Clinical implications of the oral-gut microbiome axis and its association with colorectal cancer (Review)

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Abstract. Colorectal cancer (CRC) is a common form of carcinoma with an increasing global incidence and fatality rates. The current strategies for reducing the incidence and mortality rates of CRC include early screening, prevention, diagnosis and treatment. Additionally, modern high-throughput sequencing technologies in combination with the continuous in-depth study of the microbiome have highlighted the roles of microorganisms in the development of CRC. In particular, studies have demonstrated that oral-gut and gut-oral microbial transmission can regulate the pathogenesis of various diseases, suggesting the existence of an oral-gut microbiome axis. However, to the best of our knowledge, only a few studies to date have assessed the oral-gut microbiome axis in the context of CRC. Therefore, the present review article aimed to discuss the current literature investigating the oral-gut axis in order to further explore the association between the oral-gut microbiome axis and CRC. These data may provide a novel strategy for the early screening, prevention and treatment of CRC.

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Contents

1. Introduction

Globally, colorectal cancer (CRC) is one of the most common malignant tumors of the digestive tract. In recent years, the incidence and mortality of CRC have increased, ranking third and second relative to other carcinomas, respectively. In 2020 alone, it was estimated that there were >1.9 million new cases of CRC and ~935,000 CRC-associated deaths worldwide (1). Thus, the exploration of novel early screening methods, as well as the development of early prevention and treatment strategies is of utmost importance. Modern microbial information technology has allowed in-depth research into microbial species, biological characteristics and disease. Furthermore, each microbial habitat exhibits distinct microbial populations that may have varying effects on physiological homeostasis. In humans, the gut and oral microbiomes are the two major microbial ecosystems that play a significant role in microbiome-related diseases (2). Recently, Park *et al* (3) demonstrated that both the oral and gut microbiomes interdependently regulate physiological functions and pathological processes, and that the oral-to-gut and gut-to-oral microbial transmission can shape and/or reshape microbial ecosystems in both habitats. Such transmissions modulate disease pathogenesis, suggesting the existence of an 'oral-gut' microbiome axis.

The present review aims to comprehensively discuss the oral and gut microbes of the oral-gut axis and their roles in the occurrence, early screening and prevention of CRC. In

addition, novel prevention and treatment strategies drawn from the literature are suggested.

2. Theoretical basis for the oral-gut axis

In recent years, with advancements being made in the development of microbiology and bioinformatic strategies, research into microbial species, biological characteristics and diseases has become increasingly extensive. Microbial dysbiosis is associated with multiple diseases in humans, where each microbial habitat exhibits distinct patterns of microbial populations. Modern medicine has proposed the concept of several organ microbial axes related to gut microbes, such as the 'lung-gut' microbial axis (4) and the 'brain-gut' microbial axis (5,6), amongst others. It is hypothesized that the mutual influence and interaction of gut microbes with other organs results in the occurrence and development of diseases. In addition to the gut, the oral compartment is the other largest microbial habitat in the human body. The oral cavity is the first component of the digestive tract. It is well understood that this region and the intestinal tract are continuous areas connected by the gastrointestinal tract. Due to the oral-gut barrier, the distribution of microbiota between the oral cavity and the gut tract is well separated. In the following sections, the question of whether there is also a micro-ecological oral-gut axis that plays a major role in microbiome-related diseases will be discussed.

Microecology oral-gut axis from an anatomical perspective. The human digestive system consists of the digestive tract and accessory digestive organs, including the liver and pancreas. The digestive tract begins in the oral cavity and ends in the gut, or more precisely, the anus. Thus, the oral cavity and gut are anatomically contiguous regions connected by the gastrointestinal tract. There is also a chemical link as saliva and digested food pass through the gastrointestinal tract (7). Importantly, the oral cavity is the initial site of the digestive tract, which provides several different binding sites for the adhesion and colonization of microorganisms. Therefore, there is a plausible association between oral microbes, and the induction and development of gastrointestinal tumors. The pathogenesis of a disease is a comprehensive reflection of the interaction between microorganisms and the host immune system. Under normal circumstances, the microorganisms in the oral biofilm are in a dynamic balance that can resist the interference of the external environment, participate in the natural immune defense mechanism of the host, and play an important role in maintaining the health of the host. However, when the disturbance exceeds the regulatory capacity of the bacterial biofilm, the oral microbial community structure will become dysregulated, thereby affecting oral and, potentially, systemic health (8,9). Relevant studies have indicated that the imbalance of oral microbes can cause periodontitis and periodontitis-associated systemic diseases, including digestive tract diseases. Furthermore, periodontitis may influence the occurrence and development of digestive tract tumors (10,11).

Oral-gut axis from a microecological perspective. The basic level of the human micro-ecosystem can be divided into micro-ecological subsystems, micro-ecological regions and micro-ecological niches. The oral cavity and gut tract belong to the microbial ecosystem, and changes to its local microbial ecology can affect the changes of the microecology elsewhere or elicit whole-body changes. Therefore, the oral microbial ecosystem and gut microbial ecosystem are organically linked as a whole, the interrelationship of which influences structure, function and pathological changes. Normally, the oral and gut microbiomes are well segregated due to the presence of the gut-gut barrier, physical distance and chemical barriers, such as gastric acid and bile (12,13). However, when the oral-gut barrier is damaged, it can lead to the displacement and communication between organs, which can lead to the occurrence of disease.

Effect of oral microorganisms on the gut microbiome (oral-gut translocation). Bacteria in the oral cavity are not strictly localized to the oral cavity. Oral microorganisms can migrate to the gut and other parts of the body, and affect their physiological functions. Typical oral-resident species have been detected in pathological conditions of the gastrointestinal tract (14,15), such as inflammatory bowel disease (IBD), where the gut mucosa of patients is heavily enriched with *Haemophilus* and *Veillonella* bacteria, which are known oral commensal microorganisms (16). Atarashi *et al* (17) confirmed that *Klebsiella* bacteria in saliva that have been transplanted into the gut can induce chronic enteritis. Additionally, Kong *et al* (18) found that the intestinal *Firmicutes* and salivary *Chloroflexi* bacteria were strongly associated with autism spectrum disorder (ASD). Furthermore, it was found that intestinal *Bifidobacterium*, *Escherichia coli* and *Clostridium* species levels were positively associated with bacterial genera in the oral cavity and/or with ASD pathophysiology (19-21). Sasaki *et al* (22) found that actinomycetes and fecal atrophic bacteria colonized the gut, and only selectively colonized the oral cavity. This observation may explain the pathogenicity of endocarditis-related disease. Finally, the gut microbiome in patients with colon cancer contains several oral taxa, including *Clostridium* (23), indicating that the oral microbiota can disrupt and colonize the intestinal mucosa to become opportunistic pathogens.

Influence of the gut microbiota on oral microbes (gut-oral translocation). In general, gut microbes rarely colonize the oral cavity; however, poor hygiene and/or immunocompromising conditions may promote the translocation of microbes from the gut to the oral cavity. For example, in patients with IBD, gut microbes can directly or indirectly affect the composition of oral flora by affecting the immune function of the host (24). *Bifidobacterium* in the gut has been found in the saliva of newborns (25), and similarly, the detection rate of oral bacteria, such as *Porphyromonas*, *Fusobacterium* and *Pseudoramibacter* species in the gut of elderly individuals is higher than that of healthy adults (26,27). Furthermore, apart from *in vivo* transmission, the fecal-oral axis is also considered an important mechanism in the human-to-human transmission of pathogens. The microbiome of the human hand significantly overlaps with oral and gut microbiota patterns, suggesting that the hand is a vehicle for fecal-to-oral microbial transmission (28). Gut microbes can be transmitted by direct contact via the fecal-oral route or indirect contact with contaminated fluids and food (29). Enteroviruses, such as hepatitis A virus and hepatitis E virus are known to be

transmitted by the fecal-oral axis and are therefore easily transmitted by person-to-person contact. In addition to enteroviruses, *Helicobacter pylori*, the major pathogen of severe gastroduodenal disease, can also be transmitted by the fecal-oral route (30). In other systemic diseases, oral and gut microbial flora have common effects at the same time. For example, Bertolini and Dongari-Bagtzoglou (31) found that oral inoculation of *Candida albicans* in mice caused serious oral and gut microbial flora composition disorders.

In conclusion, oral microbes and gut microbiota are intrinsically linked. Furthermore, the bidirectional interaction of microbes from the oral-gut and the gut-oral axes can mutually shape and/or reshape the microbial ecosystems of the two habitats to ultimately regulate the physiological and pathological processes of the intestinal system. The microecological oral-gut axis formed by bidirectional crosstalk between the oral and gut microbiota plays a key role in the occurrence and development of CRC and warrants further investigation.

3. Relevant research on the oral-gut axis

In 2017, Acharya *et al* (32) proposed the oral-gut-liver axis theory on the basis of the gut-liver axis, and mentioned the oral-gut axis for the first time. Oikonomou *et al* (33) further elaborated that the microbial link between the liver and the oral cavity may lead to liver cirrhosis by impairing the permeability of the gut, allowing the direct translocation of bacteria from the oral cavity to the systemic circulation. Bajaj *et al* (34) found that periodontal therapy exerted a favorable modulating effect on the oral-gut-liver axis in patients with liver cirrhosis, while Acharya and Bajaj (2021) (35) provided further evidence supporting the oral-gut-liver axis. Imai *et al* (2021) (36) demonstrated that the ectopic colonization of oral bacteria in the gut can serve as a biomarker for gastrointestinal and liver diseases. Du Teil Espina *et al* (37) proposed the association between the oral-gut microbial axis and the pathogenesis of rheumatoid arthritis, and proposed the oral-gut microbial axis for the first time, but this did not involve the association with CRC. Lorenzo *et al* (38) suggested that changes in the oral and gut microbiota appear to play a crucial role in the pathogenesis of rheumatoid arthritis and osteoarthritis, although further research is required. The study by Bellando-Randone *et al* (39) suggested the oral microbiome as a promising diagnostic biomarker for rheumatic disorders. Li *et al* (40) found that the imbalance of oral microflora and abnormal metabolic pathways were associated with the pathogenesis of systemic lupus erythematosus. A study by Ray (41) found that oral bacteria can promote colitis in mice through intestinal colonization, and the induction and migration of bacterial-reactive T cells. Xiang *et al* (42) presented a conceptual framework for the potential impact of SARS-CoV-2 oral infection on the local and distant microbiota of the respiratory and gastrointestinal tract (oral-lung axis). De Oliveira *et al* (43) suggested that the oral-gut axis may be a pathway connecting periodontal and systemic diseases, while Byrd and Gulati (44) proposed the concept of the 'gingival-gut' axis and noted the importance of collaborative treatment and research programs between physicians and gastrointestinal physicians. Narengaowa *et al* (45) comprehensively discussed the possible mechanisms of the oral-gut-brain association related to the pathogenesis of Alzheimer's disease, and proposed an oral-gut-brain axis. Park *et al* (3) described the association between the oral-gut axis and gastrointestinal-related cancer, and first proposed the association between the oral-gut microbiota axis and CRC. However, a comprehensive and in-depth analysis has not yet been performed, at least to the best of our knowledge.

To better explain the close association between the oral-gut axis of the microbiota and the occurrence of diseases, the present study reviewed recent research on diseases related to the oral-gut axis of the microbiome (Fig. 1). The aim of this review section was to provide a robust basis for the proposal of the oral-gut axis. At the same time, it is also aimed to help better understand the importance of the microbial oral-gut axis in the pathogenesis of CRC, which may prove to be beneficial for the accurate screening/diagnosis and effective prevention and treatment of the disease.

4. Oral microbes and CRC

The oral cavity is the initial part of the digestive tract and is also the region with the most abundant species of flora in the whole body. At the species level, there are >700 different species of oral microorganisms (46). Oral microorganisms have a direct association with oral health, and can also affect the systemic health status. Changing the oral microbiota can further regulate systemic diseases, such as cardiovascular disease and gastrointestinal tumors, among others (47-50). Under normal conditions, the oral and gut microbiomes are well segregated due to the presence of the gut-gut barrier, physical distance and chemical barriers (such as gastric acid and bile) (7). When the oral-gut barrier is damaged, it will lead to the translocation and communication of microorganisms between organs, and oral microorganisms can migrate to the gut and other organs, which is considered to be another mechanism of oral microbial dysbiosis causing systemic diseases (51,52). The study by Atarashi *et al* (17) demonstrated that the rooting of *Klebsiella pneumoniae* in the oral cavity in the gut can trigger the excessive activation of T-helper 1 (Th1) cells, leading to the occurrence of IBD, thereby initiating the inflammatory-cancer transformation of the intestine. The study by Kitamoto *et al* (53) found that the oral microbial disorder caused by periodontitis can induce the production of Th17 cells, and that Th17 cell migration to the intestine is amplified under the action of bacterial antigens, which promotes the occurrence of gut tumors.

In addition, *Fusobacterium nucleatum* (Fn) is a Gram-negative anaerobic bacterium colonized in the human oral cavity; it plays a critical role in the occurrence, metastasis and disease outcomes of CRC (54-56). An imbalance in the oral and gut microecology can lead to the occurrence of gut inflammation, and thus the development of CRC (57). Studies have found that the main mechanisms of Fn and CRC occurrence are as follows: Fn can promote the production of TNF-α, activate NF-κB signaling and the STAT3 signaling pathway, and enhance the migration and invasion ability of tumor cells (58). FadA, as a toxic protein secreted by Fn, binds to E-cadherin in intestinal epithelial cells, activates the β-catenin signaling pathway, enhances Wnt transcriptional activity, and promotes inflammatory factors and cancer cell proliferation (59). Fn in CRC tissues can increase the content

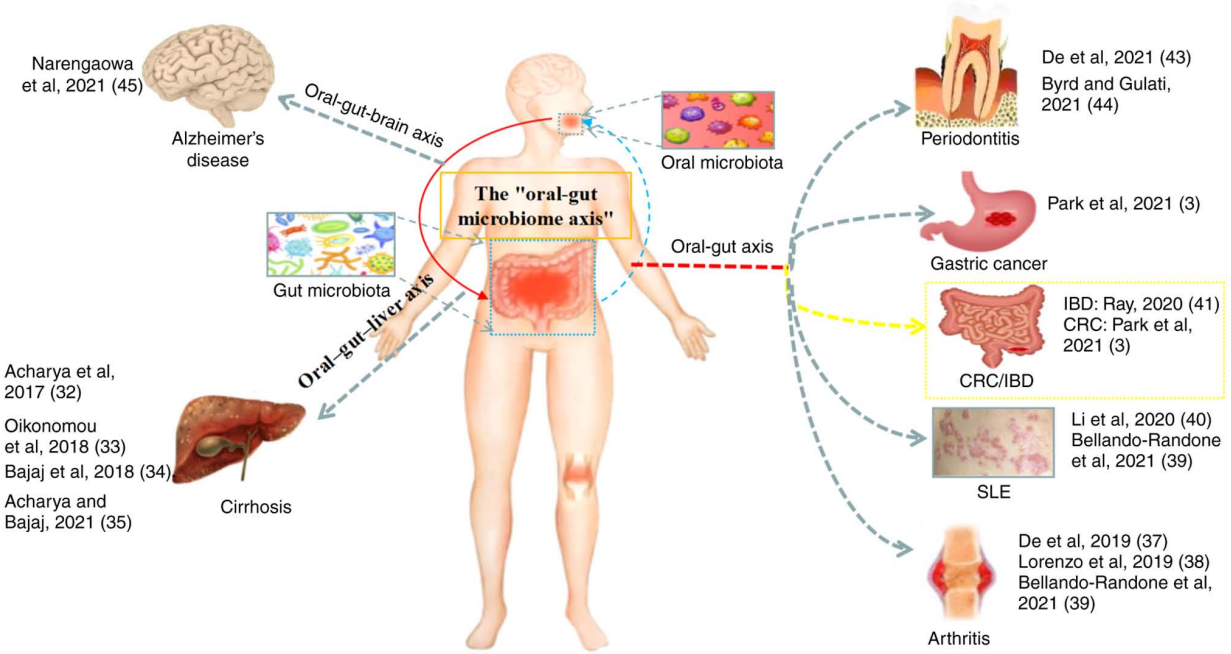

Figure 1. 'Oral-gut microbiome axis' and its effects on other systems. Numerous studies have found that the 'oral-gut microbiome axis' is closely associated with various diseases, which provided the theoretical basis for the present review. CRC, colorectal cancer; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus.

of reactive oxygen species in the gut, leading to the occurrence of microsatellite instability, which in turn promotes the occurrence of CRC (60).

5. Gut microbes and CRC

The gut is the largest and most characteristic microbial ecosystem in the human body. The gut microbes are dominated by anaerobic bacteria, which are composed of five main phyla: Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria and Verrucomicrobiota. Of these, Bacteroidetes and Firmicutes account for >90% of all bacteria present (61). When the balance of the microbial ecosystem is affected, the number of probiotic species decreases and pathogenic bacteria have the opportunity to multiply, causing an imbalance in the intestinal flora. The mucosal barrier is transferred to tissues and organs other than the gut and even the blood, which further leads to gut flora imbalances, which has a marked effect on the host's immune system and body stability (62). Intestinal dysbiosis is closely associated with several diseases, such as obesity, IBD, adenoma and CRC (63). The pathogenesis of CRC is attributed to a variety of factors. Two studies successively reported that *E. coli* and Fn can induce CRC in humans (59,64); these were the first studies to explore the mechanism of CRC from the perspective of intestinal bacterial infection.

Inflammation is a recognized risk factor for CRC, and the balance of the gut flora in patients with IBD who have an increased risk of CRC is affected (65); the gut flora can regulate the mucosal and systemic immune systems, which in turn affects the progression of CRC. Cytolethal distending toxin, as one of the components of bacterial toxins (cyclomodulins) that regulates the eukaryotic cell cycle, can promote intestinal colonization and induce the pro-inflammatory molecules, NF-κB, TNF, IL-6 and cyclooxygenase 2 (COX-2), which are involved in carcinogenesis. *E. coli* is one of the characteristic bacteria associated with IBD; its colonization in the intestinal mucosa of patients with IBD is abnormal, and it can induce the expression of COX-2 in macrophages. Intestinal inflammation plays a role in the development of CRC (66). With regard to bacteria closely associated with CRC, in addition to Fn, several studies have found that enterotoxigenic *Bacteroides fragilis* can also promote the release of epithelial pro-inflammatory factors and further stimulate the activation of the NF-κB signaling pathway, which is involved in CRC pathogenesis; *Bacteroides fragilis* can also play an indirect role by secreting *Bacteroides fragilis* toxin, a zinc-dependent metalloproteinase toxin that can cleave the tumor suppressor protein-E-cadherin, resulting in enhanced Wnt/β-catenin signaling that ultimately leads to CRC cell proliferation (67-69).

6. Association between the oral-gut axis and the occurrence of CRC

Deleterious alterations in the oral and gut microbiomes have been associated with the occurrence and development of tumors. Previous research has indicated that the risk of cancer due to microbial infection is ~16.1% (70). The microecological oral-gut axis formed by the bidirectional displacement and interaction between the oral and gut microbiomes is rarely studied in the occurrence and development of CRC. Under normal circumstances, due to the existence of the gut-gut barrier, the oral and gut microbiomes are well segregated and in a dynamic balance. When host immunity is reduced or affected by external factors, a microecological imbalance can occur. The dysregulation of the microecological oral-gut axis can then facilitate the onset of disease. When the oral

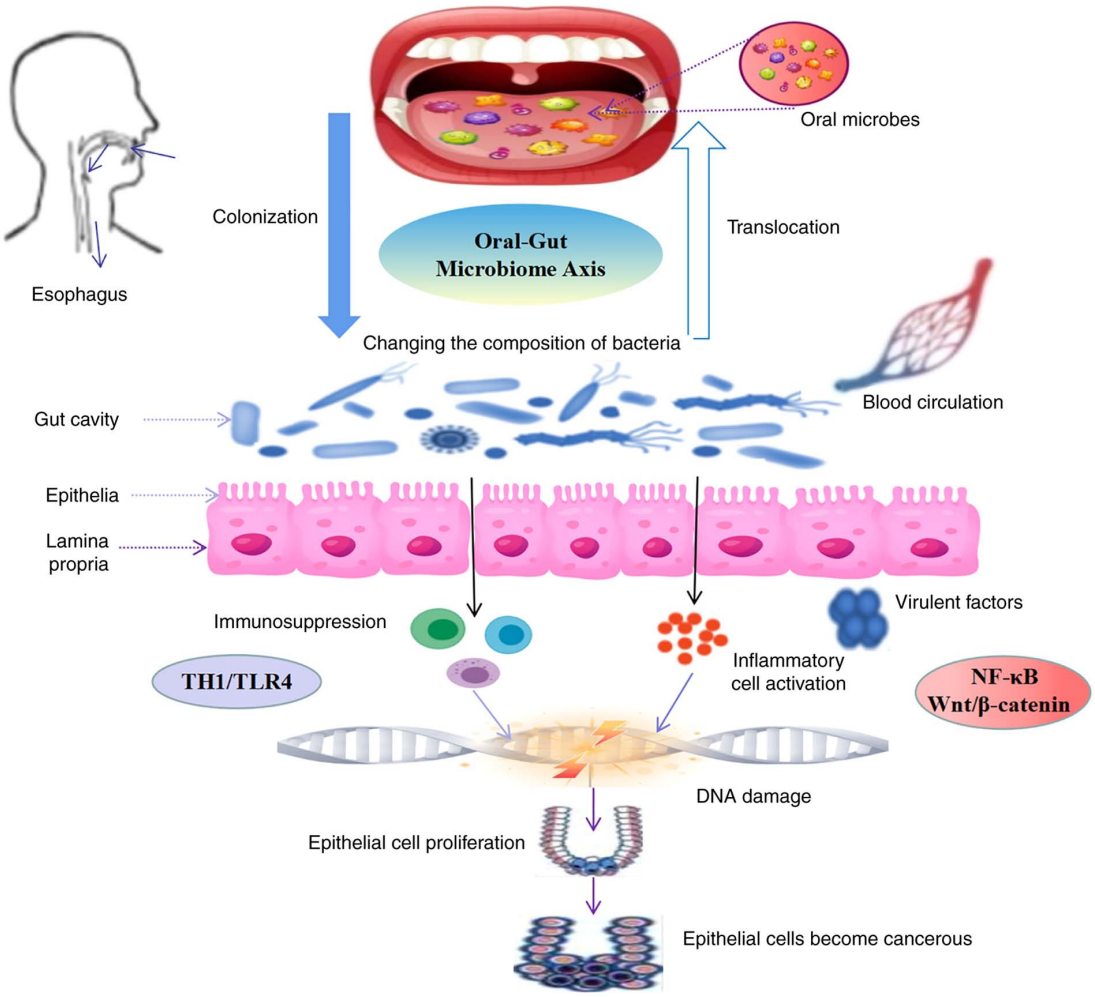

Figure 2. Pathogenesis of CRC induced by the oral-gut microbiome axis. When the oral-gut microbiome axis is affected, oral microbes will colonize the gut and gut microbes will also be present in the oral cavity. This alters the gut microecology, thereby causing the body to produce immunosuppressive factors, activating the inflammatory pathway. This affects the NF-κB and/or Wnt/β-catenin signaling pathways, which are involved in the occurrence and development of CRC. CRC, colorectal cancer; TH1, T-helper 1; TLR4, toll-like receptor 4.

microbial flora is in a state of imbalance, lesions may appear within the oral cavity. This phenomenon is commonly observed in periodontitis, glossitis, gingivitis, oral ulcers and oral cancer. Furthermore, the translocation/colonization of oral microbial flora to the gut may induce or even exacerbate gut diseases (3,51,52). For example, *Porphyromonas gingivalis* is the main pathogen of periodontitis, and its colonization in the gut tract can cause the disorder of the microbial community structure and increase serum endotoxin levels, which induce gut inflammation (71). Subsequently, excessive inflammation initiates the inflammation-cancer pathway, leading to the occurrence and development of CRC. Patients with IBD are a high-risk group for colon cancer development and often exhibit extraintestinal manifestations of disease, such as chronic periodontitis and oral ulcers, suggesting that the process of colitis-cancer evolution is not an isolated event (72,73). Despite these data, further studies are required to elucidate the association between the microbial oral-gut axis and CRC. However, it is well understood that microbial alterations, whether in the oral-gut pathway or the gut-oral pathway, affect the NF-κB and/or Wnt/β-catenin signaling pathway, and are involved in the occurrence and development of CRC (59,74) (Fig. 2).

In conclusion, the multi-factor and multi-pathway occurrence of CRC has been demonstrated by a number of previous studies, and the association between the microecological oral-gut axis and the occurrence of CRC has become one of the hot spots in CRC research. To clarify the association between the microecological oral-gut axis and the occurrence and development of CRC, the precise screening and prevention of CRC may be realized by manipulating the microecological oral-intestinal axis. This will provide further insight into the clinical diagnosis and treatment.

7. Clinical significance of oral-gut axis in CRC prevention and treatment

Early screening of CRC: Exploring oral-specific microbial markers. Early screening can effectively reduce the morbidity and mortality rates in patients with CRC, and is essential for CRC prevention and treatment. Microbes play a crucial role in the body's metabolism, immune regulation and inflammatory response, and as aforementioned, are closely associated with the development of CRC. It has been shown that there are key differences in the oral microbial structure between patients

with CRC and healthy individuals. Using oral microorganisms and their metabolites, scientists and clinicians can construct new CRC screening tools to improve screening efficiency. Yamaoka *et al* (75) demonstrated that the abundance of Fn was significantly increased in patients with stage IV CRC. Furthermore, the study demonstrated that patients with CRC with a higher abundance of Fn had larger tumors and a shorter survival time, suggesting that Fn abundance could predict the prognosis of CRC. Therefore, *Klebsiella pneumoniae* and Fn in the oral cavity may be useful oral-specific microbial biomarkers for CRC, which may be useful for early screening.

A novel model of CRC prevention: The importance of oral hygiene and the early intervention of oral disease. At present, the most effective strategy with which to improve CRC outcomes is prevention and early detection. CRC prevention guidelines recommend a multi-fiber diet, avoiding the intake of carcinogens, and emphasize the importance of early treatment of colorectal adenomas. Owing to advancements being made in scientific tools and protocols, the understanding of CRC pathogenesis is being increasingly improved upon and a large variety of microorganisms have been associated with the occurrence and development of the disease. According to oral microbiota analysis (76), *Fusobacterium* levels are higher in patients with oral squamous cell carcinoma than in normal healthy individuals. Therefore, the early intervention and treatment of oral hygiene and oral diseases, respectively, are two important strategies with which to prevent the occurrence and development of CRC. Considering these data, a new model of CRC prevention is proposed, namely the early intervention and early treatment of oral hygiene and oral diseases.

Proposing a novel concept: Simultaneous oral and gut treatment for management of CRC. The treatment of CRC primarily includes surgery, radiotherapy, chemotherapy, biologically targeted therapy and adjuvant traditional Chinese medicine (TCM) therapy, among others; however, these strategies are focused on the treatment of colorectal intestinal lesions. To date, only a few studies have assessed the treatment of CRC combined with oral disease intervention. The present review discussed the micro-ecological oral-gut axis and its role in the screening, incidence and treatment of CRC. The novel concept breaks away from the traditional concept of symptomatic treatment and rather focuses on the 'holistic' perspective for disease management. A new treatment concept for CRC is proposed, namely the oral-gut simultaneous treatment strategy. This new concept of oral-gut co-treatment not only conforms to the requirements of modern evidence-based medicine, but also reflects the 'holistic view'. Whilst several studies support this strategy, large-scale experiments and clinical trials are urgently required to substantiate this hypothesis/treatment strategy.

8. Conclusions

In conclusion, the occurrence of CRC is closely associated with microbial dysbiosis in the oral and gut microbiomes. It has proposed that the oral-gut axis is a novel system that may be of interest in the early screening, prevention and treatment of CRC. However, whether it is possible to correct the imbalances in the oral-gut axis through novel oral-gut treatment strategies warrants further investigation.

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Authors' contributions

FL, DS, HZ, HCL, QZ, BC and DLR helped write and review the manuscript. FL wrote the original draft. DS and HZ created the figures. HCL and QZ performed the formal analysis. BC and DLR corrected the final version. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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