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FACULDADE DE MEDICINA DENTÁRIA
VISEU

Oral health and the Microbiome Dysbiosis in Inflammatory Bowel Disease

Dissertação apresentada à Universidade Católica Portuguesa
para obtenção do grau de Mestre em Medicina Dentária

Por:
Catarina Pereira Cardoso

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Orientador: Doutora Ana Peixoto Gomes
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Viseu, 2025

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“Foi o tempo que dedicaste à tua rosa
que a fez tão importante”
Antoine Saint Exupéry, O Pequeno Príncipe

À minha família, que sempre me ensinou a lutar pelos meus sonhos e a viver com dedicação e alegria em cada passo deste caminho. Dedico este trabalho, com todo o meu amor, à minha mãe, ao meu pai e às minhas irmãs.

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Resumo

A doença inflamatória do intestino (DII), que abrange a doença de Crohn e a colite ulcerosa, é uma doença inflamatória crónica do trato gastrointestinal ligada a desequilíbrios do microbioma. Embora o papel do microbiota intestinal na DII seja amplamente explorado, a contribuição do microbioma oral para esta patologia continua a ser menos conhecida. A disbiose do microbiota oral em doentes com DII tem sido associada a um aumento da prevalência de doenças orais como a cárie e a periodontite. Para além disso, as intervenções terapêuticas para a DII podem alterar a composição microbiana, com algumas bactérias a surgirem como potenciais preditores da resposta ao tratamento.

Este estudo tem como objetivo rever sistematicamente a literatura sobre a disbiose do microbioma na DII e o seu impacto na saúde oral dos pacientes. Foi realizada uma pesquisa sistemática abrangente utilizando as bases de dados eletrónicas PubMed, Scopus e Cochrane para identificar estudos com dados relevantes. Esta revisão foi efetuada de acordo com as diretrizes *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA), abordando uma questão de investigação estruturada utilizando a estrutura População, Intervenção, Comparação e Resultados (PICO). Foram identificados quatrocentos e sessenta e nove artigos potencialmente relevantes e, após a aplicação das diretrizes PRISMA e dos critérios de inclusão/exclusão, foram incluídos doze artigos nesta revisão.

Os resultados sugerem uma disbiose consistente do microbioma oral e intestinal na DII, marcada pela redução da diversidade e enriquecimento de bactérias pró-inflamatórias, particularmente *Prevotella*, *Veillonella* e *Fusobacterium*. Os resultados confirmam ainda estreita relação entre a saúde oral e a DII, com manifestações orais comuns como a periodontite, reforçando a relevância do microbioma oral como um espelho e potencial impulsionador da inflamação sistémica. Estes conhecimentos realçam a necessidade de cuidados dentários e gastrointestinais integrados.

No entanto, é necessário um maior investimento em estudos de investigação mais abrangentes de forma a confirmar os marcadores microbianos, compreender os mecanismos causais e avaliar de que forma as intervenções podem restaurar o equilíbrio microbiano e melhorar os resultados clínicos.

Palavras-Chave: Microbioma Oral, Microbiota Oral, Doença Inflamatória Intestinal

Abstract

Inflammatory bowel disease (IBD), encompassing Crohn's Disease and Ulcerative Colitis, is a chronic inflammatory condition of the gastrointestinal tract closely linked to microbiota imbalances. While the role of gut microbiota in IBD has been extensively explored, the contribution of the oral microbiome remains less understood. Dysbiosis of the oral microbiota in IBD patients has been associated with an increased prevalence of oral diseases such as caries and periodontitis. Moreover, therapeutic interventions for IBD can alter microbial composition, with some bacteria emerging as potential predictors of treatment response.

This study aims to systematically review the literature on microbiome dysbiosis in IBD and its impact on patients' oral health. A comprehensive systematic search was performed using the electronic databases PubMed, Scopus, and Cochrane to identify studies with relevant data. This review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, addressing a research question structured using the Population, Intervention, Comparison, and Outcomes (PICO) framework. Four hundred and sixty-nine articles potentially relevant were identified and after applying PRISMA guidelines and inclusion/exclusion criteria, twelve articles were included in this review.

The results suggest a consistent dysbiosis of the oral and gut microbiome in IBD, marked by reduced diversity and enrichment of pro-inflammatory bacteria, particularly *Prevotella*, *Veillonella*, and *Fusobacterium*. It also emphasized the close relationship between oral health and IBD, with common oral manifestations such as periodontitis, reinforcing the relevance of the oral microbiome as both a mirror and potential driver of systemic inflammation. These insights highlight the need for integrated dental and gastrointestinal care.

Further research is needed to confirm microbial markers, understand causal mechanisms, and assess how interventions may restore microbial balance and improve clinical outcomes.

Keywords: Oral Microbiome; Oral Microbiota; Inflammatory Bowel Disease

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Abbreviations

IBD	Inflammatory bowel disease
UC	Ulcerative Colitis
CD	Chron Disease
HMP	Human Microbiome Project
GIT	Gastrointestinal Tract
TLR	Toll-like Receptor
TH17	T-helper 17 cells
IL-Iβ	Interleukin - 1β
MyD88-NF-kB	Immune signaling pathway
TLR2	Toll-like Receptor 2
TLR4	Toll-like Receptor 4
TNF	Tumor Necrosis Factor
RAS	Recurrent aphthous stomatitis
CAL	Clinical Attachment Level
PICO	Population, Intervention, Comparison, Outcome
JBI	Joanna Briggs Institute
HC	Healthy Controls
qCD+S/-S	Quiescent Chron Disease with/without symptoms
TM7	Termite Group 7 (phylum)
SR1	Sulfur River 1 (phylum)
IL-6	Interleukin-6
IL-8	Interleukin-8
TNF- α	Tumor Necrosis Factor-alpha
MCP-1	Monocyte Chemoattractant Protein-1
IgA	Immunoglobulin A
tnaA gene	Tryptophanase A gene
H_2S	Hydrogen Sulfide
QoL	Quality of Life

1. INTRODUCTION

1.1 Microbiome

We coexist with a large number of microbiomes that live inside and outside of our bodies. Those microbes and their genes are known as the human microbiome (1). Bacterias, viruses, and yeasts can live in different areas of the human body, such as gut, skin, lungs and oral cavity (2).

Microbes play an important role in the physiology of the human body and can significantly impact the risk of disease development.

Even though we have acquired vast knowledge of the human microbiome, the key remains on how much we know how to manage it to achieve health benefits(1).

The terms microbiome and microbiota may appear similar; however, they have distinct meanings. Microbiome refers to the collection of genomes from microorganisms, encompassing structure, metabolism and environment interactions. In contrast, microbiota refers to living microorganisms found in a restrained environment such as oral and gut microbiota. The composition of this microbiota varies depending on the specific site (2).

As previously referred, the human body hosts various types of microbiota. Among them, gut microbiota is regarded as the most critical for maintaining balance and overall health(2). The oral microbiota is the second most important and comprises various habitats. for microorganisms to thrive, such as saliva, tooth surfaces, tongue, mucosa, hard and soft palate, gums/gingiva, and both supragingival and subgingival plaque. Additionally, the oral cavity is particularly prone to pH changes, bacterial interactions which often lead to significant imbalances. Generally, the primary bacteria groups found in this microbiota are *Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, and Fusobacteria(2).*

The lungs also host microbiota within their tissues, primarily consisting of *Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria* (2). However, their composition can change due to microbial migration, variations in reproduction rate and elimination processes.

The skin microbiota typically includes *Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, and Proteobacteria (2).* However, as with other microbiota, the chemical and physical variations across the different skin sites can lead to distinct bacterial compositions(2).

In the gut, bacterial composition varies between species and commonly includes *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia,* with *Firmicutes* and *Bacteroidetes* being predominant (1). Moreover, the gut hosts fungi such as *Candida, Saccharomyces, Malassezia, and Cladosporium*. Maintaining symbiosis is crucial, as gut microbiota plays a vital role in protecting against pathogens, fermentation, stimulation of the immune response and producing vitamins essential to human life. The human microbiome, particularly the gut microbiome, can be influenced and modified through dietary changes, medical interventions, and other factors (1). The intestinal barrier, composed of mucus, commensal microbes, intestinal epithelium, lamina and associated immune cells, serves as a protective boundary between the human body and the intestinal microbes, food antigens, toxins and viruses. When the gut barrier is compromised, harmful bacteria can penetrate and cause damage

However, in a healthy individual, this barrier functions effectively, preserving the mucus layer and its physiological function, promoting homeostasis, crucial for the body's dynamic balance (1,3).

1.2. The Gut-Oral Axis

As stated before, microbes play an important role in the physiology of the human body, preventing a wide spectrum of diseases, autoimmune diseases, cardiovascular, respiratory, gastrointestinal and metabolic disorders. Perturbation on the microbiome is called dysbiosis. Understanding how to manage the interplay between microbes and their host may lead to discovering the etiology and the therapeutic of any of these disorders (4,5).

Relying on HMP *(*Human Microbiome Project, 2007*)*, the gut and the oral cavity are the most crucial environments (ecologically and taxonomically) once they harbor the most diverse microbial community of the human body (4,5).

These two environments are interconnected both physically and chemically. Recent studies confirm that the intestinal colonization of oral microbiota and fecal-oral

transmission are common occurrences and may influence pathological processes, forming what is referred to as the Gut-Oral Axis, an integrated complex (5).

Understanding Oral - Gut connection is essential to recognizing their impact on host microbiome in the as well as the pathophysiological process undergoing, such as Inflammatory Bowel Disease (IBD) or even colorectal cancer(4).

1.2.1. Oral Cavity and Gut: Connected through Gastrointestinal Tract

According to several studies, oral health conditions and the oral microbiome can contribute to the development of pathologies, including gut-related pathologies, like IBD (5).

Even though the gut and oral cavity are opposed to each other, they are anatomically continuous sites of the gastrointestinal tract (GIT). As referred previously, these two environments are not only connected physically but chemically as well, using saliva as a medium of transport.

The GIT is composed of a series of hollow organs interconnected, responsible for digestion, nutrients absorption, and residuals elimination, starting in the mouth and ending the anus, in a long tube of mucosa, passing through esophagus, stomach and the small and large intestine. The digestive system is formed by these components, and by solid organs, comprising liver, pancreas and gallbladder. This system is the second most extensive interface between the body and the environment, after the respiratory system. However, it operates in a contradictory way: while the GIT must remain permeable to allow the absorption of nutrients into circulation, it also needs to block the entry of pathogens and other harmful microbes. It becomes obvious that oral cavity serves as the primary entry point of both beneficial and harmful microbes, the home of unique microbial environments, with distinct microbial communities, contributing to a wide diversity of taxa (4).

This may happen, initially through the respiratory and digestive system due to their physical interaction, and via circulatory system due to the mouth´s high vascularization. At this stage the critical interface host/microbial community is established (4).

1.2.2. Oral microbiome composition

The oral cavity carries distinct habitats for microbial communities. It includes buccal mucosa, sub and supragingival plaque, hard palate, tongue, tonsil, keratinized gingiva, saliva and throat. The site that shows the lower density of habitats are the buccal and palatal mucosa. Despite the niche location, all the healthy sites bear *Streptococcus, Gemella, Veillonella, Haemophilus, Neisseria, Porphyromonas, Fusobacterium, Actinomyces,* and *Prevotella*(5) at the genus level. Relying on the structure of the microbial community, within niches, each of which is well sharply distinguished in terms of bacterial composition, they can be characterized into 3 different groups:

- Group 1—buccal mucosa, keratinized gingiva, and hard palate;
- Group 2—saliva, tongue, tonsils, and throat;
- Group 3—subgingival and supragingival plaque(5).

The segregation in niches, is explained by a range of factors: pH, redox potential, oxygen, diet, salinity. The standard practice that molds the oral microbiome is dental hygiene. Furthermore, dental hygiene is another significant factor(5).

Several studies suggested the potential role of the oral microbiome composition as a link between periodontitis and gut disease, namely cancer and IBD. *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Prevotella intermedia, Prevotella nigrescens, Parvimonas micra, Campylobacter rectus and Fusobacterium nucleatum* (5)are some of the bacteria that have been correlated through the oral–gut axis as a primary pathway of exposure. Furthermore, oral bacteria found in IBD patients encompass members of the genera *Fusobacterium, Porphyromonas, Veillonella and Campylobacter*, with an increase in the genera *Prevotella* and *Veillonella* (5).

Veillonella sp., important biofilm member, usually present in periodontal health, develops on early colonizers (*Streptococcus*, *Neisseria* and *Rothia* species)(5). However, *Veillonella* sp. is recognized to produce catalases and nutrients that encourage the proliferation of other anaerobes such as *F. nucleatum* and typical anaerobic bacteria generally linked with periodontitis such as *P. gingivalis, P. intermedia, T. forsythia and T. denticola(5).*

In the gut, *F. nucleatum* adheres to mucosal tissues, and stimulates immunoreaction via membrane vesicles and activation of Toll-like receptor (TLR)–MyD88–NF-κB pathways. *P. gingivalis,* a bacterium associated with periodontal disease, shifts to the gut during periodontitis. It transcribes virulence factors and bacterial components, such as lipopolysaccharides, gingipains and extracellular vesicles, creating immune response promoting inflammation. This is possible by the stimulation of TLR2 and TLR4 and inducing T helper 17 cells. It will lead to the expression of tumor necrosis factor (TNF) and interleukin-1β (IL-1β) in the colon (5).

As well, periodontitis and an increase in *Klebsiella* and *Enterobacter* species may lead to the creation of oral TH17 cells. TH 17 cells will migrate from the oral lymph to the intestinal lamina propria, where they are activated by oral *Klebsiella spp*. It will lead to aggravated gut inflammation, suggesting a shared inflammatory mechanism that connects the oral cavity and intestines (5).

1.2.3. The Gut microbiome composition

The largest and well-defined microbial ecosystem in our body, that holds 500 to 1000 species in more than 50 distinct phylas is the gut. Composed mostly of anaerobes, he harbors five major phyla: *Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia.* However, it is only dominated by two of them: *Bacteroidetes and Firmicutes* (above 90%) (5).

At the genus level, the most common is *Bacteroides.* At the phylum level, the most abundant is *Firmicutes* in the oral cavity, whereas in the stool microbiota is Bacteroidetes. The partition at the phylum level could be related to the gastric acid (in the stomach) and to the bile acids (in duodenum) (5).

1.2.4. Interconnection between Oral and Gut Microbiomes

The good segregation that characterizes the oral and gut microbiomes due to the physical presence of the oral–gut barrier, is enhanced chemically by the gastric acid and bile acid. Nonetheless, this interface of the oral -gut barrier allows microbial migration and interaction, through the organs.

Babies or neonates and elderly people exhibit immature or compromised function of the barriers in the human body. Neonatal gut reveals *Bifidobacterium* (5) as the most prolific bacterial genus. As a curiosity, *Bifidobacterium* (5) has also been observed in the oral fluid of babies. In elderly people the most prevalent oral bacteria in the gut in comparison to healthy adults are *Porphyromonas, Fusobacterium,* and *Pseudoramibacter* (5).

Besides, being low gastric acidity a factor of shaping the gut microbiota composition towards the oral microbiome, this may imply migration of oral microbiota to the gut under the oral–gut barrier dysbiosis, meaning of conditions of disrupted homeostasis of the mucosa. *In vitro* studies had shown (*Li et al.*) (5) that the oral microbiota may translocate and invade the gut. This migration has the capability to reorganize the gut microbiota (5).

We can deduce that oral microbes can overcome both physical and chemical barrier oral-gut, invading and colonizing the gut mucosa, emerging as opportunistic pathogens. Particularly, common oral-resident species have been noticed in the gastrointestinal tract, under pathological conditions. Inflammatory bowel disease, as one of the pathological conditions, had remarkable cultivation of *Haemophilus* and *Veillonella* in the gut mucosa. These two species are considered part of oral commensal microbes.

Following HMP, the oral and gut microbiome show strong correlation, even though they were taxonomically different. Oral microbiota can be transported into the gut more broadly than expected, in health or pathological state (5)

1.3. Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a chronic, idiopathic and relapsing inflammatory process of the GIT(6). IBD primarily includes two distinct inflammatory conditions: Crohn's disease (CD) and ulcerative colitis (UC). While Crohn disease affects the large intestine and terminal ileum, involving any part of the gastrointestinal tract, from the anal tract to oral cavity with transmural inflammation, ulcerative colitis mostly affects the colon and rectum (7). Both are chronic and persistent, leading the patient to deal with significant problems, such as morbidity, health care costs, and in

the worst scenario, mortality (8,9). The most common clinical manifestations of IBD, both UC and CD include pus and bloody stool, tenesmus, abdominal pain, diarrhea, and weight loss (10). Some patients can also experience extraintestinal problems, such as oral, eye, skin, bone, and joint lesions. It's interesting to note that oral lesions tend to appear months or years before intestinal symptoms or signs (7).

In children, IBD is characterized by rapid progression and severe type of developing intra and extra intestinal entanglement, and potential need of surgery. The symptoms referred are abdominal discomfort/pain, diarrhea, and bloody stool, that often replace and delay (4). These children also present growth disorders and retardation of puberty. However, they usually have a better response to the therapy, if treated in the early stages. Treating in early stages in IBD is a major concern to avoid complications, like obstruction, abnormal narrowing, need of surgery and the need of hospitalization (7). Although treatment has improved in recent years, the focus, nowadays, remains in depressing the immune response, carrying substantial risks with long-term immunosuppression (10).

Even though the cause remains unclear, there is a possible complex association between the immune system, environment, gut microbiome, and the GIT (disrupted regulation of intestinal mucosa, recurrent infections, genetic factors) (6). This complex interwork results in an inflammatory response in susceptible individuals (4). There is, in fact, a failure in the balance of immune response towards the gut microbiota (9). In fact, emerging evidence suggests a "mouth-gut axis," with the oral cavity reflecting extra-intestinal manifestations of IBD (11,12).

1.3.1 IBD and Oral health

IBD has the power to have repercussions on the gastrointestinal tract, from the oral cavity to the anal tract, (especially CD), therefore, oral conditions have been recognized as extraintestinal manifestations. In fact, there is a relation between the severity of IBD and the imbalance in the oral microbes community (4,9).

These extraintestinal conditions can manifest as various lesions in the oral cavity, mostly in the form of: aphthous, RAS (recurrent aphthous stomatitis), granulomas, gingival inflammation, periodontitis, and angular cheilitis. How severe they present themselves and their prevalence can be correlated with the extent of the intestinal inflammation (4).

Studies have demonstrated that the act of ingesting a considerable amount of unbalanced oral bacteria, for example, as consequence of periodontitis, can lead to the disruption of gut barrier, resulting in compromised gut function, change in intestinal bacteria, and immunological dysfunction (4).

IBD patients have a predisposition from the most severe form of periodontitis, in the most severe forms, compared to patients with periodontal disease without chronic inflammation, having higher level of probing depths, higher levels of plaque, bleeding on probing, calculux, and bigger loss of attachment (CAL - Clinical attachment level) (4). Having this in mind, IBD patients are more likely to develop periodontitis, while periodontitis itself can increase the risk of developing IBD (3).

The literature reveals that more than 250 species of bacteria colonize oral cavity, including a few numbers of bacterial pathogens that are involved in the progression of cavities and periodontal disease, namely, *Tannerella forsythia*, *Streptococcus mutans*, *Aggregatibacter actinomycetemcomitans* and *P. gingivalis* (1). These bacteria, when present in the oral cavity, outside of the normal average quantity, can travel through the circulatory system. Mechanical actions, like brushing or dental procedures, might trigger transmission from the mouth to the blood. Oral bacteria invade and colonize macrophages and dendritic cells, entering the bloodstream, until reaching and spreading along the intestinal tract, which is highly vascular (4). All this process is greatly facilitated by saliva, working as a transporter. Saliva composition (protein, lipids, water and mucin) provides the right protection against stomach acid, allowing pathogens survival (13).

Although the role of the gut microbiome has already been studied in IBD, few are those that focus on the role of the oral microbiome in the development of this pathology and the oral diseases associated with these patients.
The goal of this study is to systematically review the literature on the oral microbiome dysbiosis in IBD patients and its impact on oral health status.

This systematic review aims to examine the purpose of discovering the impact of microbiome dysbiosis in IBD patients. Particularly, understanding how oral microbiome influences IBD and how IBD affects oral health, provides insights into the bidirectional relationship between these conditions, shedding light on shared pathophysiological mechanisms. The literature reveals that the bacteria that colonize oral cavity, including

bacterial pathogens involved in the progression of cavities and periodontal disease, are the ones involved in IBD. This work can identify specific microbial patterns or biomarkers in the oral microbiome that may serve as early indicators or predictors of IBD activity or severity. Gathering all this information in a systematic manner may contribute to determine the best way to manage and treat the condition in early stages, helping to develop evidence-based clinical guidelines for managing oral health in IBD patients. These guidelines can address both prevention and treatment through targeted interventions, such as probiotic therapies, oral hygiene practices, or dietary adjustments that benefit both oral and gut health.

Furthermore, using the query proposed, none of the articles achieved represent a systematic review. This review will be the first one on that theme, emerging as an important subject to work on, ensuring that all available evidence is evaluated, minimizing knowledge gaps and avoiding biases from relying on limited or non-representative studies.

2. MATERIALS AND METHODS

This systematic review was performed following the systematic review's guidelines [Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA)] guidelines and has been registered in OSF Registries, with the registration DOI https://doi.org/10.17605/OSF.IO/SU42T.

The target question was driven according to the PICO strategy (Population, Intervention, Comparison and Outcome), where:

PICO	**Population (P):** Patients with inflammatory bowel disease (IBD).
	Intervention (I): Assessment of oral microbiome and/or oral health.
	Comparison (C): Healthy controls or non-IBD individuals.
	Outcome (O): Differences in oral microbiome composition

***Figure nº 1**- Pico Strategy*

The systematic literature search was carried out in electronic databases, such as PubMed, Scopus, and Cochrane on October 3rd, 2024.

The search was performed to recognize articles with pertinent data to answer the PICO question: How do the oral microbiome and oral health (I) in patients with IBD (P) differ from healthy individuals (C), and how are these differences linked to IBD activity (O)?

The search was performed by using the following query: (Oral microbiome [Title/Abstract] OR oral microbiota [Title/Abstract]) AND Inflammatory bowel disease [Title/Abstract])

To narrow the analysis only cross-sectional and cohort studies performed in Humans and published in English that identified the main phyla, genera, and species in oral and/or stool and/or colon samples were included. Revisions, Systematic revisions and Meta-Analysis were not included. Studies that did not meet all the inclusion criteria or in which the population observed had other systemic pathologies than IBD, that could influence the results, were excluded. *In vitro* and animal studies were also excluded.

The results of the different databases were combined into Rayyan (14) to help to eliminate duplicated documents and articles were screened by title and abstract for eligibility. When the title or abstract did not provide sufficient information regarding the inclusion criteria, full text was obtained and analyzed. Two researchers independently

participated in the processes (CC and AG), including article selection and data extraction.

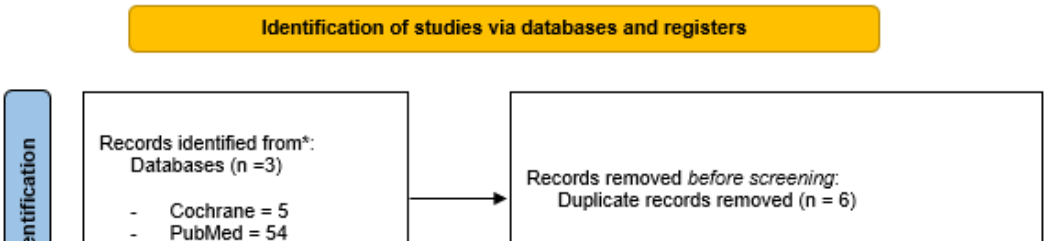
To evaluate methodological quality of the studies, the critical assessment tool - Joanna Briggs Institute (JBI) was used (15).

The data collected was organized in Excel. The first excel spread sheet will include PMID, year, number of participants, sample, sequencing approach, and platform. The second sheet incorporates the outcome. The outcome will refer to saliva samples and/or fecal samples, at phyla, genera and species levels.

3. RESULTS

Data were collected between September and October 2024, and a systematic literature search was carried out which identified 469 potentially relevant references, 54 of which came from the PubMed/Medline database, 410 from Scopus, and 5 from Cochrane. Six duplicates were found and excluded. Based on the information provided in the title and abstract, 447 were considered ineligible. The main reasons for not including the articles were as follows: (1) unrelated topic; (2) wrong outcome; (3) review; (4) wrong population; (5) wrong publication type; (6) wrong study design; (7) wrong study duration. Forty-nine articles were analyzed in full to gather more detail information, being excluded by the following criteria: (1) animals; (2) meta-analysis; (3) in vitro; (4) randomized controlled trials; (5) longitudinal study. Four more reports were excluded due to (1) no DNA sequencing and (2) associated pathologies

Finally, twelve articles were included in the following review. The study selection process is shown in Figure 1.



The quality of the studies selected were accessed using JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies (15) and the results are summarized in Table 2. Most studies had clearly defined components, however the study by Said, H.S., 2014 (16) et al. lacked detailed descriptions of the study population and setting and did not identify potential confounding factors.

***Table 1**- Results of the analysis of the Critical Appraisal tools checklist for the critical evaluation of cross-sectional studies*

Author, Year	1. Were the criteria for inclusion in the sample clearly defined?	2. Were the study subjects and the setting described in detail?	3. Was the exposure measured in a valid and reliable way?	4. Were objective, standard criteria used for measurement of the condition?	5. Were confounding factors identified?	6. Were strategies to deal with confounding factors stated?	7. Were the outcomes measured in a valid and reliable way?	8. Was appropriate statistical analysis used?
Abdelbary, M.M.H., **2022**	Y	Y	NA	Y	Y	Y	Y	Y
Golob, J., **2024**	Y	Y	NA	Y	Y	Y	Y	Y
Elzayat, H., **2023**	Y	Y	NA	Y	Y	Y	Y	Y
Dinakaran, V., **2019**	Y	Y	NA	Y	Y	Y	Y	Y
Docktor, M. J., **2012**	Y	Y	NA	Y	Y	Y	Y	Y
Elmaghrawy, K., **2023**	Y	Y	NA	Y	Y	Y	Y	Y
Han, A., **2024**	Y	Y	NA	Y	Y	Y	Y	Y
Kang, S.B., **2023**	Y	Y	NA	Y	Y	Y	Y	Y
Qi, **2021**	Y	Y	NA	Y	Y	Y	Y	Y
Said, H.S., **2014**	Y	U	NA	Y	N	N	Y	Y
Somineni, H.K., **2021**	Y	Y	NA	Y	Y	Y	Y	Y
Xu, J., **2023**	Y	Y	NA	Y	Y	Y	Y	Y

Y- Yes; N- No; U- Unclear; NA- Not applicable.

Table 2 presents a comparative summary of the principal characteristics of the multiple studies included that evaluate microbiome in patients with IBD, encompassing both CD and UC, in contrast to healthy controls (HC). All these studies employed 16S rRNA gene sequencing to profile the microbial communities, though they varied in their sampling strategies, population sizes, sequencing platforms, and analysis methods.

Across the studies, several biological samples were collected: only saliva was used in four studies (16–19) only stool in one study (20), oral swab also was used in one study (21),same as buccal mucosa and oral cytologic brush (22) as long as colon specimens (23). Some of them used saliva and stool or multiple oral sites (24–27). The number of IBD participants ranged from smaller cohorts of around 14 individuals to larger datasets involving over 300 patients, often including both adult and pediatric populations. The control groups similarly ranged in size and composition.

All studies used 16S rRNA sequencing, differing in the target hypervariable regions – some studies focused on the V1-V2 or V3-V4 regions, while others used V4 or did not specify. Illumina platforms were the most used sequencing technologies, particularly Miseq and NovaSeq, although other technologies such as Oxford Nanopore and HOMIM were also employed. A few studies integrated computational tools such as PICRUSt2 or QIIME2 to infer microbial functions or diversity metrics from the sequencing data.

Table 3 summarizes the main findings of each included study, highlighting microbiome alterations in patients with IBD, including CD and UC, compared to healthy controls (HC). Across the studies, a consistent trend emerges of reduced microbial diversity in both oral and gut samples of IBD patients, accompanied by significant compositional shifts indicative of dysbiosis.

***Table 2**-Principal characteristics of the 12 studies included in this systematic review*

Author, Year	Sample(s)	IBD Group	Control Group	Sequencing approach	Sequencing platform
Abdelbary, M.M.H., 2022	Saliva and Stool	14 IBD (UC 7 and CD 7) – 4 with active phase of UC	12 HC	16s rRNA (V4 region)	Illumina Miseq
Golob, J., 2024	Stool	334 CD patients (39 qCD+S; 274 qCD-S; 21 aCD)	50 HC	16s rRNA (V1-V2 region)	Illumina NovaSeq
Elzayat, H., 2023	Saliva	40 CD	40 HC	16s rRNA	Illumina NovaSeq
Dinakaran, V., 2019	Colon specimens	13 UC+13 CD	13 HC	16s rRNA	HOMIM
Docktor, M. J., 2012	buccal mucosa and oral cytology brush	Pediatric patients under 18 years with CD (40) + UC (31)	43 HC	16s rRNA	Illumina Miseq
Elmaghrawy, K., 2023	Oral swab	Pediatric patients under 16 years old with IBD (146), 94 CD + 52 UC	102 HC	16s rRNA (V1-V2 region)	Mk1C Oxford Nanopore
Han, A., 2024	Saliva and stool	80 IBD, 69 CD+11UC	24 HC	16s rRNA (V3-V4 region)	Illumina NovaSeq
Kang, S.B., 2023	Saliva	127 CD + 175 UC	100 HC	16s rRNA	PICRUSt2
Qi, 2021	Saliva	UC (10) + CD (12)	8 HC	16s rRNA (V3-V4 region)	QIIME2
Said, H.S., 2014	Saliva	21 CD+ 14 UC	24HC	16s rRNA	UniFrac distance
Somineni, H.K., 2021	DNA swabs form saliva, the tongue, plaque, and buccal mucosa	Pediatric patients under 19 years old – 47 IBD – 30 CD + 17 UC	18 HC	16s rRNA	QUIIME2
Xu, J., 2023	Salivary, buccal, and stool samples	31 UC + 17 UC_OU	28HC + 18 HC_OU	16s rRNA (V3-V4 region)	Illumina Miseq

***Table 3**-Main findings of the 12 studies included in this systematic review.*

Author, Year	Diversity	Oral Microbiome Composition			Fecal Microbiome Composition		
		Phylum	Genus	Species	Phylum	Genus	Species
Abdelbary, M.M.H., 2022	**Alpha** - number of detected taxonomic groups (Shannon index), was significantly lower in samples from the IBD group. **Beta** - significant differences among the IBD and control groups.	Both groups exhibited dominant levels of Firmicutes, Bacteroidetes, and Proteobacteria. In IBD patients, there was a higher abundance of Firmicutes, Bacteroidetes, and Actinobacteria, while Proteobacteria, Fusobacteria, and Patescibacteria were less prevalent compared to controls.	IBD patients showed higher abundance of Veillonella, Prevotella, Megasphaera, Atopobium, and Rothia, with Veillonella and Prevotella comprising up to 47.6% of the oral microbiome. In contrast, 17 genera were more abundant in healthy controls, suggesting a balanced microbiome. Five dominant genera—Neisseria, Streptococcus, Haemophilus, Porphyromonas, and Fusobacterium—accounted for 38.8% of the	P*revotella salivae* was significantly more abundant in IBD patients, while *Fusobacterium periodonticum*, *Veillonella rogosae*, and *Haemophilus pittmaniae* were increased in healthy controls.	Firmicutes, Actinobacteria, and Bacteroidetes dominated both groups. Proteobacteria was generally low but significantly higher in IBD. IBD patients had more Firmicutes and Actinobacteria and less Bacteroidetes, though differences were not statistically significant.	Eight genera, including Blautia, Faecalibacterium, and Bacteroides, dominated the fecal microbiome, comprising 51.4% in controls and 46.7% in IBD patients. IBD patients had lower levels of Subdoligranulum, UCG-002, Coprococcus, Roseburia, and Ruminococcus, and higher levels of Clostridium sensu stricto 1, Streptococcus, Escherichia-Shigella, and Lactobacillus. Blautia and Faecalibacterium were more abundant in IBD but not significantly or disease-specific.	IBD patients had increased *Blautia luti*, *Fusicatenibacter saccharivoran*s, *Blautia obeum*, *Gemmiger formicilis*, and *Bacteroides uniformis*. In contrast in controls were associated with *Eubacterium rectale*, *Anaerobutyricum hallii*, *Ruminococcus bromii*, and *Oscillibacter ruminantium*.

			salivary microbiome.				
Golob, J., 2024	**Alpha (Shannon index)**: Significantly **reduced** in patients with qCD+S when compared to controls, qCD-S and aCD.	NA	NA	NA	qCD+S showed increased oral and sulfidogenic bacteria, and depletion of beneficial Firmicutes (which often include butyrate producers)	qCD + S: Increased oral microbiota genera such as Streptococcus, Rothia, and Fusobacterium, and also sulfidogenic genera like Bilophila and Prevotella. This group had also a depletion of butyrate-roducing genera, notably: Faecalibacterium, Eubacterium and Roseburia, whem compared to the other groups.	Enriched in qCD + S (compared to qCD - S): -Rothia dentocariosa: -Fusobacterium nucleatum -Prevotella copri -Streptococcus spp. Depleted in qCD + S: -Eubacterium rectale Faecalibacterium prausnitzii (Both are key producers of butyrate and indole, important for gut barrier health)
Elzayat, H., 2023	CD patients showed significantly reduced alpha diversity (Observed Species, Chao1, ACE), indicating lower microbial richness, while Shannon and Simpson indices remained unchanged, suggesting stable evenness.	Firmicutes and Bacteroidetes levels were similar between groups, though CD patients showed a non-significant decrease in the Firmicutes/Bacteroidetes ratio. Tenericutes and Spirochetes were significantly reduced in CD, indicating phylum-level dysbiosis.	Sixteen genera were significantly more abundant in healthy controls, indicating a loss of beneficial taxa in CD. Dolosigranulum was the only genus significantly enriched in CD. Oral disease–associated genera (Streptococcus, Lactobacillus, Fusobacterium, Bacteroides) varied with oral health and disease status. Medications	Enriched in CD: Veillonella dispar, Megasphaera stantonii, Prevotella jejuni, Dolosigranulum pigrum, and Lactobacillus backii. Fusobacterium periodonticum was elevated in patients with caries; Streptococcus mutans and Lactobacillus spp. in those with periodontal	NA	NA	NA

	Poor oral health, especially with both periodontitis and caries, was linked to the lowest alpha diversity. Beta diversity showed no significant differences between CD and healthy controls or among CD subgroups.		strongly influenced the microbiome: monoclonal antibody treatment increased Simonsiella, while combination therapies raised levels of Proteobacteria-associated genera like Escherichia, Salmonella, Klebsiella, and Pseudomonas.	disease. Even CD patients with good oral health harbored pathogens like Prevotella jejuni and Porphyromonas gingivalis. Simonsiella muelleri was found only in patients on monoclonal antibodies, while Klebsiella pneumoniae, Escherichia coli, Salmonella enterica, and Pseudomonas aeruginosa were enriched in those on combination therapy.			
Dinakaran, V., 2019	Increased microbial diversity in diseased colon tissues compared to healthy adjacent tissues. Beta diversity showed that microbiome profiles in diseased tissues differed from those of healthy tissues.	NA	NA	NA	Bacteroidetes (46.9%), Firmicutes (27.8%), and Proteobacteria (24.5%) were dominant across all samples. Healthy colon tissues were enriched in Bacteroidetes, while diseased tissues showed increased Firmicutes, especially oral-	At the **genus and species level**, a clear pattern of **enrichment of pathogenic bacteria** in diseased tissues was observed. Diseased colon samples (both CC and UC) were significantly enriched with **oral-origin pathogens** such as *Streptococcus*, *Staphylococcus*, *Gemella*, *Peptostreptococcus*, *Lactobacillus*, and	Diseased colon tissues showed higher abundance of Blautia producta, Faecalibacterium prausnitzii, Anoxybacillus kestanbolensis, Ruminococcus gnavus, and Eubacterium dolichum—species that may contribute to inflammation when dysregulated. In contrast, healthy tissues were enriched with anti-

	significant **inter-individual variability** and the presence of outliers were also observed, particularly among African American patients, suggesting demographic influences on microbial composition				associated taxa, indicating dysbiosis. Fusobacteria and Proteobacteria were also elevated in diseased tissues, both linked to inflammation.	*Porphyromonas*, as well as gut pathogens like *Pseudomonas*, *Fusobacterium*, *Aggregatibacter*, and *Corynebacterium.*	inflammatory species from Actinobacteria and Bacteroidetes, including Corynebacterium kroppenstedtii, Collinsella stercoris, Kocuria rhizophila, Propionibacterium acnes, Bacteroides fragilis, B. eggerthii, and Parabacteroides distasonis.
Docktor, M. J., 2012	CD patients showed significantly reduced microbial diversity in tongue samples, indicating pronounced oral dysbiosis. No significant diversity differences were observed in UC patients or in buccal samples, though CD patients showed a non-significant trend toward reduced diversity in the buccal mucosa.	Reduced diversity in CD tongue samples was driven by significant loss of Firmicutes and Fusobacteria. In UC patients, Fusobacteria also decreased, while Spirochaetes, Synergistetes, and Bacteroidetes increased, though these shifts did not significantly affect overall diversity.	The HOMIM array did not provide genus or species-level data, but phylum-level trends indicated a shift from normal commensals toward a microbiota more prone to inflammation and colonization by opportunistic pathogens.	Not evaluated			

Elmaghrawy, K., 2023	alpha diversity did not differ significantly between IBD patients and healthy controls. However, within IBD, patients with low serum albumin (<37 g/L) or severe disease showed reduced alpha diversity, indicating that systemic inflammation is linked to lower microbial richness. Beta diversity analysis showed significant divergence in the oral microbiome of IBD patients with greater variation especially in severe cases, suggesting disease severity strongly influences microbial composition.	In severe pediatric IBD, Firmicutes showed a shift with increased Bacilli (e.g., Streptococcus, Lactobacillus, Staphylococcus) and decreased Clostridia (e.g., Lachnospiraceae, Ruminococcaceae), indicating dysbiosis. Proteobacteria were also affected, with elevated Klebsiella and Pseudomonas, especially in CD, suggesting potential oral pathobionts linked to intestinal inflammation.	IBD patients showed significant depletion of beneficial oral genera such as Veillonella, Prevotella, Fusobacterium, Leptotrichia, Porphyromonas, and Oribacterium. In contrast, Streptococcus, Corynebacterium, Pseudomonas, Ottowia, Lautropia, and Staphylococcus were enriched, with Klebsiella and Pseudomonas notably elevated in severe cases due to their pro-inflammatory potential.	Not evaluated	NA	NA	NA

Han, A., 2024	IBD patients showed significantly reduced alpha diversity in both fecal and saliva samples across multiple indices (Chao1, Shannon, Faith's PD, Pielou's evenness), indicating loss of microbial richness and evenness. Beta diversity (PCoA) revealed distinct microbial community structures, confirming significant microbiome alterations in IBD.	IBD patients had increased Proteobacteria and Firmicutes were increased. However, Fusobacteria and Actinobacteria were significantly decreased.	Genera such as Prevotella, Streptococcus, Neisseria, Haemophilus, Veillonella, Fusobacterium, and Porphyromonas were abundant across all groups. IBD patients showed a significant increase in Neisseria and a significant decrease in Fusobacterium and Actinomyces.	Not evaluated	IBD patients: Proteobacteria was significantly increased. Bacteroidetes, Fusobacteria, and Actinobacteria were significantly decreased.	Bacteroides, Prevotella, Shigella, Faecalibacterium, Ruminococcus, and Roseburia were prominent genera. IBD patients had increased Shigella and decreased Prevotella, Faecalibacterium, and Roseburia. Clostridium (Lachnospiraceae) was enriched in CD, while Ruminococcus was more abundant in UC.	Shigella flexneri and Shigella sonnei were significantly enriched in IBD fecal samples. These pathogens correlated positively with inflammation markers (CRP, ESR, calprotectin, neutrophils, LDH) and negatively with nutritional and hematological indices (albumin, hemoglobin, lymphocytes), linking them to disease severity.
Kang, S.B., 2023	Alpha diversity was significantly reduced in IBD patients compared to healthy controls, with HC showing higher richness than UC and CD. No significant	Phylum and Family Levels: Lachnospiraceae was the most abundant family across all groups. Flavobacteriaceae was significantly more abundant in IBD patients than in HC. No substantial differences between CD and UC at the family level.	Top genera frequently selected in machine learning models for: IBD vs. HC: Included genera like Prevotella, Veillonella, and Streptococcus. CD vs. UC: Included Rothia, Neisseria, and Fusobacterium.	The study identified 2711 phylotypes, but species-level resolution was not the primary focus. Instead, genus-level markers were emphasized for diagnostic modeling.	NA	NA	NA

	difference was found between CD and UC except for the Chao1 index. Beta diversity (PCoA) showed distinct clustering of HC from IBD, with notable heterogeneity among IBD samples.						
Qi, 2021	No significant differences in alpha diversity among UC, CD, and HC groups. However, beta diversity analysis showd distinct clustering in IBD patients, indicating that while species richness was similar, microbial community structure and interactions were markedly altered in IBD.	Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria, Actinobacteria, TM7, and SR1 were dominant across all samples. TM7 was significantly enriched in both UC and CD, and SR1 in CD. Actinobacteria levels differed significantly between CD and UC. These shifts indicate oral microbiota dysbiosis in IBD patients.	Streptococcus and Rothia were significantly depleted in IBD patients, while Leptotrichia, Prevotella, Bulleidia, Atopobium, and Parvimonas were enriched. Leptotrichia was particularly elevated in UC, and Bulleidia in CD.	specific amplicon sequence variants (ASVs) within TM7 and SR1 that were strongly associated with IBD, and these were positively correlated with inflammatory markers.	NA	NA	NA
Said, H.S., 2014	No significant differences in species richness, evenness, or overall	Salivary microbiota of IBD patients showed a significant increase in Bacteroidetes and a concurrent decrease in Proteobacteria compared	A total of 107 genera were identified, with 14 dominant genera comprising over 90% of the dataset.	Specific OTUs corresponding to Prevotella melaninogenica, Veillonella sp., Streptococcus	NA	NA	NA

	diversity among CD, UC, and HC groups (Shannon, Simpson, Chao1, ACE indices). However, beta diversity (weighted UniFrac) showed distinct clustering of IBD samples, indicating significant differences in microbial composition despite similardiversity levels.	to healthy controls. Firmicutes remained the most dominant phylum across all groups, followed by Bacteroidetes, Actinobacteria, Proteobacteria, and Fusobacteria. Minor phyla such as TM7, SR1, and others were also detected but represented less than 1% of the total reads.	Notably, Prevotella and Veillonella were significantly enriched in CD and UC patients, while Streptococcus and Haemophilus were significantly depleted. Neisseria and Gemella also showed reductions, particularly in CD. These microbial shifts indicate a dysbiotic state, marked by an overrepresentation of anaerobes and a decline in key commensal genera.	mitis, Gemella sanguinis, Neisseria mucosa, and Haemophilus parainfluenzae showed significant abundance differences between IBD patients and healthy controls. These species-level alterations aligned with genus-level trends and were validated by quantitative PCR, supporting the accuracy of the sequencing data.			
Somineni, H.K., 2021	Buccal mucosa showed significantly lower microbial diversity than saliva, tongue, and plaque (Shannon index), though species richness (Chao1 index) did not differ among oral sites. In IBD patients, stool samples exhibited	The dominant phyla identified were Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. In saliva, Firmicutes comprised 46%, Proteobacteria 25%, Bacteroidetes 12%, and Actinobacteria 10%. Compared to stool, oral samples had lower Firmicutes and higher Proteobacteria. In IBD patients, Actinobacteria, Bacteroidetes, and Spirochaetes were enriched across oral sites, while Firmicutes, Fusobacteria, and	The study revealed site- and taxa-specific dysbiosis in IBD patients. Notably, the order Bacillales and family Carnobacteriaceae (both Firmicutes) were significantly reduced in plaque, buccal mucosa, and saliva. In contrast, the family Actinomycetaceae and genus Actinomyces (Actinobacteria) were enriched. These microbial	Not evaluated	NA	NA	NA

	significantly reduced diversity and richness, consistent with previous reports. Saliva samples showed a non-significant trend toward reduced richness, while other oral sites showed no significant differences in diversity or richness compared to healthy controls.	Proteobacteria were generally depleted.	changes were most pronounced in plaque, which showed the greatest number of significantly altered taxa, suggesting it is particularly sensitive to IBD-associated shifts.				
Xu, J., 2023	Alpha diversity: Fecal samples showed the highest microbial richness and diversity. Salivary and buccal samples had similar, lower diversity compared to feces. Notably, UC patients with oral ulcers (UC_OU) exhibited increased	In saliva and buccal samples, Firmicutes and Proteobacteria dominated. In UC_OU patients: There was a notable increase in Actinobacteria and Bacteroidetes. Firmicutes and Proteobacteria were generally depleted compared to healthy controls.	In saliva: UC_OU patients showed increased abundance of Klebsiella, Arthrobacter, and Barnesiella. Decreased levels of Blautia, Clostridium III, and Faecalibacterium were observed. These shifts suggest a pro-inflammatory microbial profile. In buccal samples:	Not evaluated	In feces, Firmicutes and Bacteroidetes were most abundant.	In feces: -UC_OU patients had reduced alpha diversity. -Enrichment of Alloprevotella, Granulicatella, Lactobacillus, and Holdemanella distinguished UC_OU from UC alone. -Escherichia/Shigella was elevated in both UC and UC_OU groups.	Not evaluated

	salivary microbial diversity and evenness relative to UC patients without ulcers and healthy controls. Beta diversity: Significant differences were found between fecal and oral microbiota. Salivary and buccal communities were more like each other than to fecal communities. UC_OU patients displayed distinct microbial community structures across all three niches, indicating unique dysbiosis associated with oral ulceration.	Abiotrophia, Cardiobacterium, and Klebsiella were enriched in UC_OU patients. Actinobacillus was depleted. These genera are associated with inflammation and mucosal barrier disruption.		

Three studies directly compared the oral and gut microbiome constitution using saliva and stool samples, respectively. These studies illustrate key findings on microbial diversity and composition in IBD patients, emphasizing the consistent presence of dysbiosis across different biological niches. The results from Abdelbary et al. (2022) (24) revealed significantly lower alpha diversity and distinct beta diversity in IBD patients' oral and fecal microbiota. In saliva, IBD patients showed higher levels of *Veillonella*, *Prevotella*, and *Megasphaera*, while *Neisseria*, *Streptococcus*, and *Fusobacterium* were more common in healthy individuals. At the species level, *Prevotella salivae* was increased in IBD, whereas *Fusobacterium periodonticum* and *Veillonella rogosae* were reduced. Fecal samples from IBD patients had increased *Firmicutes*, *Actinobacteria*, and *Proteobacteria*, and decreased *Bacteroidetes*. Pathogenic genera like *Clostridium sensu stricto 1* and *Escherichia-Shigella* were more abundant in IBD, while beneficial genera such as *Ruminococcus* and *Roseburia* were depleted. Han et al. (2024) (25) reported significant decreases in both oral and fecal microbial diversity in IBD patients, accompanied by increased abundance of *Shigella* in feces and depletion of *Faecalibacterium* and *Roseburia*, supporting a dysbiotic and inflammatory profile. Xu et al. (2023) (27) focused on UC patients with and without oral ulcers, revealing that those with ulcers had increased microbial diversity and unique microbial profiles across oral and fecal niches, with increases in *Klebsiella*, *Arthrobacter*, and *Barnesiella*, and decreases in beneficial genera such as *Faecalibacterium*.

Other three studies evaluate the oral microbiome in the pediatric population with IBD. Docktor et al. (2012)(22) demonstrated significantly reduced microbial diversity in the tongue of pediatric CD patients, with loss of *Firmicutes* and *Fusobacteria*, whereas UC patients showed compositional shifts without significant diversity changes. In the same population, Elmaghrawy et al. (2023) (21) found no overall difference in oral alpha diversity between IBD and healthy controls, but significant reductions were observed in those with severe disease or low serum albumin. Increased levels of *Streptococcus*, *Pseudomonas*, and *Klebsiella* were seen in pediatric IBD patients, while beneficial genera were depleted. In the same way, Somineni et al. (2021) (26) found that pediatric IBD patients had reduced diversity in buccal samples and altered oral microbiota,

particularly with depletion of *Carnobacteriaceae* and enrichment of *Actinomyces* and *Actinomycetaceae*, with plaque being most affected.

Golob et al. (2024)(20) focused the study on quiescent CD patients with and without persistent symptoms. This study showed reduced diversity in stool samples of patients with quiescent CD and qCD+S (with persistent symptoms), along with an enrichment of oral-associated and sulfidogenic bacteria such as *Fusobacterium nucleatum* and *Prevotella copri*. Beneficial butyrate-producing species like *Faecalibacterium prausnitzii* were notably reduced. Although this study assessed only the gut microbiome, it was included in this selection due to the identification of bacterial species typically associated with the oral cavity.

In the oldest study in this selection, Dinakaran et al, (23) observed greater diversity in diseased colon tissue compared to adjacent healthy tissue, with enrichment of pathogenic genera of oral origin, such as *Streptococcus*, *Lactobacillus*, and *Porphyromonas*, suggesting bacterial translocation and dysbiosis. Despite the limited overall information provided, Dinakaran categorized IBD patients by ethnicity—Caucasians and African Americans—and observed notable differences in bacterial composition. Caucasians exhibited higher proportions of *Fusobacterium*, *Parabacteroidetes*, and *Proteobacteria*, whereas African Americans showed elevated levels of *Prevotella* and *Clostridia*.

Several studies have explored the salivary microbiota in IBD patients, both UC and CD, revealing alterations in microbial diversity and composition that may reflect both disease activity and oral health status. Elzayat et al.,(17) in 2023 observed that oral alpha diversity was significantly lower in CD patients, especially those with poor oral health. At genus level, the most relevant bacteria found was the pathogen *Dolosigranulum*, a gram-positive facultative anaerobic bacterium, that tended to be more expressed in IBD patients. At phyla level, non-IBD patients presented an abundance in these four types of bacteria: *Firmicutes*, *Bacteroidetes*, *Tenericutes*, *Spirochetes*. This study also showed that oral disease–associated genera (*Streptococcus*, *Lactobacillus*, *Fusobacterium*, *Bacteroides*) varied with oral health and disease status. Kang et al. (2023) (18) confirmed reduced oral microbial diversity in IBD patients, with *Prevotella*, *Veillonella*, and *Streptococcus* being key genera

distinguishing IBD from controls. Machine learning strategies identified *Rothia*, *Neisseria*, and *Fusobacterium* as important in differentiating CD from UC. Qi (2021) (19)noted no significant differences in alpha diversity across UC, CD, and controls, but observed distinct microbial compositions in IBD patients, including elevated TM7 and SR1 phyla and increased *Prevotella* and *Parvimonas*, alongside depletion of *Streptococcus*.
Said et al. (2014) (16) echoed similar results, showing no difference in diversity metrics but altered community composition, with *Prevotella* and *Veillonella* enriched in IBD and depletion of *Streptococcus* and *Haemophilus*.

Overall, the studies consistently highlight a microbial signature in IBD involving reduced diversity, enrichment of pathobionts, depletion of beneficial commensals, and compositional shifts influenced by disease phenotype, severity, medications, and oral health status.

Microbiome in IBD

Across multiple studies, a consistent pattern of dysbiosis is observed in patients with IBD, including CD and UC, affecting both oral and gut microbiomes. At the phylum level, the most dominant taxa in both healthy individuals and IBD patients are *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, and *Fusobacteria*. However, in IBD patients, especially those with active disease or more severe forms, the balance of these phyla is often disrupted. A notable increase in *Proteobacteria* and a reduction in *Fusobacteria* and *Actinobacteria* were commonly found in IBD cases, particularly in the gut. *Firmicutes* also show divergent patterns; while generally dominant, some studies report their depletion in oral sites and enrichment in inflamed colonic tissues, often associated with pathobionts.(21,23)

At the genus level, healthy controls show higher abundances of commensal and beneficial genera such as *Streptococcus*, *Neisseria*, *Haemophilus*, *Porphyromonas*, and *Fusobacterium* in the oral cavity, and *Faecalibacterium*, *Roseburia*, *Subdoligranulum*, and *Ruminococcus* in fecal samples. In contrast, IBD patients demonstrate enrichment of potentially pathogenic and pro-inflammatory genera such as *Prevotella*, *Veillonella*, *Streptococcus*, *Bilophila*, and *Escherichia/Shigella*. This is especially evident in patients with active or severe disease, where oral and gut samples contain higher levels of sulfidogenic and oral-origin bacteria.(20)

Species-level data, where available, reveal enrichment of *Shigella flexneri*, *Shigella sonnei*, *Prevotella salivae*, and *Faecalibacterium prausnitzii* in diseased tissues. Interestingly, *F. prausnitzii*, typically considered anti-inflammatory, is often depleted in active CD, underscoring the loss of protective species. Conversely, species such as *Fusobacterium nucleatum* and *Rothia dentocariosa*, typically associated with oral environments and inflammation, are enriched in the intestines of CD patients with persistent symptoms.(20,23)

Oral vs Gut Microbiome in IBD

The oral microbiome is emerging as a valuable, non-invasive biomarker for IBD, offering practical advantages over fecal sampling due to its ease of collection, patient acceptability, and relative stability over time.(18) Studies consistently report reduced alpha diversity in the oral microbiota of patients with UC and CD, indicating diminished microbial richness. Beta diversity findings are more variable, with some studies noting similarities to healthy controls, while others report significant compositional shifts. Notably, microbial alterations appear to be site-specific within the oral cavity, particularly in the tongue(18,26)

Compared to the gut microbiome, the oral microbiota is less diverse but more functionally stable due to protective factors like salivary antimicrobials. However, its composition is influenced by environmental factors such as oral hygiene, smoking, and diet, contributing to inter-individual variability. Despite these factors, IBD-associated oral dysbiosis shows recurring patterns: genera such as *Prevotella*, *Veillonella*, *Megasphaera*, *Atopobium*, and *Rothia* are consistently enriched, while *Streptococcus*, *Neisseria*, *Haemophilus*, *Fusobacterium*, and *Porphyromonas* are typically depleted. (18,27)

Species, such as *Prevotella salivae*, have been linked to both IBD and oral diseases, suggesting overlapping pathogenic roles(24). Studies also report the presence of known oral pathogens grouped in various microbial complexes, with UC and CD patients showing patterns associated with gingivitis and periodontitis. Interestingly, the Gram-positive to Gram-negative bacterial ratio remains relatively stable across IBD and healthy individuals. (16,23)

These microbial shifts correlate with inflammatory markers and may be driven by host immune responses or competition among microbes. For example, the replacement of *Clostridia* by *Streptococcus*, *Staphylococcus*, and *Lactobacillus* could reflect immune modulation or niche takeover by pathobionts (16,21,24). Pediatric studies reinforce these findings, showing that oral dysbiosis can exist independently of age, sex, or oral health, and often aligns with disease severity (21).

Functionally, *Prevotella* and *Veillonella* are notable for their nitrate- and sulfate-reducing activities, producing nitric oxide and hydrogen sulfide—molecules implicated in mucosal inflammation and IBD pathogenesis. These metabolic features suggest that

the oral microbiota may actively contribute to disease mechanisms, not merely reflect systemic inflammation (24,28,29).

Overall, current evidence supports the oral microbiome as a promising diagnostic and predictive tool for IBD. Despite some inconsistencies across studies, the recurring patterns of microbial diversity loss, taxonomic imbalance, and functional dysregulation point to a robust and disease-relevant signature of oral dysbiosis in IBD.

The relation with the inflammatory state

The microbial shifts reported early have clear implications for the inflammatory state. The depletion of butyrate- and indole-producing bacteria, including *Eubacterium rectale* and *F. prausnitzii*, impairs epithelial barrier integrity and immune modulation, facilitating chronic inflammation. Enrichment of oral bacteria like *Streptococcus*, *Fusobacterium*, and *Prevotella* in the gut supports the theory of microbial translocation along the oral-gut axis. Furthermore, functional analyses revealed disruptions in sulfur and tryptophan metabolism, essential for maintaining mucosal health. The presence of sulfidogenic and pro-inflammatory species correlates with elevated inflammatory biomarkers such as CRP, calprotectin, and ESR, particularly in CD and UC patients with more severe disease activity (20).

IBD patients exhibit distinct systemic and local inflammatory profiles. Elevated blood and stool markers—including neutrophils, granulocyte-to-lymphocyte ratio, CRP, ESR, and fecal calprotectin—accompany reduced RBCs, hemoglobin, albumin, and liver/kidney function (19,25).These changes are paralleled by oral dysbiosis, where pro-inflammatory cytokines like IL-6, IL-8, TNF-α, and MCP-1 are elevated, particularly in UC and CD saliva (16). IgA is also increased, especially in UC with oral symptoms.

Oral taxa such as *Streptococcus* and *Lautropia* negatively correlate with inflammatory markers, while *Prevotella*, *TM7*, *SR1*, *Eikenella*, and *Campylobacter* show positive associations(19). *Prevotella*, *Actinomyces*, and *Veillonella* are linked to inflammation, whereas *Streptococcus*, *Rothia*, and *Haemophilus* are inversely related(16,21,24). Salivary lysozyme is reduced in IBD, mirroring immune changes seen in periodontal disease, while fecal lysozyme increases(16) .Antibody responses to oral bacteria (e.g., *Gemella*, *Peptostreptococcus*, *Streptococcus*) suggest microbial translocation (21).

Pathobionts like *Veillonella* and *Fusobacteria* may trigger systemic immunity after gut colonization, explaining their oral depletion(21). In symptomatic quiescent CD, oral microbiomes show reduced anti-inflammatory metabolites (e.g., butyrate, indole) and altered tnaA gene variants(20) ,alongside disrupted amino acid metabolism and increased H_2S production—linking oral microbes to gut pathology.

Fusobacterium, *Oribacterium*, *Campylobacter*, and *Klebsiella* are enriched in treatment-resistant UC, while *Klebsiella*-specific Th17 responses support oral-gut immune axis involvement (27). Reduced thiamine biosynthesis and disrupted styrene degradation in UC patients with ulcers indicate more severe disease (27). Increased *Bacteroidetes* in saliva correlates with higher cytokines and IgA (17).

Elzayat et al(17). demonstrated that salivary CRP and fecal calprotectin negatively correlate with microbial diversity but positively correlate with disease activity, supporting their potential as biomarkers(17). Calprotectin, a calcium and zinc binding protein and constitutes about 60% of the neutrophil cytosolic proteins (30) has been well-established as a reliable indicator of mucosal inflammation in fecal samples. However, recent findings suggests that salivary calprotectin may not be a dependable marker for monitoring IBD, as it shows no consistent correlation with disease activity. (31) Nevertheless, enrichment of *Fusobacterium*, *Veillonella*, and *Klebsiella* in feces, typically oral in origin, further supports the role of oral microbes in gut inflammation. (17)

Together, these findings highlight a dynamic oral-gut axis in IBD. Oral microbial and immune alterations not only reflect systemic inflammation but may actively contribute to disease progression, supporting their value as diagnostic and therapeutic targets.

Oral Health implications

In recent years, a growing body of evidence has pointed to a potential "mouth-gut axis" in the development of gastrointestinal disorders, including IBD. The oral cavity is often affected by extra-intestinal manifestations of IBD, which has led clinicians to adopt a broader focus that extends beyond the intestinal tract (32,33).

While some studies suggest that poor oral health may have a protective effect against IBD(34,35),numerous others(31,36) have demonstrated a significant association between IBD and various oral health issues, including periodontitis, xerostomia(37), and an increased risk of dental caries (38). Notably, oral changes may precede the onset of intestinal symptoms. These findings underscore the impact of IBD on oral health and the importance of interdisciplinary collaboration between dental and gastrointestinal specialists to provide comprehensive care for affected patients.(39)

The relationship between oral health and microbial composition is especially pronounced.(17) Poor oral health—marked by caries and periodontitis—is associated with lower alpha diversity and increased abundance of periopathogens such as *Porphyromonas gingivalis* and *Lactobacillus spp.* in CD patients. Studies suggest that even IBD patients with clinically good oral hygiene can harbor a dysbiotic oral microbiota rich in inflammatory species. These findings underscore the role of the oral cavity as a reservoir for gut colonization by pathobionts. For instance, genetically identical strains of *Streptococcus* have been found in both the saliva and feces of IBD patients, suggesting oral-gut transmission. Additionally, the degree of oral dysbiosis has been positively correlated with systemic inflammation and disease severity, and in some studies, has been shown to reverse following successful treatment, such as exclusive enteral nutrition (17) .

Recent studies reveal that both oral and gut microbiota play critical roles in IBD pathogenesis, including CD and UC. *Neisseria*, commonly found in the oral cavity, is elevated in IBD patients, potentially linked to nitrate-rich diets, frequently consumed by CD patients—though causality remains unconfirmed.(16,18,24,25)

Significant microbial shifts, particularly among Bacteroidetes and Firmicutes, have been observed in inflamed colon tissues (23). Oral bacteria like *Fusobacterium nucleatum* and *Campylobacter s*pp. are associated with gut inflammation and treatment resistance in UC. The oral microbiome, which can rapidly recover from disturbances, shows promise as a biomarker for monitoring IBD therapy (27). Also, pathogenic oral bacteria—including *F. periodonticum*, *L. fermentum*, *S. mutans*, and *P. gingivalis*—are more abundant in IBD patients, even in those without oral disease symptoms. Nevertheless, poor oral health in CD correlates with increased abundance of pathogens like *P. gingivalis*, *Prevotella*, and *B. fragilis* (17). Dysbiosis in CD is influenced by disease activity, relapse frequency, and especially medication use.

Immunosuppressive therapies promote the growth of *Proteobacteria* such as *E. coli*, *Salmonella*, *Klebsiella*, and *Pseudomonas*, which trigger immune responses and inflammation (17).

Several studies have already stated that age, particularly over 55, is associated with worse periodontal health, reflected by higher PESS (Periodontal Screening Score) scores (40). CD patients generally experience worse oral outcomes than UC patients or healthy controls (40,41). IBD independently lowers oral health-related QoL, regardless of stress, age, or tooth count (40). IBD-specific QoL is further reduced in patients with oral symptoms (e.g., tooth loss), particularly in those with CD, depression, and high disease activity(40). Bertl (42)also linked tooth loss—a sign of severe periodontitis—to greater IBD-related disability. Periodontitis is associated with systemic diseases such as diabetes and cardiovascular disease, and while its treatment offers short-term benefits, long-term impact remains unclear.

The relationship between periodontitis and IBD likely involves systemic inflammation, bacterial translocation, and gut microbiota disruption (42). IBD can also impair oral health by altering the oral microbiome and bone metabolism. Madsen (41) confirmed high rates of periodontitis and oral disorders in UC and CD patients, such as mucosal ulcers and gingivitis. More recently, Rodrigues et al, (31) confirms the high incidence of periodontal disease, particularly among patients with UC.

Yin (34) unexpectedly found that poor oral hygiene (e.g., tooth loss, high plaque) was associated with reduced IBD risk, possibly supporting the hygiene hypothesis. This theory suggests limited microbial exposure impairs immune tolerance. Thus, excessive hygiene may promote dysbiosis, while less hygiene might enhance microbial diversity and tolerance. Oral damage from over-cleaning could also facilitate immune disruptions. Rodrigues (31)emphasized shared microbial alterations in oral and gut sites in CD patients, with reduced diversity in both. Still, as Yin (34) cautions, confounding factors—diet, socioeconomic status, medication, or even toothpaste—may influence these findings.

Thus, IBD patients—especially those with CD—face higher risks of periodontal disease, which negatively impacts QoL. Meanwhile, oral dysbiosis may contribute to IBD onset or severity. The relationship appears bidirectional, shaped by immune, microbial, and environmental interactions. Further research is needed to clarify these

mechanisms and explore diagnostic or therapeutic use of the oral microbiota. Nevertheless, these findings underscore the need for increased awareness among healthcare providers regarding the oral health challenges faced by these patients.(31)

Proposed Microbial Biomarkers panel for IBD (CD, UC) Diagnosis and Monitoring and Associated Oral Diseases

From these studies, a panel of microbial biomarkers could emerge with potential diagnostic and monitoring value for IBD (table 4). The oral cavity, which often exhibits extra-intestinal manifestations of IBD, harbours microbial shifts that not only reflect intestinal disease activity but are also closely associated with oral complications such as periodontitis, gingivitis, and dental caries.

In IBD patients, certain oral bacterial taxa are consistently enriched and may serve as biomarkers of both systemic inflammation and local oral disease. *Prevotella salivae*, *Veillonella*, *Megasphaera*, *Atopobium* and *Rothia* are commonly elevated and have been associated with mucosal inflammation and oral pathologies(16–21,24,25). Fusobacterium *nucleatum*—a known periodontal pathogen—and *Prevotella* species, such as *P. jejuni*, have been found in greater abundance in CD patients with poor oral health(17,20). These bacteria are known contributors to gingival inflammation, periodontal disease, and in some cases, systemic immune activation.(43,44)

Additionally, high levels of *Streptococcus mutans* and some *Lactobacillus* species, all cariogenic, have been identified in the IBD patient's samples and are linked to an increased incidence of dental caries(17). *P. gingivalis*, member of the red complexes associated with severe periodontitis, are also enriched in CD patients, even in the absence of explicit oral disease symptoms(17). Their presence supports the hypothesis that oral dysbiosis in IBD is often subclinical yet biologically active.

Conversely, health-associated oral taxa such as *Streptococcus*, *Neisseria*, *Haemophilus*, *Fusobacterium periodonticum*, and *Gemella* are consistently depleted in IBD patients, suggesting a microbial imbalance conducive to oral disease progression(16,17,24,45). These depleted genera typically maintain mucosal homeostasis and have protective roles in oral immunity.

From a functional perspective, taxa like *Prevotella* and *Veillonella* are not only abundant in the oral cavities of IBD patients but also positively correlate with pro-inflammatory cytokines such as IL-1β and the production of reactive metabolites like nitric oxide and hydrogen sulphide. (24,45,46)These compounds have been implicated in both mucosal damage and oral inflammatory conditions. Conversely, *Streptococcus* and *Haemophilus* exhibit inverse correlations with inflammatory cytokines and are positively associated with protective factors such as lysozyme, an important salivary antimicrobial protein that is reduced in IBD patients with periodontal disease.(16,45)

Together, these microbial markers reflect a robust oral dysbiotic signature in IBD that overlaps with known pathogenic mechanisms in oral diseases. Thus, incorporating oral microbial profiling—particularly of taxa linked to periodontitis and caries—into routine assessment could not only aid in early IBD diagnosis but also identify patients at risk for oral complications, supporting integrated gastroenterological and dental care.

Table 4- *Proposed Microbial Biomarkers panel for IBD (CD, UC) Diagnosis and Monitoring and Associated Oral Diseases*

Microbial Taxa	Enrichment/ Depletion	Associated With	Oral Disease Implication	Implications
Prevotella salivae	Enriched	IBD (CD and UC)	Periodontitis, caries, gingival inflammation	Linked to IL-1β and H_2S production; inflammophilic behavior
Veillonella spp.	Enriched	IBD (CD and UC)	Periodontitis	Sulfate-reducing; correlated with mucosal inflammation
Megasphaera	Enriched	IBD	Less characterized in oral disease	Found elevated in IBD saliva
Atopobium	Enriched	IBD	Associated with poor oral health	Frequently enriched in dysbiotic oral communities
Rothia spp.	Enriched	IBD	Opportunistic oral pathogen	Also detected in IBD fecal samples; oral–gut link
Fusobacterium nucleatum	Enriched	IBD, treatment-resistant UC	Periodontitis, systemic inflammation	Oral-origin pathobiont; contributes to gut inflammation
Streptococcus mutans	Enriched	IBD	Dental caries	High cariogenic potential
Porphyromonas gingivalis	Enriched	CD	Periodontitis	Member of red complex; key periodontal pathogen
Prevotella jejuni	Enriched	CD with poor oral health	Periodontitis	Elevated in absence of clinical oral symptoms
Streptococcus spp.	Depleted (oral)	IBD	Health-associated; reduced in caries protection	Negatively correlated with inflammation; positively with lysozyme
Neisseria spp.	Depleted (oral)	IBD	Health-associated; often reduced in periodontitis	Common in healthy oral microbiota
Haemophilus spp.	Depleted (oral)	IBD	Reduced oral protection	Inverse relationship with inflammation
Fusobacterium periodonticum	Depleted (oral)	IBD	Periodontitis	Normally protective; reduced in IBD patients
Gemella spp.	Depleted (oral)	IBD	Commensal oral genus	Stimulates mucosal immunity; antibody response seen in IBD

Despite the promising findings from the several studies herein explored, there are several limitations that must be addressed. First, there is considerable heterogeneity in the study designs, particularly regarding the sample types used, including saliva, stool, oral swabs, and mucosal biopsies. Variability in sequencing methods (e.g., V1-V2 versus V3-V4) and analytical pipelines also thwarts direct

comparisons between studies. The lack of standardization across studies in terms of disease activity, oral health status, and sampling locations also hinders the comparability and generalizability of results.

Furthermore, the population studied in most research is limited to specific geographic or ethnic groups, which raises concerns about the global applicability of these findings. The role of lifestyle factors such as diet, medication, and oral hygiene practices, which could all influence the oral microbiota, has also not been fully controlled in many studies, leading to potential confounding factors.

5. Conclusion

This systematic review highlights a consistent pattern of oral and gut microbiome dysbiosis in IBD, characterized by reduced microbial diversity and a shift toward pro-inflammatory taxa. Notably, oral microbes—particularly *Prevotella*, *Veillonella*, and *Fusobacterium*—are strongly implicated in disease progression and systemic inflammation, suggesting a pivotal role in the oral–gut axis. These findings support the utility of the oral microbiome as a non-invasive biomarker for both diagnosis and monitoring of IBD, including subtype differentiation (CD vs. UC).

Also, this work also highlighted the significant interplay between oral health and IBD, reinforcing the relevance of the oral microbiome as both a mirror and potential driver of systemic inflammation. Patients with IBD, particularly those with CD, frequently exhibit oral manifestations such as periodontitis, mucosal lesions, and dysbiosis characterized by reduced diversity and a shift toward pro-inflammatory taxa. These findings support the importance of integrated care between dental and gastrointestinal professionals to improve patient outcomes and quality of life.

However, further longitudinal, multicenter, and mechanistic studies are needed to validate these microbial markers, explore causality, and determine how therapeutic interventions or lifestyle modifications may restore microbial balance and improve outcomes. Ultimately, integrating oral microbiome profiling into routine IBD assessment could enhance early detection, personalized therapy, and disease management.

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