus*, *Escherichia coli*, and *Clostridium bolteae*, and decreased levels of *Faecalibacterium prausnitzii* and *C. hathewayi* have been observed in IBD [26]. Furthermore, patients with IBD have shown a reduction in gut bacteria that produce short-chain fatty acids (SCFAs) [27]. The oral cavity, with >700 species, is the second-largest microbial library after the gastro-intestinal tract [28]. The diversity of species increases even more under diseases such as periodontitis [29]. IBD affects oral bacterial composition, with an abundance of bacteria such as TM7 and *Veillonella* in the oral cavity of patients with IBD compared with HCs [30]. Additionally, the oral bacterial community composition differs in patients with both IBD and periodontitis ($n = 6$) compared with those with periodontitis alone ($n = 6$). The periodontitis-only group also exhibited a greater prevalence of Actinobacteria, Bacteroidetes, and Fusobacteria, whereas the CD combined with periodontitis group showed higher levels of Firmicutes and Proteobacteria [31]. Chen *et al.* [32] found that, compared with the periodontitis-only group, *Eikenella*, *Capnocytophaga*, *Prevotella_2*, and *Prevotella* were more abundant in the CD combined with periodontitis ($n = 14$) group than in the periodontitis-only group ($n = 14$). Furthermore, *Capnocytophaga* and *Streptococcus oralis* were identified in CD combined with periodontitis-associated predominant microbial species, whereas *Streptococcus* and Bacillales were identified as periodontitis-associated predominant bacteria [31]. Elmaghrawy

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et al. [9] developed a prognostic model for IBD and achieved an area under the receiver-operating characteristic curve of 0.762 (IBD, $n = 156$; HCs, $n = 102$) based on IBD-related oral microbial dysbiosis. Thus, periodontal diseases that can cause oral bacterial dysbiosis are more prevalent in IBD, and IBD itself significantly influences the composition of oral bacteria.

Under normal conditions, interactions between oral and gut bacteria are limited. However, oral bacteria can ectopically colonize the gastro-intestinal tract and cause detrimental digestive diseases under certain circumstances [33]. Hematogenous and enteral dissemination have been proposed as potential routes of ectopic colonization from the mouth to the gut [2]. Oral bacteria can survive with dendritic cells and macrophages, aiding their movement from the oral cavity to the intestinal compartment. Oral bacteria easily and frequently disseminate into the blood through oral wounds, gingival crevices, and other untreated carious lesions [13, 34]. For instance, the presence of *P. gingivalis* has been identified in the bloodstream of patients with periodontal diseases [35]. An adult human is estimated to consume approximately 600 times daily and generate ∼1.5 L of spit containing 1.5×10^{12} bacteria [2, 34]. Balanced gastric acidity serves as the first barrier against ectopic colonization from the oral cavity to the gut [2, 36], but patients with IBD experience a decrease in gastric acidity, potentially enabling the transfer of oral bacteria, such as *S. salivarius* [2, 36]. Given that IBD is more susceptible to medications that affect pH, including proton-pump inhibitors (PPIs), it is plausible that the use of PPIs may also encourage the abnormal colonization of oral bacteria. Additionally, some oral pathological bacteria, such as *P. gingivalis*, can tolerate acidic environments and translocate to the gut [37]. Colonization resistance, provided by gut-resident bacteria, acts as a secondary barrier against ectopic colonization; however, this is attenuated by microbial dysbiosis and gut inflammation in IBD [6, 38]. The pathological changes in IBD establish the foundation for the migration of oral bacteria to the intestines. Consistently, the gut bacteria exhibited greater resemblance to the oral bacteria in patients with IBD ($n = 60$) compared with those with HCs ($n = 45$), indicating a higher prevalence of ectopic gut colonization by oral bacteria in IBD [3]. *In vivo* experiments with germ-free mice receiving saliva samples from patients with CD revealed that most fecal bacterial species were minor components of salivary bacteria [34]. These findings verify that oral bacteria can translocate to the gut. Furthermore, salivary bacteria can disrupt the balance of intestinal bacteria. Rats treated with periodontitis saliva samples exhibited increased levels of *Roseburia* and *Lactobacillus*, accompanied by lower relative abundances of *Oscillibacter*, *Colidextribacter*, and *Bacteroides* [39]. Saliva samples collected from both periodontitis patients and healthy individuals, when administered to mice groups, resulted in variations in the gut microbiota composition between the two groups. These differences were particularly notable in DSS-induced colitis, with significant changes in the genera *Blautia*, *Aerococcus*, *Ruminococcus*, and *Helicobacter* [23]. Oral-derived bacteria such as *P. gingivalis*, *F. nucleatum*, and *Klebsiella* spp. (e.g. *K. pneumoniae*) have been reported to exacerbate gut inflammation *in vivo* [2, 10]. Additionally, oral administration of *P. gingivalis* leads to alterations in the intestinal bacterial composition [40]. For instance, there was a notable increase in the proportions of unclassified Coriobacteriaceae, Gemellaceae, and Clostridiaceae, whereas the proportions of unclassified S24-7, Prevotellaceae, Mogibacteriaceae, *Dorea*, *Butyricicoccus*, and *Bilophila* showed a significant decrease after *P. gingivalis* administration [40]. In addition to bacteria, the presence of *P. gingivalis* in mice had an impact on the structure and diversity of the gut mycobiome [41]. *Pyricularia pennisetigena* and *Alternaria alternata* are positively correlated with *P. gingivalis* [41].

Relationship between oral microbes and IBD from a metabolic perspective

Metabolic nature of IBD

Metabolic alterations have also been described in patients with IBD [42]. Metabolites play important roles in the pathogenesis of IBD [43–45]. Metabolomics refers to the systematic profiling of small-molecule metabolites in biological samples, encompassing sugars, amino acids, organic acids, nucleotides, and lipids [46–48]. Proton nuclear magnetic resonance spectroscopy and mass spectrometry including liquid chromatography and gas chromatography are the most widely used tools in metabolomics [49]. Metabolomics primarily involves two approaches: targeted and untargeted. Targeted metabolomic studies are hypothesis-driven, focusing on the precise and accurate measurement of predefined sets of metabolites. In contrast, untargeted metabolomic studies involve the simultaneous measurement of a wide spectrum of metabolites within the sample. The samples utilized in metabolomics in IBD mainly include serum, plasma, feces, and urine [42, 50–52]. Different samples provide different types of biochemical information. Serum and plasma provide an insightful snapshot of systemic metabolism, whereas feces reflect digestive metabolism, including microbiota-related metabolites, host–microbial co-metabolites, and microbial transformation of dietary components [50]. Urine is a better indicator of host, microbial, and exogenous metabolites such as drugs [50]. Several major pathways affected by bacteria in IBD include lipid, amino acid, and bile acid metabolism [53]. Lipids include fatty acyl glycerophospholipids and sphingolipids. Fatty acids are classified as SCFAs, medium-chain fatty acids (MCFAs), and long-chain fatty acids (LCFAs). SCFAs are found at lower levels in the feces of patients with IBD than in that of patients with HCs and are related to disease activity [27, 54, 55]. MCFAs, such as pentanoate, hexanoate, heptanoate, octanoate, and nonanoate, were significantly decreased in patients with IBD (IBD, $n = 151$; HCs, $n = 40$) [56]. Polyunsaturated fatty acids (PUFAs), a subtype of LCFAs, are classified as n-3 and n-6 PUFAs. Consumption of a diet characterized by an elevated ratio of n-6 to n-3 PUFAs is linked to increased susceptibility to CD [57]. Moreover, a higher intake of n-6 PUFAs increased the risk of UC [58, 59]. Conversely, the intake of n-3 PUFAs has been linked to a reduced risk of UC [58, 59]. Monounsaturated fatty acids (MUFAs), a subtype of LCFAs, exhibit decreased levels in both the blood and intestinal mucosa. However, the therapeutic effectiveness of MUFAs for IBD remains controversial [60–62]. Lysophosphatidylcholine (LysoPC) and lysophosphatidylcholine (LysoPS) levels are elevated in the stool and blood of patients with IBD [63–65]. LysoPC and LysoPS have been identified to impair the epithelial and immune barrier [62]. Sphingolipids are the most differentially abundant metabolites in the stool of IBD patients and perturbed sphingolipid metabolism contributes to the inflammation process [63, 66]. Disordered amino acid and bile acid metabolic pathways have also been observed in IBD. Tryptophan levels in both serum and feces were also reduced in IBD [67, 68]. A pivotal study conducted by Vantrappen *et al.* [69] involving 13 non-operated patients with CD, 10 patients with UC, and 10 HCs revealed that patients with CD, but not UC, displayed a reduced size of the bile acid pool in comparison with those with HCs. Furthermore, a reduction in the size of the bile acid reservoir showed an inverse correlation with the Colitis Disease Activity Index and the percentage of

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unconjugated bile acids increased in IBD [69]. Perturbation of metabolites in IBD is believed to be associated with gut microbial dysbiosis [70, 71]. Additionally, the existence of *Akkermansia municiphila*, *Oscillibacter* spp., and *Bilophila wadsworthia* was related to the levels of dicarboxylic acids, sebacate, dodecanedioate, taurine, and *N*,*N*,*N*-trimethyl-alanyl-proline betaine [72]. Caprylic acid was positively correlated with *Alistipes shahii*, *A. putredinis*, and *A. finegoldii*, whereas it was significantly and negatively correlated with the abundance of *R. gnavus* [66]. Recent studies have demonstrated the interaction between oral microbes and IBD through the metabolic pathway.

Inflammatory metabolites provide the basis for ectopic colonization

Microbiota-mediated colonization resistance has been implicated as a mechanism for separating oral and colonic niches in gnotobiotic murine experiments [6]. However, whether this mechanism is essential in humans remains unknown [73]. Rashidi *et al.* [73] recruited healthy volunteers ($n = 43$) exposed to a short course of a single antibiotic, patients with acute leukemia ($n = 39$), and stem cell transplant recipients ($n = 29$). The latter two groups had only one oral species colonizing the gut, even considering the influence of antibiotics and the extent of damage to the gut microbiota. This suggests that colonization resistance was dispensable in oral and gut microbiota segregation [73]. The colon possesses certain physicochemical traits (such as reduced oxygen levels and fecal toxins) and there are various antimicrobial defenses from the mouth to the colon (including gastric acid, bile salts, mucosal immunoglobulins, and antimicrobial peptides) [73]. By eliminating microbiota-mediated colonization resistance, these barriers may be effective enough to prevent ectopic colonization [73]. However, within the context of persistent inflammation such as IBD, the chemical barrier against ectopic colonization is destroyed, leading to dysbiotic microbiota and creating opportunities for ectopic colonization. For instance, *Veillonella parvula*, an oral microbe that derives its energy from organic acids, was abundant in the gut of patients with IBD [5]. Subsequent investigations revealed that nitrate, as a specific metabolite of inflammation, could provide fundamental conditions for oral microbes, such as *V. parvula*, to translocate from the oral cavity to the gut because nitrate respiration allows oral microbes to use amino acids and peptides as carbon sources [5].

Ectopic colonization of oral microbes promotes metabolic disorders

Oral bacteria have been demonstrated to affect gut and serum metabolites (Table 2). Salivary bacteria of periodontitis, when administered to rats, significantly affected metabolites related to lipids, indoles, and their derivatives [39]. When saliva samples from periodontitis patients were administered to DSS-treated mice via gastric gavage, it was found that salivary bacteria exacerbated DSS-induced colitis [23]. Periodontitis salivary bacteria alter the levels of anti-inflammatory metabolites, including SCFAs and tryptophan-related metabolites, and increase metabolites related to inflammation, such as arachidonic acid, in DSS-induced colitis [23]. SCFAs derived from bacteria play crucial roles in preserving host immune homeostasis and reinforcing epithelial integrity [62]. This is achieved through their interactions with receptors such as GPR41, GPR43, GPR109a, and OLFR78 (in mice) or OR51E2 (in humans), as well as via host epigenetic modifications, in both a G protein-coupled receptor (GPCR)-independent and -dependent manner [62]. Tryptophan, an essential aromatic amino acid, is primarily metabolized through three major pathways. Gut bacteria facilitate the conversion of tryptophan into different compounds, which include ligands of the aryl hydrocarbon receptor [77]. Additionally, the kynurenine pathway functions in immune and epithelial cells through indoleamine 2,3-dioxygenase (IDO) 1 [77]. The third pathway involves the production of serotonin (5-hydroxytryptamine) in enterochromaffin cells via tryptophan hydroxylase 1 [77]. The kynurenine pathway comprises ≥90% of tryptophan catabolism [78]. Inflammatory cytokines such as IFN-γ, TNF-α, and IL1β are abundant in IBD and induce the upregulation of IDO 1 [78]. Therefore, we hypothesized that oral bacteria might affect tryptophan levels through microbial dysbiosis or by exacerbating inflammation. For arachidonic acid metabolism, the upregulation of prostaglandin I2, prostaglandin F2α, and dihydroxyeicosatrienoic acid was observed following the administration of saliva in periodontitis [23]. *Aerococcus* and *Ruminococcus* exhibited a strong positive correlation with arachidonic acid metabolism but a negative correlation with the biosynthesis of unsaturated fatty acids [23]. In contrast, *Blautia* and *Helicobacter* displayed a contrasting association [23]. Periodontitis salivary bacteria exacerbate DSS-induced colitis and enhance colitis-induced anxiety-like behaviors via metabolic pathways [23, 74]. The histidine metabolism plays a critical role in the underlying pathway in this process because periodontitis salivary bacteria alter histidine metabolism in both gut and brain metabolomics [74]. Additionally, the supplementation of histidine-related metabolites had a similar anxiety-worsening impact to periodontitis salivary bacteria [74]. The serum metabolome of mice was modified by administering *P. gingivalis* orally, resulting in increased levels of alanine, glutamine, histidine, tyrosine, and phenylalanine [40]. In addition, *P. gingivalis* can alter the serum metabolome by influencing gut mycobiomes such as *Amphiamblys*, *P. pennisetigena*, and *Valsa malicola*. For instance, *P. gingivalis* administration enriched the presence of *P. pennisetigena*, which showed a positive connection to metabolites related to lipid metabolism-related metabolites, such as LysoPC. Additionally, it displayed a negative relationship with indole-3-acetamide, 5-hydroxy-tryptophan, and indoleacetaldehyde [41]. Certain oral pathogens, such as *Klebsiella*, were positively correlated with primary and conjugated bile acids, including cholic acid, taurocholic acid, and glycochenodeoxycholic acid, or taurochenodeoxycholic acid (IBD, $n = 32$; HC, $n = 23$) [12, 76]. Certain oral bacteria including *Atopobium*, *Fusobacterium*, *Veillonella*, *Prevotella*, *Streptococcus*, and *Aggregatibacter* which are positively correlated with the severity of intestinal disease, metabolize sulfur-containing amino acids into hydrogen sulfide (H2S), an inflammatory mediator [2]. *Atopobium parvulum* is recognized as the principal pathobiont and plays a pivotal role as a central hub within the H2S network (IBD, $n = 131$; HC, $n = 63$) [75]. *Atopobium parvulum*-induced colitis in interleukin-10-deficient ($IL10^{-/-}$) mice was mitigated by the H2S scavenger bismuth [75]. In contrast, germ-free $IL10^{-/-}$ mice monocolonized with *A. parvulum* did not experience significant colitis, indicating that other microbes or their byproducts are necessary for the development of *A. parvulum*-driven colitis [75]. It is possible that *A. parvulum* promotes the growth of colitogenic pathogens by inducing H2S, which can stimulate pro-inflammatory molecules such as cyclooxygenase-2, IL-8, and CCAAT enhancer-binding protein beta in epithelial cells and facilitate T-cell activation [79]. Other indigenous oral bacteria, such as *Streptococcus* and *Neisseria*, can generate acetaldehyde through the catabolism of ethanol and glucose [80]. Considering the pro-inflammatory potential of acetaldehyde, which can disrupt epithelial barrier function [2, 81], it is conceivable that the ectopic colonization of the gut by these oral bacteria may trigger gut

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Table 2. The effect of oral bacteria in IBD via the metabolic pathway

Author, year	Subjects	Oral microbiota	Sample	Metabolites	Detection methods	Action
Rojas-Tapias DF, 2022 [5]	Mouse, vitro	*V. parvula*	–	Nitrate	–	Nitrate facilitates ectopic colonization of oral *V. parvula* in the intestine
Qian J, 2022 [23]	Mouse	Periodontitis salivary microbiota	Gut	(i) Anti-inflammatory metabolites: SCFAs and tryptophan-related metabolites (ii) Inflammatory metabolites: arachidonic acid metabolism including PGI2, PGF2α, and dihydroxyeicosatrienoic acid (iii) Unsaturated fatty acid biosynthesis	LC–MS (Thermo Ultimate 3000 system)	(i) Periodontitis salivary microbiota decreased SCFAs, tryptophan-related metabolites, and unsaturated fatty acid biosynthesis, and increased arachidonic acid metabolism (ii) *Aerococcus* and *Ruminococcus* were significantly positively related to arachidonic acid metabolism and negatively correlated with unsaturated fatty acid biosynthesis, whereas *Blautia* and *Helicobacter* showed the opposite correlation with less significance
Kato T, 2018 [40]	Mouse	*P. gingivalis*	Serum	Alanine, Glutamine, Histidine, Tyrosine, and Phenylalanine	NMR spectrometer (Bruker Avance II 700; Bruker Biospin, Rheinstetten, Germany)	*P. gingivalis* administration elevated alanine, glutamine, histidine, tyrosine, and phenylalanine in the serum
Chen S, 2022 [41]	Mouse	*P. gingivalis*	Serum	(i) Lipid metabolism: LysoPC (ii) Tryptophan metabolism: indole-3-acetamide, 5-hydroxy-tryptophan, and indoleacetaldehyde	Untargeted metabolomics profiling (Thermo UHPLC-Q Exactive Mass Spectrometer)	*P. gingivalis* administration altered metabolic pathway through gut mycobiome (i) *P. gingivalis* elevated *P. pennisetigena* (ii) *P. pennisetigena* was positively correlated with LysoPC, and negatively correlated with indole-3-acetamide, 5-hydroxy-tryptophan, and indoleacetaldehyde
Qian J, 2023 [74]	Mouse	Periodontitis salivary microbiota	Caecum content	Histidine metabolism	LC–MS, UHPLC, and AB SCIEX TripleTOF 6600	(i) Periodontitis salivary microbiota altered the gut and brain metabolites via gut microbiota (ii) Bacteroidaceae were closely associated with gut metabolites, including NAH and L-Dopa, whereas only Enterobacteriaceae were associated with brain metabolites
Mottawea W, 2016 [75]	Human, mouse	*A. parvulum*	Mucosal-luminal interface samples	H2S	16S rDNA sequencing, qPCR, HPLC-ESI-MS/MS	*A. parvulum* playing a pivotal role as the central hub within the H2S network
Yang ZH, 2021 [76]	Human	*Klebsiella*	Feces	Cholic acid, taurocholic acid, and glycochenodeoxycholic acid or taurochenodeoxycholic acid	Targeted metabolomics profiling (Waters XEVO TQ-S mass spectrometer)	*Klebsiella* was positively correlated with the primary and conjugated bile acids including cholic acid, taurocholic acid, and glycochenodeoxycholic acid or taurochenodeoxycholic acid

SCFAs = short-chain fatty acids, PGI2 = prostaglandin I2, PGF2α = prostaglandin F2α, LC–MS = liquid chromatography–mass spectrometry.

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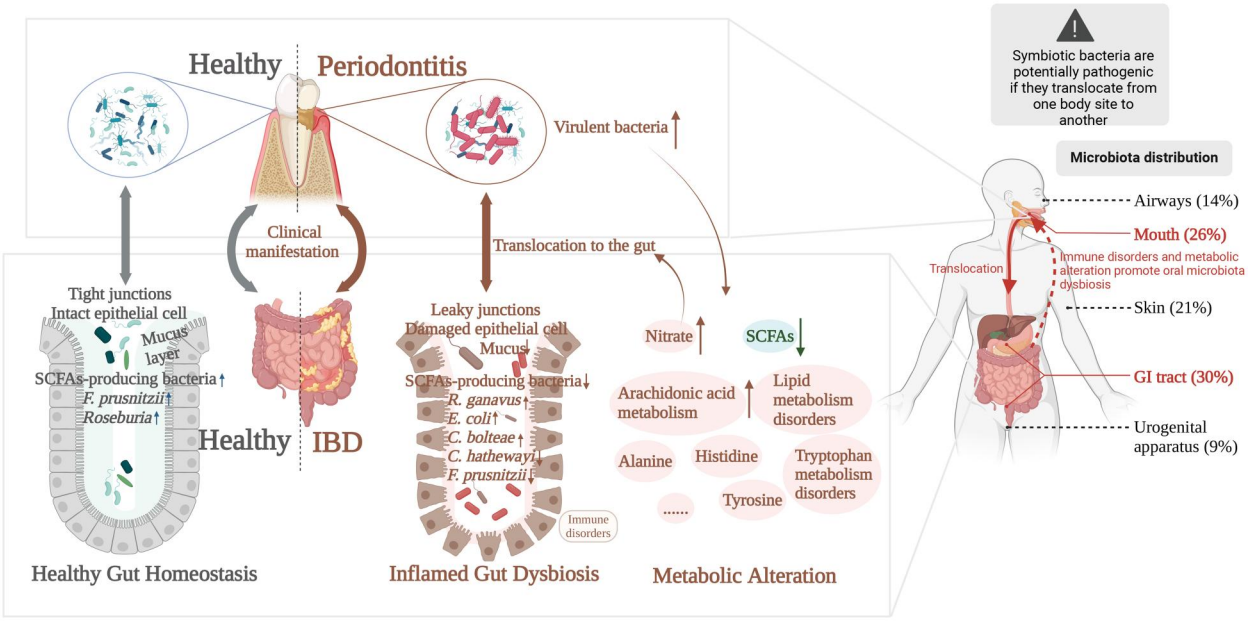

Figure 1. Mutual interaction between oral microbiota dysbiosis and IBD. Patients with IBD have more pronounced oral clinical manifestations and periodontitis is associated with active disease. Virulent oral bacteria worsen IBD and contribute to oral microbiota dysbiosis, leading to metabolic alteration and immune disorders. Translocation of oral bacteria results in metabolic alteration such as increased arachidonic acid metabolism and decreased SCFAs in IBD. Specific metabolites in IBD such as nitrate facilitate ectopic colonization of oral bacteria in the gut. (Created using BioRender.com.) IBD = inflammatory bowel disease, SCFA = short-chain fatty acid.

inflammation. These findings revealed that oral pathogens elevate anti-inflammatory metabolites and decrease inflammation-related metabolites.

Perspectives

Microbial studies on IBD have focused on the bacteria in the gut. The translocation of oral bacteria to the gut in IBD highlights the role of the oral–intestinal microbial axis. We hypothesized that ectopic colonization of oral pathological bacteria could promote IBD, which in turn boosts oral bacterial dysbiosis (Figure 1). Accumulating evidence supports an underlying association between oral microbes and IBD. Additionally, the oral cavity is an easily accessible site for microbial community assessment. The convenience and non-invasiveness of saliva collection compared with blood and feces make it an ideal candidate for the diagnosis or monitoring of IBD. However, prediction models based on a combination of oral and gut bacteria have yet to be developed. However, the association between oral bacteria and IBD remains unclear. Most studies on the oral–intestinal microbial axis are based predominantly on second-generation sequencing of 16S rRNA, yet this is insufficient for species identification in most bacteria. With advancements in sequencing technology, more precise and comprehensive sequencing technologies such as metagenomic techniques can be used to explore the association between oral bacteria and IBD. Additionally, the effects of oral bacteria on IBD have mainly been studied from the perspective of the immune response. Research on metabolic shifts resulting from ectopic colonization of oral bacteria is in its nascent stages and deserves further investigation.

Authors' Contributions

B.X. and J.H. conceived the original idea for this study. B.X. performed a literature search and formulated the study protocol. M. Z., J.H., and M.Z. revised the manuscript. All authors reviewed and approved the final draft of the manuscript.

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Conflicts of Interest

The authors declare that there is no conflict of interests in this study.

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