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The interplay between oral microbiota, gut microbiota and systematic diseases

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ABSTRACT

Over the past two decades, the importance of microbiota in health and disease has become evident. The human gut microbiota and oral microbiota are the largest and second-largest microbiome in the human body, respectively, and they are physically connected as the oral cavity is the beginning of the digestive system. Emerging and exciting evidence has shown complex and important connections between gut microbiota and oral microbiota. The interplay of the two microbiomes may contribute to the pathological processes of many diseases, including diabetes, rheumatoid arthritis, nonalcoholic fatty liver disease, inflammatory bowel disease, pancreatic cancer, colorectal cancer, and so on. In this review, we discuss possible routes and factors of oral microbiota to affect gut microbiota, and the contribution of this interplay between oral and gut microbiota to systemic diseases. Although most studies are association studies, recently, there have been increasing mechanistic investigations. This review aims to enhance the interest in the connection between oral and gut microbiota, and shows the tangible impact of this connection on human health.

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Introduction

The human gut microbiota is the largest microbiota in the human body, which contains more than 10 trillion microbes that reside in the human intestine. The gut microbiota is broadly classified by six major phyla, namely Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia. The phyla Firmicutes and Bacteroidetes represent 90% of gut microbiota [1]. The dysbiosis of gut microbiota is related to many systemic diseases, such as obesity [2], diabetes [3], rheumatoid arthritis [4] and gastrointestinal diseases [5]. The human oral microbiota is the second-largest microbiota in the human body, after gut microbiota. The oral microbiota consists of over 700 bacterial species along with fungi, viruses and protozoa, with only 54% are validly named species, 14% are unnamed (but cultivated) and 32% are known only as uncultivated phylotypes [6]. This complex microbiota colonizes teeth, prosthodontics surfaces and mucosal surfaces, and it exists in a surface-attached community called dental plaque. Saliva also contains an enormous number of oral bacteria, and the salivary microbiota is more stable than that of dental plaque [7]. Given that the oral mucosa and gastrointestinal mucosa are physically connected, and saliva is ingested every day by the gut, literature has demonstrated interrelationships between the oral and gut microbiota [8–10]. In this review, we will focus on the routes and influences of oral microbiota on gut microbiota, and also on possible factors of oral microbiota to affect gut microbiota. Lastly, we will review the link between oral microbiota, gut microbiota and systematic diseases.

Routes of oral microbiota to affect gut microbiota

Enteral route

People swallow 0.75 ~ 1.5 L saliva per day which contains numerous resident oral bacteria [11]. Salivary microbes from both periodontitis patients and healthy controls could survive in the gut of mice for at least 24 hours [12], suggesting that the enteral route may be an important route for oral microbiota to affect the gut microbiota. However, gastric acid and alkaline bile pose a great bottleneck for oral microbiota to localize in the gut, there

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Importance: The human gut microbiota and oral microbiota are the largest and second-largest microbiome in the human body respectively, and they are physically connected. Emerging and exciting evidence has shown complex and important connections between gut microbiota and oral microbiota, but a systemic review of this connection is lacking. This review summarizes possible routes and factors of oral microbiota to affect gut microbiota, and the contribution of this interplay between oral and gut microbiota to systemic diseases. This review aims to enhance the interest in the connection between oral and gut microbiota, and shows the tangible impact of this connection on human health.

is a heavy debate about whether oral microbiota can colonize the gut through the enteral route. A recent study indicated that there was no evidence for the colonization of oral bacteria in the distal gut of healthy adults [13]. On the contrary, Schmidt et al. concluded that at least one in three oral microbiota can settle the gut in healthy adults, and patients with bowel cancer and rheumatoid arthritis had more mouth-to-gut microbial transmission than their healthy counterparts [14]. Gut diseases such as gastritis, inflammatory bowel disease, colorectal cancer, and so on, allow translocated oral bacteria to colonize and expand in the gut [10]. Saliva contains mucus (comprised of water, lipids and proteins such as mucins) which can protect microbiota from gastric acid for survival along the gastrointestinal tract [15]. Oral gavage of periodontitis-related saliva can aggravate mice models of diabetes [16], colitis [17], Alzheimer's disease [18] and osteoporosis [19]. Patients with severe periodontitis were estimated to swallow approximately 10^{12}-10^{13} *Porphyromonas gingivalis (P. gingivalis)* bacteria per day [20–22], and oral gavage of *P. gingivalis* in mice could alter gut microbiota [23–25].

Hematogenous route

Oral mechanical injuries caused by daily dental activity (e.g. hard mastication, brushing) and dental procedures (e.g. scaling and root planning, orthodontics, extraction) enable oral bacteria to spread into the systemic circulation [26,27]. Besides, periodontitis causes vascularization and gingival ulceration in periodontal pockets which allow periodontal pathogens to readily enter the bloodstream [28]. The hematogenous route may be the preferred way over the enteral route for oral fusobacteria to reach colon tumors [29].

Immune cell migration route

Some oral bacteria can survive intracellularly in immune cells, such as dendritic cells and macrophages, indicating that oral bacteria may hijack host immune cells to serve as Trojan horses for dissemination from oral mucosa to gut mucosa [28]. In addition, immune cells derived from oral draining of lymph nodes can migrate to other lymphoid tissues, including but not limited to the gut [30]. Oral pathobiont-reactive T helper 17(Th17) cells can migrate to an inflamed gut. When in the gut, Th17 cells of oral origin can be activated by translocated oral pathobionts and cause the development of colitis [31].

Factors of oral microbiota to affect gut microbiota

The salivary microbiome affects the gut microbiota

Transplanting saliva of severe periodontitis patients into mice by oral gavage could alter gut microbiota, beta diversity of gut microbiota was significantly different from that of the control group, *Porphyromonadaceae* and *Fusobacterium* were increased, and *Akkermansia* was decreased [12], suggesting salivary microbiota could change gut microbiota by the enteral route. Transplanting saliva of periodontitis patients into mice with colitis by oral gavage could accelerate colitis, and change inflammatory bowel disease–associated microbiota, such as *Blautia*, *Helicobacter* and *Ruminococcus* [17] (Table 1).

P. gingivalis affects gut microbiota

P. gingivalis is one of the most important pathogenic bacteria in periodontitis. It is also the most studied oral pathogenic bacteria affecting gut microbiota. To investigate the effects of *P. gingivalis* on gut microbiota, we should first clarify the following questions: 1. Can *P. gingivalis* colonize the oral cavity in animal models? 2. Can *P. gingivalis* colonize the gut? 3. What is the effect of *P. gingivalis* on gut microbiota? These three aspects will be discussed in the following.

P. gingivalis colonizes mouse oral cavity and affects oral microbiota

It is generally believed that *P. gingivalis* can colonize the oral cavity of mice. *P. gingivalis* could be detected in the oral cavity of mice 7 days after *P. gingivalis* inoculation [35]. Four weeks and 8 weeks after stopping *P. gingivalis* topical application in the gingiva of mice, *P. gingivalis* DNA could still be detected in the oral cavity, suggesting that *P. gingivalis* can colonize and proliferate in mouse gingiva [36]. *P. gingivalis* inoculation in oral cavities of mice leads to elevation of the total cultivatable commensal bacterial load and changes the qualitative composition of oral microbiota [35], increases oral microbial diversity and allows the colonization of potential opportunistic species [37].

Can P. gingivalis colonize the gut?

Due to the harsh environment of gastric juice and bile, whether *P. gingivalis* can colonize the gut is still uncertain. To simulate the gastric environment *in vitro*, *P. gingivalis* was exposed to artificial gastric juice (AGJ). Only 1% of *P. gingivalis* planktonic cells were viable after 2 h of exposure to AGJ at pH 5 which is equivalent to the pH immediately after a meal. The survival rate was dramatically increased by the

Table 1. Studies about the effects of oral bacteria and salivary microbiota on gut microbiota.

Objects	Groups	Duration	Application	Samples	α diversity	β diversity	Phylum	Genus
8w C57BL/6J mice [32]	*Aggregatibacter actinomycetemcomitans vs.* control	6 × per week for 6 weeks	10^8 CFU by oral gavage	Feces	No		No	*Turicibacter*↓
3w female Wistar rats [33]	*Fusobacterium nucleatum vs.* control	2 w, 4 w, 8 w	3.6×10^{11} CFU/ml in the open pulp to induce apical periodontitis	Rectum			Proteobacteria↑ Firmicutes↑ Bacteroidetes↓ Verrucomicrobia↓	*Akkermansia muciniphila*↓
8w male C57BL/6 mice [34]	*Streptococcus mitis vs.* control	5 × per week for 2 weeks	10^9 CFU by oral gavage	Feces				*Turicibacter*↓ *Lactobacillus*↓
8w male C57BL/6 mice [34]	*Streptococcus salivarius vs.* control	5 × per week for 2 weeks	10^9 CFU by oral gavage	Feces				*Bacteoides*↑ *Lactobacillus*↓
8w male C57BL/6 mice [34]	*Prevotella nigrescens vs.* control	5 × per week for 2 weeks	10^9 CFU by oral gavage	Feces				*Bacteoides*↑ *Lactobacillus*↓
7w male C57BL/6 mice [12]	Saliva of periodontitis patients *vs.* saliva of periodontal healthy controls	Once a day for 2 weeks	200 μL by oral gavage	Feces	No	Yes		*Porphyromonadaceae* ↑ *Fusobacterium*↑ *Akkermansia*↓
7w male C57BL/6 mice with colitis [17]	Saliva of periodontitis patients *vs.* saliva of periodontal healthy controls	Every other day for 2 weeks	100 μL by oral gavage	Feces	No	Yes		*Blautia* ↓ *Helicobacter*↓ *Aerococcus*↑

Comparison condition A *vs.* condition B: ↑ Increase in condition A relative to condition B, ↓ Decrease in condition A relative to condition B. CFU, colony forming units.

formation of a *P. gingivalis* biofilm. Almost 100% of cells survived at pH 5 [38]. Because *P. gingivalis* forms complex biofilms with a variety of bacteria in the oral cavity, the results of this *in vitro* experiment cannot be deduced *in vivo*. Li et al. attempted to address this question by using germ-free mice. They developed a human oral microbiota-associated mouse model (HOMA) by swabbing human saliva in the mouth of germ-free mice, and also developed a human microbiota-associated mouse model (HMA) by intragastrical gavage of human fecal suspension in germ-free mice. Then, they cohoused HOMA and HMA model. The cohoused model showed increased *Porphyromonas* and decreased *Turicibacter* in the small intestine, compared with the HMA model. This result suggested that *Porphyromonas* played a key role in competing with gut microbiota for colonization in the small intestine [39].

P. gingivalis affects gut microbiota

Numerous studies have shown that *P. gingivalis* could change gut microbiota composition [23–25,34,37,38,40–48] (Table 2), and the duration time ranges from 2 days after oral gavage of *P. gingivalis* for once [25] to 10 weeks of repeatedly applying *P. gingivalis* [42]. Most studies used oral gavage [23–25,34,38,41,43–45,47], while some applied *P. gingivalis* in the oral cavity [37,40,46,48], and one study used intravenous injection [42]. Three studies reported no significant change in alpha diversity [25,44,45], and two reported decreased alpha diversity [40]. Five studies showed significant difference in beta diversity [24,25,37,43,48], and one study demonstrated no difference in beta diversity [44]. *P. gingivalis* belonged to the phylum Bacteroidetes, at the phyla level, and some studies showed the proportion of Bacteroidetes was increased [23–25,37,40] while some were contrary [38,43,48]. Firmicutes were another major phylum in gut microbiota, with one study showing an increased abundance of Firmicutes [38], and other studies showing decreased Firmicutes [23–25,40]. Interestingly, *P. gingivalis* induced opposite changes in some gut microbiota species in wild-type mice (WT) and streptozocin-induced mice (STZ). The abundance of *Lactobacillus* was decreased in WT mice but was increased in STZ mice. The abundance of *Turicibacter* was increased in WT mice but was decreased in STZ mice. This shows that hyperglycemia may influence bacterial growth and alter the composition of gut microbiota in mice [44].

Fusobacterium nucleatum affects gut microbiota

Fusobacterium nucleatum (*F. nucleatum*), which is involved in the development of periodontal disease and apical lesions, has been reported to affect the gut microbiota. After inducing apical periodontitis in rat molars by infecting the dental pulp with *F. nucleatum*, *F. nucleatum* can be detected in the gut at 2 weeks, and change gut microbiota, with confirmed infection in the large intestines [33].

Aggregatibacter actinomycetemcomitans affects gut microbiota

Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans) is frequently detected in severe periodontitis and is associated with local aggressive periodontitis [50]. After administering *A. actinomycetemcomitans* by oral gavage in mice for 6 weeks, the genus *Turicibacter* in the gut was significantly decreased [32]. This genus correlates with the production of butyric acid [51], and a decrease in butyrate has been associated with insulin resistance [52].

Gut microbiota affect oral microbiota

Since the oral cavity is physically connected to the intestine, some researchers reported that the change in gut microbiota could also affect oral microbiota. Branchereau et al. found that different types of gut microbiota correlate to different types of oral microbiota. After a long-term fat-enriched diet, gut microbiota profiles of mice could be classified into three types: diabetic-resistant, intermediate and diabetic-sensitive. Only the periodontal microbiota of diabetic-sensitive mice showed the abundance of the genera *Prevotella* and *Tannerella*, which are major periodontal pathogens, suggesting the interaction of gut microbiota and oral microbiota [53]. Similarly, Xiao et al. found that diabetes caused oral microbiota to become more pathogenic. After the onset of hyperglycemia, the oral microbiota had increased levels of *Enterobacteriaceae, Aerococcus, Enterococcus and Staphylococcus*, which are often associated with periodontitis [54].

Oral microbiota, gut microbiota and systemic diseases

The bidirectional relationship between oral and systemic diseases has been documented in many studies [55–62]; however, the role of oral-gut axis in systemic diseases has been recently proposed [63–68]. Herein we summarized the contribution of interplay between oral microbiota and gut microbiota to systemic diseases. Although most studies are association studies, recently, there have been increasing mechanistic investigations. Researches in diabetes and inflammatory bowel disease showed stronger associations between oral-gut axis and disease progression, while other studies showed weaker associations, such as in nonalcoholic fatty liver disease, rheumatoid arthritis,

Table 2. Main studies about the effects of *P. gingivalis* on the gut microbiota.

Objects	Groups	Duration	Application	Phylum	Class	Order	Family	Genus
8 w male C57BL/6N mice [23]*	Pg (W83) *vs.* control	2 × per week for 5 weeks	10^9 CFU of live Pg by oral gavage	Firmicutes↓ Bacteroidetes↑		Bacteroidales↑		
7 w male C57BL/6 mice [25]	Pg (W83) *vs.* control	6, 24, or 48 hours	10^9 CFU of live Pg by oral gavage	At 48 h Firmicutes↓ Bacteroidetes↑				*S24–7*↑ *Prevotella*↑ *Clostridiales*↓
7 w male DBA/1J mice [38]	Pg (W83) *vs.* *P. intermedia* (ATCC2561)	2 × per week for 5 weeks	10^9 CFU of live bacteria by oral gavage	Firmicutes↑ Bacteroidetes↓				*Bacteroides*↓ *Prevotella*↓ *Allobaculum*↑
8 w male ApoE$^{-/-}$ mice [40]	Pg (strain 381) *vs.* control	5 × per week for 3 weeks	Pg applied to the buccal surface of the maxillary gingiva	Bacteroidetes↑ Firmicutes↓ Tenericutes↑	Bacilli↓ Clostridia↓		S24–7↑ Lachnospiraceae↓ Ruminococcaceae↓ Anaeroplasmataceae↑	
8 w C57BL/6J mice, HFD [42]	Pg *vs.* control	2 × per week for 10 weeks	10^8 CFU of sonicated Pg by intravenous injection	Tenericutes↓ Proteobacteria↓			Alcaligenaceae↑ Erysipelotrichaceae↑ Dehalobacteriaceae↓	*Bilophila*↓ *Dehalobacterium*↓ *Sutterella*↑ *Allobaculum*↑
7 w male C57BL/6 mice [43]	Pg (W83) *vs.* control	2 × per week for 5 weeks	10^9 CFU of live bacteria by oral gavage	Deferribacteres↑ Bacteroidetes↓			S24–7↓ Paraprevotellaceae↓ Mogibacteriaceae↓ Deferribacteriaceae↑ Gemellaceae↑ Clostridiaceae↑	*Coriobacteriaceae*↑ *Gemellaceae*↑ *Clostridiaceae*↑ *S24–7* and *Dorea*↓ *Prevotellaceae*↓ *Mogibacteriaceae*↓ *Butyricicoccus* and *Bilophila*↓
8 w male C57BL/6J mice with STZ [44]	Pg (ATCC33277) *vs.* control	2 × per week for 5 weeks	10^8 CFU of live Pg by oral gavage	Deferribacteres↑				*Lactobacillus*↑ *Turicibacter*↓ *Mucispirillum*↑ *Mucispirillum schaedler*↑
8 w male C57BL/6J mice [44]	Pg (ATCC33277) *vs.* control	2 × per week for 5 weeks	10^8 CFU of live Pg by oral gavage	Deferribacteres↑				*Lactobacillus*↓ *Turicibacter*↑ *Mucispirillum*↑ *Mucispirillum schaedler*↑
8 w C57BL/6J mice [45]	HF-Pg *vs.* HF-co	2 × per week for 6 weeks	10^8 CFU sonicated Pg by oral gavage	Proteobacteria↑ Actinobacteria↓	Coriobacteriia↓ Erysipelotrichia↓ Betaproteobacteria↑	Turicibacterales↓	Turicibacteraceae↓	*Turicibacter*↓
SKG mice [46]	Pg *vs.* control	2 × per week for 6 weeks	10^8 CFU of live Pg by oral inoculation			Bacteroides↑ Firmicutes↓ Deferribacteres↓ Clostridiales↓ Deferribacteres↓	S24–7↑	
8 w male C57BL/6 mice [34]	Pg *vs.* control	5 × per week for 2 weeks	10^9 CFU of live Pg by oral gavage					*L. salivarius*↓ *S. sciuri*↑, *B. massiliensis*↑ *B. thetaiotaomicron*↑ *L. reuteri*↑
7 w male C57BL/6N mice [49]	Pg (W83) *vs.* control	5× per week for 3 weeks	10^9 CFU of live Pg by oral gavage					*Lactobacillus*↓ *Eubacterium fissicatena*↑ *Atopostipes*↑ *Colidextribacter*↑

(*Continued*)

Table 2. (Continued).

Objects	Groups	Duration	Application	Phylum	Class	Order	Family	Genus
8 w male C57BL/6J mice [37]	Pg (strain 381) *vs*. control	5 × per week for 3 weeks, 2× per week for 3 weeks	Pg applied to the buccal surface of the maxillary gingiva	Bacteroidetes↑				*Bifidobacterium*↓ *Desulfovibrio*↓ *A. muciniphila*↓ *Coprobacter*↓ *Bacteroides*↑ *Clostridium IV*↑ *Flavonifractor*↑ *Pseudoflavonifractor*↑ *Barnesiella* ↑ *Parabacteroidetes*↑
7 w male C57BL/6 mice [24]	Pg (W83) *vs*. control	Every day for 9 weeks	10^9 CFU of live Pg by oral gavage	Bacteroidetes↑ Firmicutes↓	Clostridia↓	Clostridium↓	Muribaculaceae↑ Christensenaceae↓	*Ruminococcaceae*↑ *Eubacterium*↓ *Ruminococcaceae*↓ *Tyzzerella* and *Dubosiella*↓ *Lachnospiraceae*↓ *Tyzzerella*↓ *Marvinbryantia*↓
8 w male C57BL/6J mice [48]	Pg (strain 381) *vs*. control, Western diet	5 × per week for 3 weeks	Pg applied to the buccal surface of maxillary gingiva				Lachnospiraceae↓	*Anaerosporobacter*↓ *Flavonifractor*↓ *Eisenbergella*↓
8 w male C57BL/6J mice [48]	Pg (strain 381) *vs*. control, Control diet	5 × per week for 3 weeks	Pg applied to the buccal surface of maxillary gingiva	Bacteroidetes↓				*Alistipes*↑*Robinsoniella*↑ *Bacteroides*↓ *Flavonifractor*↓ *Coprobacillus*↓ *Clostridium*↓

Comparison condition A *vs*. condition B: ↑ Increase in condition A relative to condition B, ↓ Decrease in condition A relative to condition B. Pg, *Porphyromonas gingivalis*. CFU, colony forming units. *Samples are illum content. While samples are feces in other studies. STZ, streptozotocin. HF, high fat.

pancreatic cancer, colorectal cancer, atherosclerotic disease and Alzheimer's disease.

Diabetes

For type 1 diabetes mellitus patients, there was a decreased abundance of oral commensal bacteria *Streptococcus salivarius*, which was associated with its decrease in the gut as well as higher abundances in facultative anaerobes including Enterobacteria. The increased Enterobacteria could drive gut inflammation, thus had an impact on diabetes progression [69]. Many studies have reported that oral microbiota could cause gut dysbiosis and insulin resistance [16,44,45,70,71] (Table 3). The mechanism of the increased insulin resistance caused by oral microbiota may lie in gut dysbiosis, increased gut permeability, systemic inflammation and metabolic derangement. *Turicibacter*, a butyrate-producing bacterium, was decreased in the gut microbiota after oral gavage of *P. gingivalis* [44,45]. Periodontitis induced by ligature also decreased butyrate-producing bacteria in the gut [16], and a decrease in butyrate has been associated with increased insulin resistance [52]. Depleting gut microbiota or transplanting healthy gut microbiota after induction of periodontitis could decrease insulin resistance, indicating that the gut microbiota may mediate the influence of periodontitis on prediabetes [16]. Another study demonstrated that saliva of periodontitis patients could not increase insulin resistance in diabetes germ-free mice, suggesting the important role of gut microbiota in mediating the influence of oral microbiota on diabetes [72].

Increased gut permeability caused by oral microbiota may be another mechanism. Oral gavage of *P. gingivalis* or *F. nucleatum* or saliva of periodontitis patients could decrease tight junction proteins in the gut [12,23,70,73–75], thus increased gut permeability allows bacteria to penetrate the intestinal epithelium, which is critical in the progression of type 1 diabetes by disturbing the intestinal immune response [76]. Inflammation in the gut also plays a significant role in diabetes progression [76]. Hepatic or adipose inflammation was significantly increased by *P. gingivalis* treatment [23,44,70], and serum levels of endotoxin, IL-6, TNF-α and IL-1β were significantly increased by oral gavage of periodontitis patients' saliva [16]. An alteration of serum metabolites, which is strongly correlated with gut dysbiosis, demonstrated that some specific microbiota-derived metabolites played a role in the pathogenesis of *P. gingivalis*-induced diabetes [70]. Metabolites in small intestinal tissues and in feces of *P. gingivalis* treatment mice also showed derangement, aggravating hyperglycemia in an obese type 2 diabetes mouse model [71].

Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is currently regarded as the most common chronic liver disease worldwide [77], affecting approximately one-quarter of the world's population [78]. NAFLD contains nonalcoholic fatty liver (NAFL), which has limited pathologic progression, and nonalcoholic steatohepatitis (NASH) which has a more severe progressive nature. The pathogenesis of NAFLD has not yet been completely elucidated. Two hits [79] and multiple hits hypotheses [80] have been suggested to explain the pathogenesis of NAFLD. Recently, the 'oral-gut-liver axis' [66] and 'oral-liver axis' [81] were promoted, indicating the role of oral microbiota in inducing NAFLD. Many studies demonstrate that *P. gingivalis* or *A. actinomycetemcomitans* can worsen NAFLD pathology [32,42,48,49,82–86]. The connection between oral microbiota and NAFLD may lie in oral bacteria or endotoxin transplantation to the liver, hepatic inflammation, systemic inflammation, and gut dysbiosis. Firstly, *P. gingivalis* and its lipopolysaccharide (LPS) can translocate from the oral cavity to the liver, and induction of NAFLD would accelerate *P. gingivalis* and its LPS translocation [87,88]. Secondly, hepatic inflammation is the driver of NAFLD [89], and *P. gingivalis* infection in the dental chamber could increase TLR2, TNF-αand IL-17 expression in the liver, *in vitro* studies showed that NLRP3 inflammasome in hepatocytes was activated by Pg-LPS [82]. Interestingly, it seems that both periodontitis and *P. gingivalis* infection are important factors in the progression of NASH since ligature-induced periodontitis without *P. gingivalis* infection only caused weak effects on liver tissue [90], and when *P. gingivalis* was pasted to the periodontal tissue of the rats without ligature placement, there was only scarce lipid deposition in the liver [83]. Elimination of *P. gingivalis* infection by local and systemic antibiotics [86] or scaling and root planning therapy [84] could alleviate NAFLD pathology, further suggesting the connection between *P. gingivalis* infection and NAFLD. Thirdly, systemic inflammation could aggravate NAFLD [91], and periodontitis is usually accompanied by low-grade systemic inflammation. Serum endotoxin was increased after *P. gingivalis*-induced periodontitis [83], and serum IL-6 was increased after ligature-induced periodontitis [90]. Lastly, gut dysbiosis is closely associated with NAFLD [92–94], and oral pathobiont could cause gut dysbiosis, so that hepatic pathology worsened by oral pathobiont may be related to gut dysbiosis. Studies have shown that *P. gingivalis* application by oral gavage [49] or

Table 3. Studies about the effects of oral bacteria and gut microbiota on diabetes.

Objects	Groups	Duration	Application	Diabetes	Possible mechanisms	Phylum	Class	Order	Family	Genus
8 w male C57BL/6J mice [16]	Silk ligature *vs.* control	6 weeks	Ligating the bilateral maxillary second molars	FBG↑ HbA1c↑ AUC↑	Gut microbiota mediates the influence of periodontitis on prediabetes				Parabacteroides↑ Desulfovibrionaceae↑	Butyrate-producing genera↓
8 w male C57BL/6J male mice [70]*	Pg (ATCC33277) *vs*. control	2 × per week for 6 weeks	10^9 CFU of live Pg by oral gavage	FBG↑ HOMA-IR↑ IPGTT-AUC↑	Gut Permeability↑ Inflammatory markers in adipose tissue↑ Altered serum metabolites correlated with gut dysbiosis	Firmicutes↓ Bacteroidetes↑				*Lachnospiraceae*↓ *Muribaculaceae*↑ *Akkermansia*↑ *Prevotella*↑ *Porphyromonadaceae*↑
8 w male C57BL/6J male mice [44]	STZ Pg (ATCC33277) *vs*. STZ control	2 × per week for 5 weeks	10^8 CFU of live Pg by oral gavage	FBG↑ Plasma insulin↑ Body weight↓	Genes of tight junctions and inflammatory markers ↑	Deferribacteres↑				*Lactobacillus*↑ *Turicibacter*↓ *Mucispirillum*↑ *Mucispirillum schaedler*↑
Obese *db/db* diabetes mice [71]	Pg (ATCC33277) *vs*. control	Every 3 days for 30 days	10^9 CFU of live Pg by oral gavage	*FBG*↑ OGTT↑	Changes in the intestinal metabolites, gluconeogenesis-related enzymes and metabolites↑	Bacteroidetes↑ Firmicutes↓			Prevotellaceae↑	*Prevotella*↑
8 w C57BL/6J mice [45]	HF-Pg *vs*. HF-control	2 × per week for 6 weeks	10^8 CFU of sonicated Pg by oral gavage	Impaired glucose tolerance and insulin resistance	Insulin signaling↓ TNF-a↑ pAkt↓	Proteobacteria↑ Actinobacteria↓ Deferribacteres↓	Coriobacteriia↓ Erysipelotrichia↓ Betaproteobacteria↑	Turicibacterales↓	Turicibacteraceae↓	*Turicibacter*↓

*Samples are colon contents, while samples in other studies are feces. FBG, Fasting blood glucose. AUC, area under the curve. HOMA-IR, The homeostatic model assessment-insulin resistance.

oral inoculation [48] or intravenous injection [42] could aggravate NAFLD and cause gut dysbiosis, however, the distinct role of gut microbiota in mediating the oral microbiota worsening NAFLD should be further studied.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation that can result in damage to articular cartilage and bone [95]. Autoantibodies to citrullinated proteins are one of the diagnostic criteria for RA. Citrullinated proteins arise from the posttranslational modification of arginine, catalyzed by peptidylarginine deiminases (PADs) [96]. *P. gingivalis* is identified as an environmental factor for RA as *P. gingivalis* is the only oral bacterium that has a bacterial PAD enzyme [97]. In RA patients, Anti-Pg-LPS IgG antibody levels were inversely correlated with activity abilities, and Serum LPS-binding protein levels were correlated with disease biomarker levels. These results suggest that substances from oral and gut microbiota may influence disease activity in RA patients [98]. Many studies have demonstrated that *P. gingivalis* administration exacerbated RA, whether *P. gingivalis* was administered before the onset of RA [99–102] or concurrently with RA [46,103] or after RA induction [102]. *P. gingivalis* is more pro-arthritic compared to other periopathogens such as *Prevotella intermedia* [38] and *F. nucleatum* [102] or commensal bacterium *Bacteroides thetaiotaomicron* [74]. *P. gingivalis* may link RA and periodontitis by affecting the gut immune system and the gut microbiota composition [38,46], as fecal microbiota transplantation (FMT) from Pg-inoculated experimental arthritis mice resulted in more joint destruction compared to FMT from experimental arthritis mice [46]. Furthermore, RA could also act back on the gut immune system and gut barrier, as arthritic mice showed downregulation of IL-10 and tight junction molecule expression in the small intestine, and a decreased number of mucus-producing goblet cells in the intestinal epithelium. This would permit *P. gingivalis* to further break down the gut barrier and increase bacterial load in the colon [74]. Concordance has been observed between the gut and oral microbiomes in RA patients, and dysbiosis was detected in the gut and oral microbiomes of RA patients, which was partially resolved after RA treatment [104].

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a group of chronic relapsing inflammatory conditions of the gastrointestinal tract, which contains two clinical types – ulcerative colitis (UC) and Crohn's disease (CD). At present, the etiology of IBD is still not fully understood, environmental and genetic factors are believed to play a significant role in IBD progression [105]. The salivary microbiota of IBD patients shows evident dysbiosis and different ecotypes, most of which exhibit the same variation tendencies in the gut of IBD patients, suggesting that saliva may be a convenient tool to identify at-risk populations of IBD [106]. Oral microbiota contains the highest abundance of *Enterobacteriaceae* compared with other mucosal sites [107], and *Klebsiella*, an oral species belonging to *Enterobacteriaceae*, can ectopically colonize and persist in the colon and cecum when gut microbiota is dysbiotic, and elicit gut inflammation in a genetically susceptible host. They induce T helper 1 cells when colonizing the gut [108]. Another study shows two ways for oral microbiota to worsen IBD. The direct pathway is the expansion of *Klebsiella/Enterobacter* species in the oral mucosa caused by periodontitis, which can ectopically colonize the lower gut and promote colitis through IL-1β. The indirect pathway is, oral Th17 cells that arise during periodontitis can migrate to the gut and contribute to gut inflammation [31].

Pancreatic cancer

Pancreatic cancer is the most aggressive cancer worldwide, with a 5-year survival rate of 8% [109]. In a prospective study using oral wash samples, increased oral pathogens such as *P. gingivalis* and *A. actinomycetemcomitans*, were associated with a higher risk of pancreatic cancer, while increased commensal oral bacteria, such as Phylum Fusobacteria and its genus *Leptotrichia,* were associated with lower risk of pancreatic cancer [110]. In another prospective study, individuals with high levels of plasma antibodies to *P. gingivalis* showed a twofold increase in pancreatic cancer compared to those with low levels. In addition, high levels of antibodies to common oral bacteria had a 45% lower risk of pancreatic cancer [111]. A recent retrospective study showed that dysbiotic gut microbiota in the pancreatic cancer patients formed a complex network with salivary microbiota, and microbiota in pancreatic cancer tissue also formed co-occurrence networks with both gut and oral microbiota [112]. Intraductal papillary mucinous neoplasms (IPMNs) are pancreatic cysts that can progress to pancreatic cancer. Increased oral bacteria including *F. nucleatum* and *Granulicatella adiacens* in cyst fluid from IPMN was found in individuals with high-grade dysplasia, suggesting the role of oral bacteria in IPMNs to pancreatic cancer [113]. Inflammation is one of the

fundamental causes of pancreatic cancer, *P. gingivalis* can migrate to the pancreas after oral gavage, and accelerate pancreatic tumor progression by increasing tumor cell proliferation and the secretion of neutrophils elastase [114].

Colorectal cancer

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer death in the world [115]. Early and convenient screening of CRC is critical. Fecal microbiota is reported to be potentially suitable for screening of CRC, with sensitivity ranging from 52.6% to 76.6% [116,117], while combining the data from fecal microbiota and oral swab microbiota, the screening sensitivity increased to 76% for CRC and 88% for polyps, with 95% specificity for both. Interestingly, gut microbiota rich in *Lachnospiraceae* was negatively correlated with oral pathogen colonization in the gut, suggesting that the gut microbiota protects against ectopic colonization of environmental bacteria in the bowel [118]. Oral bacteria, such as *Peptostreptococcus*, *Streptococcus* and *Solobacterium* spp., were at a significantly higher relative abundance in saliva and stool samples of CRC patients compared with controls, suggesting that indigenous oral bacteria may have promoted initiation of CRC carcinogenesis [119]. *F. nucleatum* is a Gram-negative commensal anaerobe as part of the gut and oral flora, generally found in human dental plaque. Compared to healthy controls, over-abundance of *F. nucleatum* was found in colorectal tissue biopsies [120] and saliva [121] in CRC patients. Identical strains of *F. nucleatum* were detected in their colorectal cancer and oral cavity, suggesting that *F. nucleatum* in CRC originates from the oral cavity [122]. Oral communities have the highest variation and the richest sequences of *F. nucleatum*, but only certain strains of *F. nucleatum* are enriched in the gastrointestinal tract, and others are diminished during translocation [123]. The hematogenous route may be the preferred way for oral *F. nucleatum* to reach colon tumors other than the enteral route [29]. *F.*

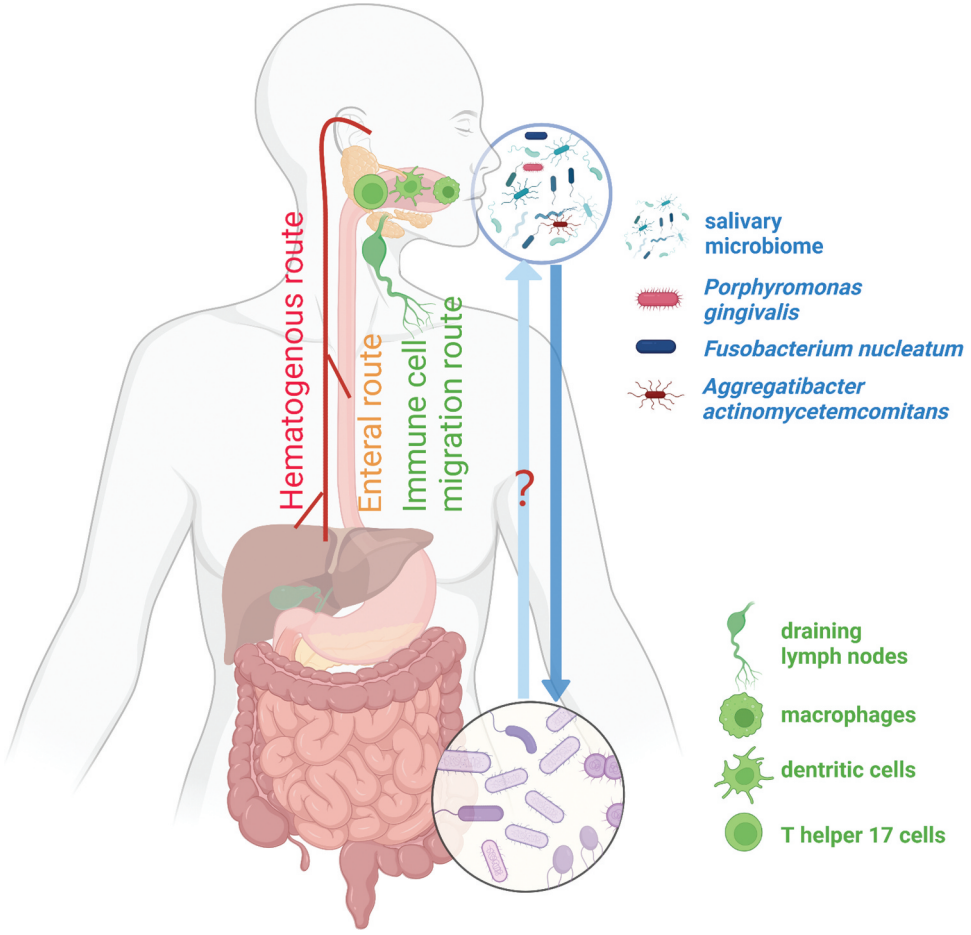

Figure 1. Routes and factors of oral microbiota to affect gut microbiota. Oral microbiota affect gut microbiota through the following [1]: Enteral route, oral microbiota in saliva are swallowed every day [2]. Hematogenous route, oral microbiota can spread into the systemic circulation and travel to the intestine; and [3] Immune cell migration route, intracellular oral bacteria can survive in immune cells and disseminate from oral mucosa to intestinal mucosa. Salivary microbiome, periodontal pathogens such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans* are reported to affect the gut microbiota. Created with BioRender.Com.

nucleatum invades CRC cells and stimulates cancer growth through binding its unique FadA adhesin to E-cadherin [124]. It modulates the tumor microenvironment, confers chemoresistance and promotes CRC metastasis [125–127]. *Porphyromonas asaccharolytica* and *P. gingivalis*, which correspond to bacterial species associated with periodontal disease, are significantly increased in feces of CRC patients, and are capable of inducing cellular senescence through the secretion of butyrate in human diploid fibroblasts. These results suggest a causal relationship between *Porphyromonas* species overgrowth and colorectal tumourigenesis which may be due to butyrate-induced senescence [128].

Atherosclerotic disease

Atherosclerotic disease is a major cause of severe disease and death among subjects with obesity. Koren et al. showed that the abundances of *Veillonella* and *Streptococcus* in atherosclerotic plaques correlated with their abundance in the oral cavity, and several additional bacterial phylotypes were common to the atherosclerotic plaque and oral or gut samples within the same individual, suggesting that the atherosclerotic plaque microbiota may at least in part be derived from the oral cavity and/or the gut [129].

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, impaired decision-making, forgetfulness and mood changes. β-amyloid (Aβ) and tau phosphorylation are pathological hallmarks of AD [130]. Besides genetic factors that contribute to AD onset, other factors such as cerebrovascular disease, diabetes, hypertension, obesity, dyslipidemia and microbial dysbiosis also contribute to AD onset and progression [131]. Gut–brain axis [132–135], oral–brain axis [67,136–138], or oral–gut–brain axis [67,138] were recently proposed to underpin the role of microbial dysbiosis in the occurrence and development of AD. Chen et al. analyzed both oral and gut microbiota in the same AD patients and healthy controls, they found an interesting phenomenon. From healthy controls to mild and moderate AD, the oral abundances of the Firmicutes and Fusobacteria showed

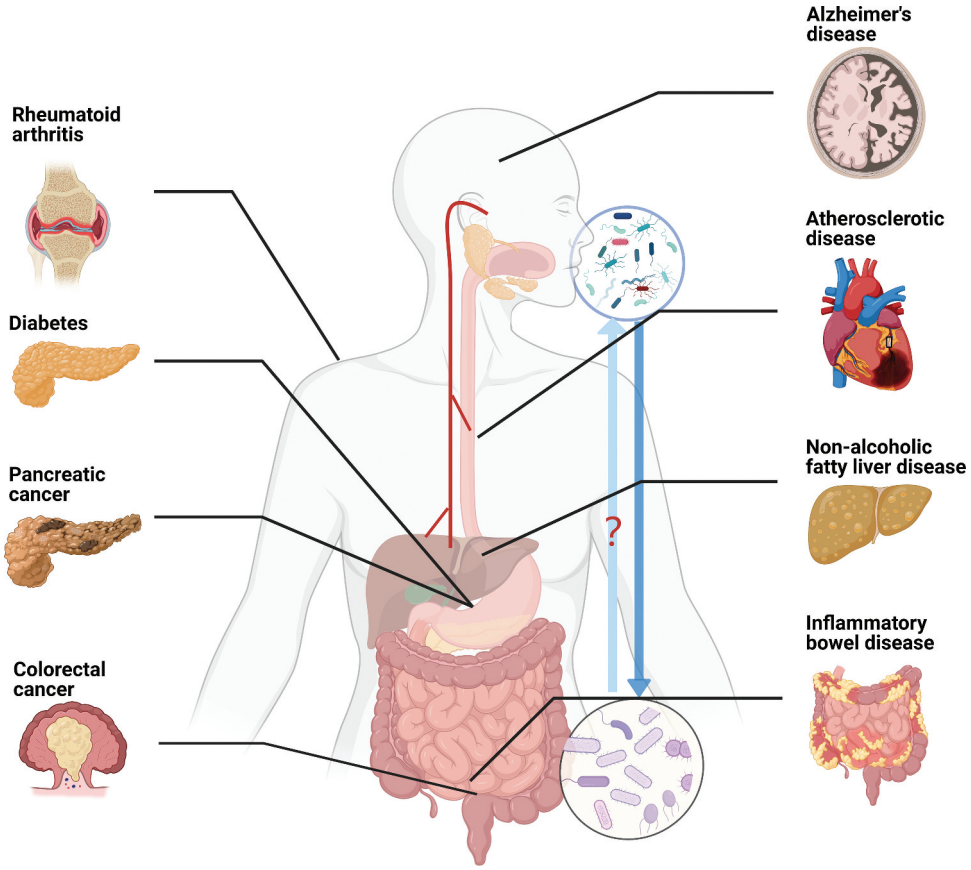

Figure 2. The interplay between oral microbiota and gut microbiota, and the contribution of this interplay on systemic diseases, including gastrointestinal system diseases like inflammatory bowel disease, colorectal cancer, pancreatic cancer and nonalcoholic fatty liver disease, nervous system diseases like Alzheimer's disease, endocrine system diseases like diabetes, immune system diseases like rheumatoid arthritis and cardiovascular system diseases like atherosclerotic disease. Created with BioRender.Com.

a gradual upward trend, while the gut abundances of the Firmicutes and Bacteroidetes decreased progressively. The overlapping of oral and gut microbiota also showed an increase in the order of AD severity, which means that moderate AD patients have more oral-to-gut transmissions than mild AD patients or healthy controls [139]. Oral gavage of periodontitis-related saliva to AD mice can impair cognitive function and increase β-amyloid accumulation and neuroinflammation. Furthermore, gut dysbiosis, intestinal proinflammatory responses, intestinal barrier impairment and systemic inflammation are also exacerbated. This suggests that periodontitis-related salivary microbiota may aggravate AD pathogenesis through the enteral route and by crosstalk with the gut-brain axis [18]. Similarly, oral infection with periodontal bacteria *F. nucleatum* exacerbated AD-related pathologies in AD-like rats, and changed gut composition, with a significant increase in the abundance of *Streptococcus* and *Prevotella* [140]. Oral gavage of periodontal bacteria *P. gingivalis* induced memory impairment in mice and caused gut dysbiosis [141].

Conclusions

Research on the interplay between oral and gut microbiota is still in its infancy. We summarized the three routes of oral microbiota to affect the gut microbiota, and factors of oral microbiota such as salivary microbiota, *P. gingivalis, F. nucleatum* and *A. actinomycetemcomitans* to affect the gut microbiota. There may be a bidirectional relationship between oral and gut microbiota, however, research on the influence of gut dysbiosis on oral microbiota is scarce (Figure 1). The contribution of this interplay between oral and gut microbiota to systemic diseases was also reviewed (Figure 2). Studies of oral microbiota and their interactions with gut microbiota are critical to understanding and improving human health, and we urge further investigation into the specific mechanisms that maintain and regulate the balance of oral and gut microbiota.

Disclosure statement

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Authors' contributions

XT and TG wrote the main manuscript text. TG, YZ, XT critically revised Manuscript. All authors read and approved the final manuscript.

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