Elghannam *et al. Egyptian Liver Journal* (2024) 14:32
https://doi.org/10.1186/s43066-024-00340-9

Egyptian Liver Journal

REVIEW

Open Access

Oral microbiome dysbiosis and gastrointestinal diseases: a narrative review

Maged Tharwat Elghannam[1*], Moataz Hassan Hassanien[1], Yosry Abdelrahman Ameen[1], Emad Abdelwahab Turky[1], Gamal Mohammed ELattar[1], Ahmed Aly ELRay[1] and Mohammed Darwish ELTalkawy[1]

Abstract

Mouth is the gateway to the total body wellness. Accordingly, oral microbiome influences overall health of an individual. Oral microbiome plays a key role in shaping up the host's health profile. Obvious differences have been reported between patients with gastrointestinal diseases and healthy controls. The oral and gut microbiome profiles are well-segregated due to the oral–gut barrier. However, the oral microbiota can translocate to the intestinal mucosa in conditions of the oral–gut barrier dysfunction. Oral bacteria can disseminate to the distal gut via enteral or hematogenous routes. The translocation of oral microbes to the gut may give rise to a variety of gastrointestinal diseases including *Helicobacter*-induced diseases, irritable bowel syndrome, inflammatory bowel disease, celiac disease, and colorectal cancer. Understanding the role of the oral-to-gut microbial translocation in the pathogenesis will contribute to precise diagnosis and effective treatment. In this review, we aim to highlight the role of oral microbiota dysfunction in various gastrointestinal disorders.

Keywords Oral microbiota, *Helicobacter*-induced diseases, IBS, IBD, CRC

Introduction

More than 10^{14}symbiotic microorganisms colonize the human body referred to as the human microbiota [1, 2]. Oral microorganisms are identified as a constituent of the oral microbiome with the aid of using the Human Oral Microbiome Database (http://www.homd.org/) and feature a better abundance in the oral cavity than in the gut samples of healthy individuals based on the NIH Human Microbiome Project (HMP1; https://hmpdacc.org/hmp/) [3]. The oral cavity is the preliminary gateway of the human digestive system and has the second-biggest and maximum various microbiota after the intestine, harboring extra than 770 species of bacteria [4]. From 12 international locations worldwide, salivary oral microbiota outcomes confirmed person specificities with few geographic variations among these subjects [5]. Firmicutes, Proteobacteria, Bacteroidetes, and Actinobacteria confirmed the very best abundance [6]. Oral microbes can spread through the body and have been found in a variety of systemic diseases, whether in sterile organs such as cardiovascular diseases and rheumatoid arthritis or in non-sterile organs such as the digestive tract [7, 8].

The oral microbiome plays a pivotal role in human health. Both inflammatory and anti-inflammatory responses may be induced in the host tissues by members of the oral microbiota [9]. The benefits to the host include resistance to infections mediated by inhibition of colonization by pathogenic microorganisms [10], maturation of both the innate and adaptive host immune systems, and fine-tuning of its reaction patterns to achieve a balance between inflammatory and anti-inflammatory reactions [11–16]. Oral microbial dysbiosis is the major causative factor of oral diseases such as dental caries and periodontal diseases [7], and

*Correspondence:
Maged Tharwat Elghannam
maged_elghannam@yahoo.com; m.elghannam@tbri.gov.eg
[1] Hepatogastroenterology Department, Theodor Bilharz Research Institute, Giza, Egypt

it is also closely associated with systemic diseases such as asthma and atopic diseases, inflammatory bowel diseases, autoimmune disease, obesity and metabolic syndrome, colon cancer, peripheral vascular disease and hypertension, aberrant responses to drugs, depression, and autism [17].

Although millions of oral and salivary microbiomes are swallowed daily with our food, their persistence and passage to the gut are affected by many factors including gastric acidity, bile acids production (BAs), digestive enzymes and antimicrobial proteins in the duodenum and beyond, intestinal architecture, peristalsis, and transit times [18]. The concentration gradient of microbes is found along the small intestine, as microbial abundance in oral samples was found to be 1000-fold higher than that of duodenal aspirates [19] (Fig. 1).

Oral pathogens had been found abnormally enriched in the gut mucosal tissues and the luminal contents in patients with gut diseases [20, 21]. Therefore, it is suggestive that the ectopic gut colonization of oral pathogens is partially responsible for the pathogenesis of gut diseases: oral-gut axis microbiota.

Gut colonization by oral bacteria

Two routes had been suggested for the oral bacteria to reach the gut: hematogenous and/or enteral.

Hematogenous route

Oral mechanical injuries caused by daily dental activity, e.g., hard mastication and brushing, and dental procedures, e.g., orthodontics and extraction, enable oral bacteria to spread into the systemic circulation [22, 23]. Oral bacteria invade and survive inside immune cells, such as dendritic cells and macrophages. These cells help dissemination of the oral bacteria from the oral to the gut mucosa [7].

Enteral route

A human being swallows about 600 times a day, and ~ 1.5 L of saliva contains numerous resident oral bacteria [24, 25]. Most of the ingested oral bacteria do not reach and/or colonize the healthy gut because of the barrier

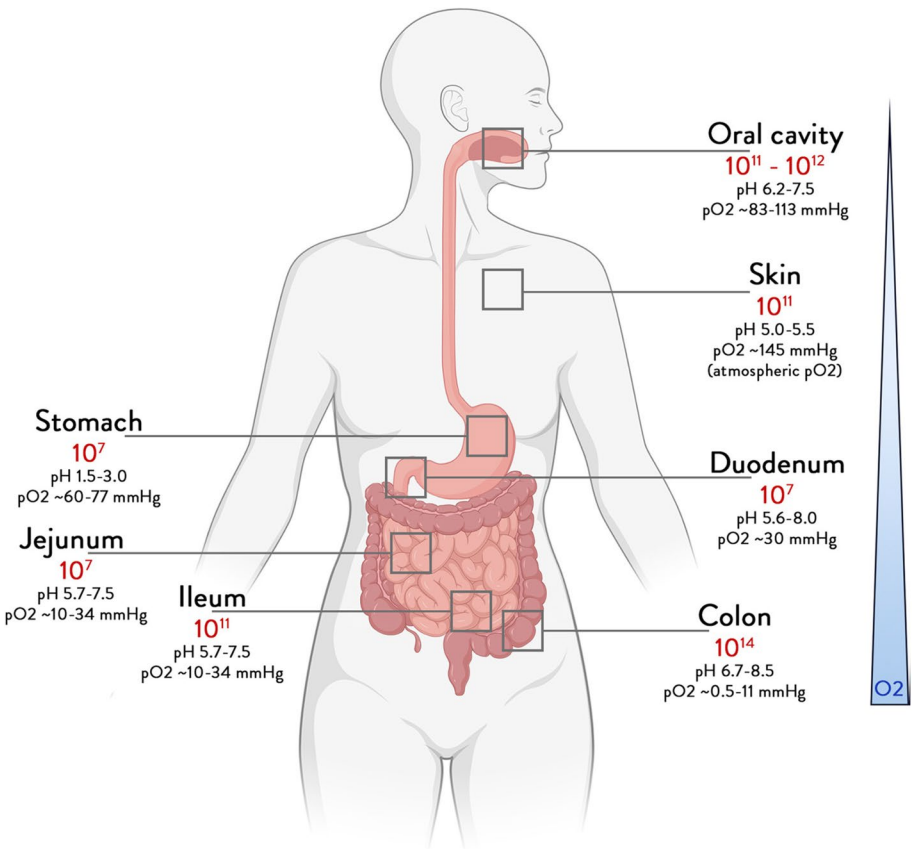

Fig. 1 Human microbiota composition in different locations. Predominant bacterial genera in the oral cavity, respiratory tract, skin, gut, and vagina. Published by Hou K. et al. in the *Signal Transduction and Targeted Therapy* (2022) 7:135

functions along the gastrointestinal tract. The gut resident microbiota is the major barrier that prevents the ectopic colonization by swallowed oral bacteria, so, gut dysbiosis is a prerequisite for the ectopic colonization of oral pathobionts.

Gut barriers dysbiosis

Gut dysbiosis-inducing factors include gut inflammation, and diets such as high fat, low-fiber diet, and artificial sweeteners are the main factors. Other possible factors include immune depression as aging, smoking, drugs, virus infection, or immune compromization as HIV [26]. The inappropriate use of antibiotic and the long-term use of proton-pump inhibitors that reduce the gastric acidity facilitate opportunistic gut colonization by oral bacteria. Other examples of the effect of impaired gastric acidity include individuals who have gastritis and gastric surgery (e.g., gastric bypass or gastrectomy) [27, 28]. These individuals have significant increase in the level of resident oral bacteria and altered bacterial composition. Worth mentioning, certain types of oral bacteria, such as *Porphyromonas gingivalis*, can tolerate the acidic environment in the stomach and consequently may pass through the stomach barrier [29].

Role of oral bacteria in *Helicobacter*-induced gastric pathology

Helicobacter pylori can be detected in the mouth and gut. The number of *H. pylori* in the mouth is actually lower than in the stomach constituting roughly 42–97% of the total gastric bacterial community [30]. Because the oral microbiome is the main source of gastric microbes, it is intimately related to the infection and transmission of *H. pylori* [31, 32].

Interactions between *H. pylori* and oral microbiome may take one or further of three main forms: co-aggregation, symbiotic biofilm formation, and endosymbiosis [33]. *Fusobacterium nucleatum* and *Porphyromonas gingivalis* which might be vital microorganism in periodontal infection can mixture with *H. pylori* cells promoting oral to gastric colonization by oral bacteria [34].

Streptococcus mutans, the fundamental cariogenic bacterium, can shape a symbiotic biofilm with *H. pylori* to increase its survival in the unsuitable atmosphere of the mouth [35]. *H. pylori* can anchor on the surface of the *Candida albicans* and mixture with *C. albicans* to form a mixed biofilm. Also, *H. pylori* plan to enter *C. albicans* yeast cells in the oral cavity and vagina [36, 37].

The interaction between *H. pylori* and members of the oral microbial community in *H. pylori*-positive people with oral complaints differs from those with gastrointestinal complaints. *P. gingivalis* has been established as a pathogenic agent of periodontitis and positively associated with *H. pylori* indicating that *H. pylori* infection may aggravate periodontal disease [38]. The transmission of oral-to-gut and gut-to-oral microorganisms can affect the ecosystem in both territories and hence regulate the pathogenesis of different diseases [39].

Role of oral bacteria in gut pathology

The presence of nearly half of the microbial species in both the mouth and gut gives evidence of oral-gut translocation even in healthy individuals [40]. This is known to modulate host immunity [41]. Hence, ectopic colonization by oral bacteria in the healthy gut may in part contribute to the physiologic development and/or maintenance of gut immunity. On the other hand and under certain conditions, gut colonization by specific oral bacteria might be linked to the pathogenesis of diseases in the gastrointestinal tract. The dissemination of oral microbes to the intestine may also exacerbate diverse gastrointestinal diseases, including irritable bowel syndrome (IBS) [42], inflammatory bowel disease (IBD) [43], celiac disease [44], and colorectal cancer (CRC) [45] (Fig. 2).

Irritable bowel syndrome

IBS is one of the most common disorder occurring in up to 4.8% of the population worldwide [46]. IBS is described as chronically recurring abdominal pain related to altered bowel habits in the absence of detectable organic disease. Recent evidence suggests the presence of IBS subgroups based on gut microbial community structure, with groups not differing from healthy controls despite GI symptoms [47, 48]. The most effective treatments for IBS and other disorders of oral-gut axis interactions include personalized diet approaches, behavioral therapies, and a few number of pharmacologic treatments to improve bowel function. As a common feature in IBS, there is an increase in the families Enterobacteriaceae and Lactobacillaceae and a decrease in the genera *Clostridium*, *Faecalibacterium*, and *Bifidobacterium*, as compared with controls [49]. The gut of patients with IBS showed enrichment of certain types of typical oral bacteria such as *Streptococcus* spp. and family Veillonellaceae [50–53]. Veillonellaceae was found abundantly in the gut of overweight patients with IBS who have significantly higher induced visceral pain scores than normal-weight patients with IBS. Veillonellaceae were also responsible for gastrointestinal colics in infants caused by the accumulation of lactate, hydrogen, or hydrogen sulfide [54]. Vervier et al. in 2022 [55] were able to stratify patients with IBS according to their gut microbiota species. Gut microbiota subtype with an enhanced clinical response to a low FODMAP diet compared with other subjects with IBS was identified. Microbiota signatures reported to be useful as biomarkers to guide IBS treatment. Recently,

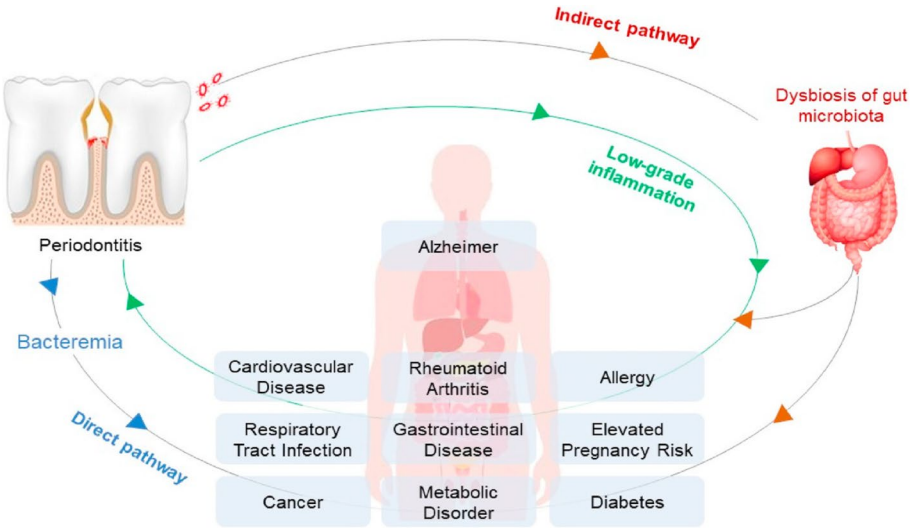

Fig. 2 The possible pathways that link periodontitis and systemic disease. Published by Deandra F. et al. in Heliyon 9 (2023) e13475

Tanaka and his colleagues [56] reported that colonic host-microbial interactions are altered in IBS-D patients during exacerbation of symptoms. However, there were no overlaps between feces and oral microbiomes. Tang and his colleagues [57] showed that the oral and fecal microbiota composition in IBS-D patients differed significantly from that in the normal population. The imbalance of Firmicutes/Bacteroidetes ratio in the oral microbiota of IBS-D patients, as compared to fecal microbiota, is of much concern. Additionally, the decrease in oral microbial richness was more directly connected to IBS-D [58].

Inflammatory bowel disease

The specific etiology of IBD stays poorly understood despite the identity of relevant risk factors, which include individual genetic susceptibility, environmental triggers, and disruption of immune homeostasis. Dysbiosis of the gut microbiota is thought to exacerbate the development of IBD. An imbalance of the gut microbiota appears to be an essential factor in the pathogenesis of IBD [59]. Gut dysbiosis in IBD is characterized by a decrease in the bacterial diversity and species richness of the microbiota. Docktor et al. [60] found a significant decrease in the overall microbial diversity of pediatric CD. Fusobacteria and Firmicutes were significantly reduced in CD, whereas Bacteroidetes were increased in UC compared with healthy controls. Said et al. [61] found that the salivary microbiota in adult IBD was significantly different from that of healthy controls, characterized by increased Bacteroidetes, *Prevotella*, and *Veillonella*, with decreased Proteobacteria, *Streptococcus*, and *Haemophilus*. Zhe et al. [62] revealed enrichment of Streptococcaceae and Enterobacteriaceae in UC, and Veillonellaceae in CD, while depletion of Lachnospiraceae and *Prevotella*in UC and Neisseriaceae in CD. Oral biofilm-forming bacteria were significantly increased in the salivary microbiota of IBD patients. Moreover, TM7 and SR1 showed a positive correlation to inflammatory cytokines associated with IBD, indicating that alterations in oral microbiota are related to altered inflammatory immune responses [63].

The best-described mechanisms of the oral microbiota in IBD occurrence are the destruction of the intestinal epithelial barrier, excessive secretion of inflammatory cytokines, disruption of the host immune system, and induction of immune escape. Oral bacteria-mediated destruction of the intestinal epithelial barrier may increase intestinal permeability and mucosal degradation, leading to the impairment of intestinal resistance to pathogens and intestinal inflammation. Ectopic colonization of oral bacteria disrupts the ecological balance among the oral microbiota, host, and immune system, leading to continuous intestinal inflammation [64]. Kitamoto et al. [65] show that the oral pathobionts during periodontitis aggravate gastrointestinal pathology via two mechanisms. Specific oral pathobionts are able to colonize the colitic gut and enhance IL-1β production. Also, oral pathobiont-reactive Th17 cells, primed in oral mucosa-draining lymph nodes, trafficked to the gut and became reactivated by periodontal microbiota traveling to the gastrointestinal tract through ingestion.

Colorectal cancer

CRC has a distinct gut microbial composition as compared with healthy individuals. Many of the bacteria enriched in colonic adenomas and carcinomas are related to the typical resident oral bacteria, including

the families Streptococcaceae and Neisseriaceae and the genera *Staphylococcus*, *Porphyromonas*, *Veillonella*, and *Fusobacterium* [66, 67] with validation from three recent large cohort studies [21, 68, 69]. The transmission rates of bacteria from the mouth to the gut are higher in patients with CRC when compared with healthy individuals in particular the transmission of *Fusobacterium nucleatum*, *Parvimonas micra*, and *Peptostreptococcus stomatis* supporting the potential link between the oral and gut microbiome in patients with CRC [70].

Porphyromonas gingivalis and *Fusobacterium nucleatum* are two famous CRC-related oral pathogens. Both of them can cause CRC through a different pathogenic pathway.

Porphyromonas gingivalis A gram-negative anaerobic bacteria was found to be responsible for both the occurrence of periodontitis [71] and was enriched in CRC patients [72]. It was positively associated with poor prognosis in CRC patients. It stimulates cellular senescence via butyrate secretion and accelerates the onset of colorectal tumors [73]. It can promote colorectal tumorigenesis by recruiting tumor-infiltrating myeloid cells and creating a proinflammatory tumor microenvironment via activation of the hematopoietic NOD-like receptor protein 3 inflammasomes [72]. It has the antiapoptotic ability of epithelial cells through inhibition of caspase 3 [74] and caspase 9 [75]. It inhibits the suppressor of cytokine signaling 3 causing apoptosis via STAT3 [76]. In addition, *P. gingivalis* contributes to accelerating epithelial cell proliferation through regulating the activity of PI3K, p53 [77], and cyclins [78], as well as activation of the WNT/β-catenin [79] and MAPK/ERK [80] pathways.

Fusobacterium nucleatum Similar strains of *F. nucleatum* are detected in both the saliva and colonic tumors of patients with CRC, indicating that *F. nucleatum* colonized in the colonic tumors originates in the oral microbiota [81]. *F. nucleatum* is highly adhesive to the gut epithelium through Fap2 adhesin promoting the proliferation of tumor cells by activation of the Wnt/β-catenin pathway [82]. The abundance of *F. nucleatum* is gradually increased from normal tissues to adenoma tissues and to adenocarcinoma tissues in colorectal carcinogenesis [83, 84]. *F. nucleatum* is increased in CRC patients after chemotherapy with recurrence, compared with those with nonrecurrence. It becomes evident that *F. nucleatum* directly promotes CRC chemoresistance to oxaliplatin and 5-fluorouracil through the activation of the autophagy pathway [85]. The high abundance of *F. nucleatum* in CRC is associated with poorer survival [81, 86]. Accordingly, *F. nucleatum* promotes the occurrence and development of CRC through localization, proliferation, immune suppression, metastasis, and chemoresistance.

Celiac disease

Patients who have celiac disease have oral flora dysbiosis. The initial metabolism of gliadin in the oral cavity may be related to the genus of *Rothia*, *Actinomyces*, *Neisseria*, and *Streptococcus* that colonized the oral cavity [87]. There is a significant increase in *Lactobacillus* species in the saliva of patients with celiac disease. This may be one of the reasons to explain gluten degradation and its higher rate in comparison to healthy people [88]. Although α-gliadin peptide could be completely degraded by dental plaque bacteria to reduce immunogenicity [88, 89], still, others report oral microbial enzymes to degrade part of gluten, which in turn increases immunogenic small molecule peptides and further induces intestinal inflammation [88].

Panelli et al. [90] investigated 52 adult patients affected with celiac disease and 31 patients with functional dyspepsia, to characterize the salivary, duodenal, and fecal microbiota composition. In addition to a general reduction of the microbial diversity in all analyzed samples from celiac disease patients, this study showed a significant abundance of Proteobacteria in active celiac disease and, importantly, confirmed the expansion of *Neisseria* spp. Moreover, they reported a better correspondence of the bacterial microbiota in the saliva with duodenal mucosa microbiome, rather than with fecal samples.

Gut microbiota therapeutic manipulation

Multiple substances can be used to modulate many physiologic functions within the body that constitute one of the risk factors in the pathogenesis of many diseases.

Prebiotics It is a selectively fermented ingredient that results in specific changes in the composition and activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health [91]. It is safe, effective, and has a great therapeutic effect and minimal side effects in maintaining IBD [92]. Fructo-oligosaccharides in CD patients increase mucosal Bifidobacteria and reduce the inflammation index [93]. Prebiotics prevent CRC in patients with its high risk and improve their immunological response [94, 95].

Probiotics These are live organisms that, when administered in adequate doses, confer a health benefit on the host [96]. IBS is the main treatment indication [97]. Butyrate-producing *Faecalibacterium prausnitzii* induces immune responses, has anti-inflammatory effects, and improves intestinal barrier function [98, 99].

Fecal microbiota transplantation and fecal virome transplantation Whether liquefied or encapsulated, preprocessed stool from a healthy donor is transferred to the recipient's colon. It is successful in the treatment of recurrent *C. difficile* infection and colitis [100, 101]. Other indications for the use of FMT include the treatment of antibiotic-resistant bacteria (ARB) gut colonization [102] and acute gastrointestinal graft-versus-host disease [103–105].

A new version of FMT is fecal virome transplantation (FVT), which uses bacteriophages to restore gut microbiota dysbiosis. However, the prophage-encoded virulence factors remain a safety issue, which limits the use of phages in medicine [106].

Microbiota metabolites These not only produce diseases but also have a therapeutic role. It has a role in the prevention and treatment of CRC [107]. The only metabolites that are anticarcinogenic are SCFAs [108] and polyphenol metabolites [109, 110]. Butyrate increases SCFAs and prevents the formation of harmful substances in the rectum [111]. Butyrate enhances the efficacy of radiotherapy in CRC patients [112], suggesting that gut microbiota-derived metabolites could be associated with modalities in cancer treatment.

MiRNA Intestinal miRNAs respond to commensals, pathogens, and probiotics. In the human intestines, miRNAs are mainly synthesized in the intestinal epithelial cells. Any deficiency in the miRNA synthesis by those cells is associated with gut microbial dysbiosis [113]. Intestinal miRNA may regulate responses to pathogenic and probiotic bacteria. Probiotic bacteria, *Bifidobacterium bifidium*, can alter intestinal miRNA in a species- and strain-specific manner [114].

Hyaluronan (HA) It is considered a novel tool for the development of novel therapeutic agents for the treatment of diseases underlying dysregulation of the microbiota–immune–gut axis [115]. HA appeared to directly modulate the promotion and resolution of IBD by controlling the recruitment of immune cells, through the release of inflammatory cytokines, and by balancing homeostasis [116]. The biological effects of HA are mediated by recruiting different receptors, such as CD44 [117], and by promoting the activation of toll-like receptors, particularly, TLR2 and TLR4, present in different cell types, including fibroblasts, smooth muscle cells, epithelial cells, immune cells, and neuronal cells [118, 119].

Nanomedicine-based approaches and extracellular vesicles

These are experiments trying to shape nanomaterials able to alter the cancer-causing dysbiotic microorganisms as well as their metabolites found in the cancer microenvironment [120]. Microbiota has the ability to interact with host cells and mitochondria, when needed, through extracellular vesicles, leading to the endocytosis of the extracellular vesicle and its content delivery [121–123]. Exosomal microRNA derived from mesenchymal stem cells plays a strategic role in modulating the gut microbiota and inflammatory status.

Conclusion

The oral-gut axis microbiota plays an important role in maintaining homeostasis. The oral cavity is an easily accessed body site for the assessment of the microbial community, with convenient sampling, noninvasiveness, and effective interventions. Hence, the oral microbiota holds great promise for diagnostic tools. New therapeutic approaches targeting the oral microbiota by facilitating beneficial bacteria and eliminating pathogenic oral bacteria may be an innovative medical strategy to prevent and treat many gastrointestinal disorders. Beyond having the pre- or probiotics, which are the traditional and first-line choice of microbial therapies, other strategies are being clinically studied such as the FMT, metabolites, phages, and miRNAs.

Abbreviations

NIH	National Institute of Health
BAs	Bile acids
FMT	Fecal microbiota transplantation
IBS	Irritable bowel syndrome
IBS-D	Irritable bowel syndrome-diarrhea
FODMAP	Fermentable, oligo-, di-, monosaccharides and polyols
IBD	Inflammatory bowel disease
CD	Crohn's disease
UC	Ulcerative colitis
TNF	Tumor necrosis factor
SCFAs	Short-chain fatty acids
MACs	Microbiota-accessible carbohydrates
EEN	Exclusive enteral nutrition
SCD	Specific carbohydrate diet
PN	Parenteral nutrition
CRC	Colorectal cancer
HA	Hyaluronic acid
MiRNA	Messenger RNA
FVT	Fecal virome transplantation

Acknowledgements

NA.

Authors' contributions

Conceptualization, MTE and MHH. Data curation, MTE and MDE. Formal analysis, MHH. Funding acquisition, NA. Investigation, NA. Methodology, MTE and ET. Article administration, GME. Resources, NA. Software, YAA and AAE. Supervision, MTE and GME. Validation, YAA and MDE. Visualization, AAE and ET. Writing — review and editing, all authors. Final approval of manuscript, all authors have read and approved the manuscript.

Funding

No funding was obtained for this study.

Availability of data and materials

All data generated and/or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
NA. This is a review article with no patients included. It does not need ethical committee of TBRI approval.

Consent for publication
NA.

Competing interests
The authors declare that they have no competing interests.

Received: 15 May 2023 Accepted: 27 April 2024
Published online: 06 May 2024

References

1. Qin J, Li R, Raes J et al (2010) A human gut microbial gene catalog established by metagenomic sequencing [J]. Nature 464:59–65
2. Sender R, Fuchs S, Milo R (2016) Revised estimates for the number of human and bacteria cells in the body [J]. PLoS Biol 14:e1002533
3. Avila M, Ojcius DM, Yilmaz O (2009) The oral microbiota: living with a permanent guest. DNA Cell Biol 28:405–411
4. Escapa IF, Chen T, Huang Y, Gajare P, Dewhirst FE, Lemon KP. New Insights into Human Nostril Microbiome from the Expanded Human Oral Microbiome Database (eHOMD): a Resource for the Microbiome of the Human Aerodigestive Tract. mSystems. 2018;3(6):e00187–18. https://doi.org/10.1128/mSystems.00187-18.
5. Nasidze I, Li J, Quinque D et al (2009) Global diversity in the human salivary microbiome. Genome Res 19:636–643
6. Bik EM, Long CD, Armitage GC et al (2010) Bacterial diversity in the oral cavity of 10 healthy individuals. ISME J 4:962–974
7. Hajishengallis G (2015) Periodontitis: from microbial immune subversion to syste0mic inflammation. Nat Rev Immunol 15:30–44
8. Graves DT, Correa JD, Silva TA (2019) The oral microbiota is modified by systemic diseases. J Dent Res 98:148–156
9. Devine DA, Marsh PD, Meade J (2015) Modulation of host responses by oral commensal bacteria. J Oral Microbiol 7:26941. https://doi.org/10.3402/jom.v7.26941
10. Beaumler AJ, Sperandi OV (2016) Interactions between the micro-biota and pathogenic bacteria in the gut. Nature 535:85–93
11. Aymeri CL, Sansonett IP. (2015) Discriminating pathogens from commensals at mucosal surfaces. In: MesteckYJ, Strobe RW, Russell MW, Kelsall BL, Cherroutr EH, Lambrecht BN, eds. Mucosal immunology, 4th edn. Amsterdam: Elsevier/Academic Press, 975–984
12. Thaiss CA, Zmor AN, Levy M, Elina VE (2016) The microbiome and innate immunity. Nature 535:65–74
13. Hond AK, Littman DR (2016) The microbiota in adaptive immune homeostasis and disease. Nature 535:75–84
14. Lee YK, Mazmanian SK (2010) Has the microbiota played a critical role in the evolution of the adaptive immune system? Science 330:1768–1773
15. Nai KS, Bouladou XN, Wilhel MC, Molloy MJ, Salced OR, Kastenmuller RW et al (2012) Compartmentalized control of skin immunity by resident commensals. Science 337:1115–1119
16. Sonnenburg JL, Beackhe DF (2016) Diet-microbiota interactions as moderators of human metabolism. Nature 535:56–64
17. Kinross JM, Darzi AW, Nicholson JK (2011) Gut microbiome-host interactions in health and disease. Genome Med 3:14
18. de Vos W, Tilg H, Van Hul M et al (2022) Gut microbiome and health: mechanistic insights. Gut 71:1020–1032
19. Barlow JT, Leite G, Romano AE et al (2021) Quantitative sequencing clarifies the role of disruptor taxa, oral microbiota, and strict anaerobes in the human small-intestine microbiome. Microbiome 9:214
20. Gevers D, Kugathasan S, Denson LA et al (2014) The treatment-naïve microbiome in new-onset Crohn's disease [J]. Cell Host Microbe 15:382–392
21. Yachida S, Mizutani S, Shiroma H et al (2019) Metagenomic and metabolomic analyses reveal distinct stage-specific phenotypes of the gut microbiota in colorectal cancer [J]. Nat Med 25:968–976
22. Lockhart PB, Brennan MT, Sasser HC et al (2008) Bacteremia is associated with tooth brushing and dental extraction. Circulation 117:3118–3125
23. Parahitiyawa NB, Jin LJ, Leung WK et al (2009) Microbiology of odontogenic bacteremia: beyond endocarditis. Clin Microbiol Rev 22:46–64
24. Humphrey SP, Williamson RT (2001) A review of saliva: normal composition, flow, and function. J Prosthet Dent 85:162–169
25. Pedersen AM, Bardow A, Jensen SB et al (2002) Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion. Oral Dis 8:117–129
26. Kitamoto S, Nagao-Kitamoto H, Hein R et al (2020) The bacterial connection between the oral cavity and the gut diseases. J Dent Res 99:1021–1029
27. Castaner O, Goday A, Park YM, Lee SH, Magkos F, Shiow STE, Schröder H. The Gut Microbiome Profile in Obesity: A Systematic Review. Int J Endocrinol. 2018;2018:4095789. https://doi.org/10.1155/2018/4095789.
28. Paganelli FL, Luyer M, Hazelbag CM et al (2019) Roux-Y gastric bypass and sleeve gastrectomy directly change gut microbiota composition independent of surgery type. Sci Rep 9:10979
29. Walker MY, Pratap S, Southerland JH et al (2018) Role of the oral and gut microbiome in nitric oxide mediated colon motility. Nitric Oxide 73:81–88
30. Schulz C, Schütte K, Koch N et al (2018) The active bacterial assemblages of the upper GI tract in individuals with and without helicobacter infection. Gut 67:216–225
31. Freitas D, Le Feunteun S, Panouillé M et al (2018) The important role of salivary a-amylase in the gastric digestion of wheat bread starch. Food Funct 9:200–208
32. Wu ZF, Zou K, Xiang CJ et al (2021) *Helicobacter pylori* infection is associated with the co-occurrence of bacteria in the oral cavity and the gastric mucosa. Helicobacter 26:e12786
33. Chen X, Zhou X, Liao B et al (2021) The cross-kingdom interaction between *Helicobacter pylori* and Candida albicans. PloS Pathog 17:e1009515
34. Park J, Shokeen B, Haake SK et al (2016) Characterization of Fusobacterium nucleatum ATCC 23726 adhesins involved in strain-specific attachment to Porphyromonas gingivalis. Int J Oral Sci 8:138–144
35. Nomura R, Kadota T, Ogaya Y et al (2020) Contribution of Streptococcus mutans to *Helicobacter pylori* colonization in the oral cavity and gastric tissue. Sci Rep 10:12540
36. Palencia SL, García A, Palencia M (2022) Multiple surface interaction mechanisms direct the anchoring, co-aggregation and formation of dual-species biofilm between Candida albicans, and Helicobacter pylori. J. Advanced Res 35:169–185
37. Saniee P, Siavoshi F, Nikbakht Broujeni G et al (2013) Localization of H pylori within the vacuole of candida yeast by direct immunofluorescence technique. Arch Iranian Med 16:705–710
38. Miller DP, Scott DA (2021) Inherently and conditionally essential protein catabolism genes of P. gingivalis. Trends Microbiol 29:54–64
39. Park SY, Hwang BO, Lim M et al (2021) Oral-gut microbiome axis in gastrointestinal disease and cancer. Cancers (Basel) 13:2124
40. Schmidt TS, Hayward MR, Coelho LP et al (2019) Extensive transmission of microbes along the gastrointestinal tract. Elife 8:e42693
41. Geva-Zatorsky N, Sefik E, Kua L et al (2017) Mining the human gut microbiota for immunomodulatory organisms. Cell 168(928–943):e911
42. Lloyd-Price J, Arze C, Ananthakrishnan AN et al (2019) Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. Nature 569:655–662
43. Leonard MM, Valitutti F, Karathia H et al (2021) Microbiome signatures of progression toward celiac disease onset in at-risk children in a longitudinal prospective cohort study. Proc Natl Acad Sci U S A 118:e2020322118
44. Mars RAT, Yang Y, Ward T et al (2020) Longitudinal multi-omics reveals subset-specific mechanisms underlying irritable bowel syndrome. Cell 183:1137–1140
45. Tilg H, Adolph TE, Gerner RR et al (2018) The intestinal microbiota in colorectal cancer. Cancer Cell 33:954–964
46. Endo Y, Shoji T, Fukudo S (2015) Epidemiology of irritable bowel syndrome. Ann Gastroenterol 28:158–159
47. Jeffery IB, O'Toole PW, Ohman L et al (2012) An irritable bowel syndrome subtype defined by species-specific alterations in fecal microbiota. Gut 61:997–1006

48. Labus JS, Hollister EB, Jacobs J et al (2017) Differences in gut microbial composition correlate with regional brain volumes in irritable bowel syndrome. Microbiome 5:49
49. Pittayanon R, Lau JT, Yuan Y et al (2019) Gut microbiota in patients with irritable bowel syndrome—a systematic review. Gastroenterology 157:97–108
50. Wyatt GM, Bayliss CE, Lakey AF et al (1988) The fecal flora of two patients with food-related irritable bowel syndrome during challenge with symptom-provoking foods. J Med Microbiol 26:295–299
51. Kassinen A, Krogius-Kurikka L, Makivuokko H et al (2007) The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. Gastroenterology 133:24–23
52. Rajilic-Stojanovic M, Biagi E, Heilig HG et al (2011) Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. Gastroenterology 141:1792–1801
53. Vich Vila A, Imhann F, Collij V et al (2018) Gut microbiota composition and functional changes in inflammatory bowel disease and irritable bowel syndrome. Sci Transl Med 10(472):eaap8914
54. Pham VT, Lacroix C, Braegger CP et al (2017) Lactate-utilizing community is associated with gut microbiota dysbiosis in colicky infants. Sci Rep 7:11176
55. Vervier K, Moss S, Kumar N et al (2022) Two microbiota subtypes were identified in irritable bowel syndrome with distinct responses to the low FODMAP diet. Gut 71:1821–1830
56. Tanaka Y, Yamashita R, Kawashima J et al (2022) Omics profiles of fecal and oral microbiota change in irritable bowel syndrome patients with diarrhea and symptom exacerbation. J Gastroenterol. https://doi.org/10.1007/s00535-022-01888-2
57. Tang B, Hu Y, Chen J, et al (2022) Oral and fecal microbiota in patients with diarrheal irritable bowel syndrome. Research Square. https://doi.org/10.21203/rs.3.rs-1772660/v1
58. Tang B, Hu Y, Chen J, Su C et al (2023) Oral and fecal microbiota in patients with diarrheal irritable bowel syndrome. Heliyon 9:e13114
59. Sartor RB (2008) Microbial influences in inflammatory bowel diseases. Gastroenterology 134:577–594
60. Docktor MJ, Paster BJ, Abramowicz S et al (2012) Alterations in the diversity of the oral microbiome in pediatric inflammatory bowel disease. Inflamm Bowel Dis 18:935–942
61. Said HS, Suda W, Nakagome S et al (2014) Dysbiosis of salivary microbiota in inflammatory bowel disease and its association with oral immunological biomarkers. DNA Res 21:15–25
62. Zhe-XQ Z, Tao X, Ning C et al (2018) Dysbiosis and ecotypes of the salivary microbiome associated with inflammatory bowel diseases and the assistance in diagnosis of diseases using oral bacterial profiles. Front Microbiol 9:1136
63. Qi Y, Zang SQ, Wei J et al (2020) High-throughput sequencing provides insights into oral microbiota dysbiosis in association with inflammatory bowel disease. Genomics 113:664–676
64. Qi Y, Wu H, Yang Z et al (2022) New insights into the role of oral microbiota dysbiosis in the pathogenesis of inflammatory bowel disease. Dig Dis Sci 67:42–55
65. Kitamoto S, Nagao-Kitamoto H, Jiao Y et al (2020) The intermucosal connection between the mouth and gut in commensal pathobiont-driven colitis. Cell 182:447–462
66. Kostic AD, Chun E, Robertson L et al (2013) Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor immune microenvironment. Cell Host Microbe 14:207–215
67. Geng J, Song Q, Tang X et al (2014) Co-occurrence of driver and passenger bacteria in human colorectal cancer. Gut Pathog 6:26
68. Thomas AM, Manghi P, Asnicar F et al (2019) Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. Nat Med 25:667–678
69. Wirbel J, Pyl PT, Kartal E et al (2019) Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. Nat Med 25:679–689
70. Schmidt TS, Hayward MR, Coelho LP et al (2019) Extensive transmission of microbes along the gastrointestinal tract. Elife 8:e42693
71. Mysak J, Podzimek S, Sommerova P et al (2014) Porphyromonas gingivalis: major periodontopathic pathogen overview [J]. J Immunol Res 2014:476068
72. Wang X, Jia Y, Wen L et al (2021) Porphyromonas gingivalis promotes colorectal carcinoma by activating the hematopoietic NLRP3 inflammasome [J]. Cancer Res 81:2745–2759
73. Okumura S, Konishi Y, Narukawa M et al (2021) Gut bacteria identified in colorectal cancer patients promote tumourigenesis via butyrate secretion [J]. Nat Commun 12:5674
74. Mao S, Park Y, Hasegawa Y et al (2007) Intrinsic apoptotic pathways of gingival epithelial cells modulated by Porphyromonas gingivalis [J]. Cell Microbiol 9:1997–2007
75. Yao L, Jermanus C, Barbetta B et al (2010) Porphyromonas gingivalis infection sequesters pro-apoptotic bad through Akt in primary gingival epithelial cells [J]. Mol Oral Microbiol 25:89–101
76. Iwahori K, Serada S, Fujimoto M et al (2011) Overexpression of SOCS3 exhibits preclinical antitumor activity against malignant pleural mesothelioma [J]. Int J Cancer 129:1005–1017
77. Kuboniwa M, Hasegawa Y, Mao S et al (2008) P. gingivalis accelerates gingival epithelial cell progression through the cell cycle [J]. Microbes Infect 10:122–128
78. Pan C, Xu X, Tan L et al (2014) The effects of Porphyromonas gingivalis on the cell cycle progression of human gingival epithelial cells [J]. Oral Dis 20:100–108
79. Zhou Y, Sztukowska M, Wang Q et al (2015) Noncanonical activation of β-catenin by Porphyromonas gingivalis [J]. Infect Immun 83:3195–3203
80. Mu W, Jia Y, Chen X et al (2020) Intracellular Porphyromonas gingivalis promotes the proliferation of colorectal cancer cells via the MAPK/ERK signaling pathway [J]. Front Cell Infect Microbiol 10:584798
81. Komiya Y, Shimomura Y, Higurashi T et al (2019) Patients with colorectal cancer have identical strains of Fusobacterium nucleatum in their colorectal cancer and oral cavity. Gut 68:1335–1337
82. Rubinstein MR, Wang X, Liu W et al (2013) Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating e-adherin/beta-catenin signaling via its fadA adhesin. Cell Host Microbe 14:195–206
83. Kostic AD, Gevers D, Pedamallu CS et al (2012) Genomic analysis identifies association of Fusobacterium with colorectal carcinoma [J]. Genome Res 22:292–298
84. Castellarin M, Warren RL, Freeman JD et al (2012) Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma [J]. Genome Res 22:299–306
85. Yu T, Guo F, Yu Y et al (2017) Fusobacterium nucleatum promotes chemoresistance to colorectal cancer by modulating autophagy [J]. Cell 170:548–63.e16
86. Mima K, Nishihara R, Qian ZR et al (2016) Fusobacterium nucleatum in colorectal carcinoma tissue and patient prognosis [J]. Gut 65:1973–1980
87. Fernandez-Feo M, Wei G, Blumenkranz G et al (2013) The cultivable human oral gluten degrading microbiome and its potential implications in coeliac disease and gluten sensitivity. Clin Microbiol Infect 19:386–394
88. Tian N, Faller L, Leffler DA et al (2017) Salivary gluten degradation and oral microbial profiles in healthy individuals and celiac disease patients. Appl Environ Microbiol 83:03330–3316
89. Di Cagno R, De Angelis M, Lavermicocca P et al (2012) Function and diversity of the healthy human microbiome. Nature 486:207–214
90. Panelli S, Capelli E, Lupo GFD et al (2020) Comparative study of salivary, duodenal, and fecal microbiota composition across adult celiac disease. J Clin Med 9:1109
91. Scott KP, Tuohy KM, Mach-Istituto FE et al (2010) Dietary prebiotics: current status and new definition. Food Sci Technol Bull Funct Foods 7:1–19
92. Naseer M, Poola S, Ali S et al (2020) Prebiotics and probiotics in inflammatory bowel disease: where are we now and where are we going? Curr Clin Pharmacol 15:216–233
93. Lindsay JO, Whelan K, Stagg AJ et al (2006) Clinical, microbiological, and immunological effects of fructo-oligosaccharide in patients with Crohn's disease. Gut 55:348–355
94. Ambalam P, Raman M, Purama RK et al (2016) Probiotics, prebiotics and colorectal cancer prevention. Best Pract Res Clin Gastroenterol 30:119–131
95. Xie X, He Y, Li H et al (2019) Effects of prebiotics on immunologic indicators and intestinal microbiota structure in perioperative colorectal cancer patients. Nutrition 1:132–142

96. Reid G (2016) Probiotics: definition, scope and mechanisms of action. Best Pract Res Clin Gastroenterol 30:17–25
97. Herndon CC, Wang YP, Lu CL (2020) Targeting the gut microbiota for the treatment of irritable bowel syndrome. Kaohsiung J Med Sci 36:160–170
98. He X, Zhao S, Li Y (2021) Faecalibacterium prausnitzii: a next-generation probiotic in gut disease improvement. Can J Infect Dis Med Microbiol 2021:67
99. Lapiere A, Geiger M, Robert V et al (2020) Prophylactic Faecalibacterium prausnitzii treatment prevents the acute breakdown of colonic epithelial barrier in a preclinical model of pelvic radiation disease. Gut Microbes 12:1–15
100. Kim KO, Gluck M (2019) Fecal microbiota transplantation: an update on clinical practice. Clin Endosc 52:137
101. Nicco C, Paule A, Konturek P et al (2020) From donor to patient: collection, preparation and cryopreservation of fecal samples for fecal microbiota transplantation. Dis 8:9
102. Bilinski J, Grzesiowski P, Sorensen N et al (2017) Fecal microbiota transplantation in patients with blood disorders inhibits gut colonization with antibiotic-resistant bacteria: results of a prospective, single-center study. Clin Infect Dis 65:364–370
103. Bilinski J, Lis K, Tomaszewska A et al (2021) Fecal microbiota transplantation in patients with acute and chronic graft-versus-host disease-spectrum of responses and safety profile results from a prospective, multicenter study. Am J Hematol 96:E88-91
104. Biliński J, Jasiński M, Tomaszewska A et al (2021) Fecal microbiota transplantation with ruxolitinib as a treatment modality for steroid-refractory/dependent acute, gastrointestinal graft versus-host disease: a case series. Am J Hematol 96:E461–E463
105. Zhao Y, Li X, Zhou Y et al (2021) Safety and efficacy of fecal microbiota transplantation for grade IV steroid refractory GIGvHD patients: interim results from FMT2017002 trial. Front Immunol 17:2405
106. Rasmussen TS, Koefoed AK, Jakobsen RR et al (2020) Bacteriophage-mediated manipulation of the gut microbiome – promises and presents limitations. FEMS Microbiol Rev 44:507–521
107. Peng Y, Nie Y, Yu J et al (2021) Microbial metabolites in colorectal cancer: basic and clinical implications. Metab 11:159
108. Nakkarach A, Foo HL, Song AAL et al (2021) Anti-cancer and anti-inflammatory effects elicited by short chain fatty acids produced by *Escherichia coli* isolated from healthy human gut microbiota. Microb Cell Fact 20:1–17
109. Rajha HN, Paule A, Aragones G et al (2022) Recent advances in research on polyphenols: effects on microbiota, metabolism, and health. Mol Nutr Food Res 16:e2100670
110. Cueva C, Silva M, Pinillos I et al (2020) Interplay between dietary polyphenols and oral and gut microbiota in the development of colorectal cancer. Nutr 12:625
111. Le Leu RK, Winter JM, Christophersen CT et al (2015) Butyrylated starch intake can prevent red meat-induced O6-methyl-2-deoxyguanosine adducts in human rectal tissue: a randomized clinical trial. Br J Nutr 114:220–230
112. Park M, Kwon J, Shin HJ et al (2020) Butyrate enhances the efficacy of radiotherapy via FOXO3A in colorectal cancer patient derived organoids. Int J Oncol 57:1307–1318
113. Liu S, Weiner HL (2016) Control of the gut microbiome by fecal microRNA. Microb Cell 3:176
114. Taibi A, Singh N, Chen J et al (2017) Time- and strain-specific downregulation of intestinal EPAS1 via miR-148a by Bifidobacterium bifidum. Mol Nutr Food Res 61:1600596
115. Axis M, Bosi A, Banfi D et al (2022) Hyaluronan: a neuroimmune modulator in the cell. Cells 11:1–20
116. Petrey AC, de la Motte CA (2019) Hyaluronan in inflammatory bowel disease: cross-linking inflammation and coagulation. Matrix Biol 78–79:314–323
117. Vigetti D, Viola M, Karousou E et al (2014) Metabolic control of hyaluronan synthases. Matrix Biol 35:8–13
118. Okun E, Griffioen KJ, Mattson MP (2011) Toll-like receptor signaling in neural plasticity and disease. Trends Neurosci 34:269–281
119. Feldman N, Rotter-Maskowitz A, Okun E (2015) DAMPs as mediators of sterile inflammation in aging-related pathologies. Ageing Res Rev 24:29–39
120. Riaz Rajoka MS, Mehwish HM, Xiong Y et al (2021) Gut microbiota targeted nanomedicine for cancer therapy: challenges and future considerations. Trends Food Sci Technol 107:240–251
121. Diaz-Garrido N, Badia J, Baldoma L (2021) Microbiota-derived extracellular vesicles in interkingdom communication in the gut. J Extracell Vesicles 10:e12161
122. Han B, Lin CCJ, Hu G et al (2019) 'Inside out'– a dialogue between mitochondria and bacteria. FEBS J 286:630–641
123. Saint-Georges-Chaumet Y, Edeas M (2016) Microbiota-mitochondria intertalk: consequence for microbiota-host interaction. FEMS Pathog Dis 12:9

Publisher's Note