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FUNCTIONAL DYSPEPSIA AND GUT MICROBIOME

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Abstract – The definitive pathophysiology of functional dyspepsia remains unclear, and effective treatments are limited. Among the mechanisms assumed to be involved in its pathogenesis, duodenal low-grade inflammation has received the most attention. Emerging evidence suggests that the oral microbiome, such as *Streptococcus spp*., may play a role in gastroduodenal motility and low-grade duodenal inflammation. In terms of treatment, traditional treatments, such as herbal medicine, are showing changes in the intestinal microbiome and its metabolites. In other words, both old and new evidence are being progressively revealed.

Keywords: Functional dyspepsia, Microbiome, Low-grade inflammation, Stomach, Duodenum.

INTRODUCTION

Functional dyspepsia (FD) is defined as the presence of one or more of the following symptoms: bothersome postprandial fullness, bothersome early satiation, bothersome epigastric pain, and bothersome epigastric burning in the absence of structural disease[1]. FD is a multifactorial disease involving motility abnormalities, visceral hypersensitivity, psychosocial factors, excessive gastric acid secretion, genetics, environment, diet, lifestyle, post-infectious FD, and the gut microbiome. Recently, it has been recognized and defined as a disorder of gut-brain interaction[2-10]. However, its definitive pathophysiology remains unclear, and effective treatments are limited. We reviewed articles published between April 2023 and March 2024 on FD and the gut microbiome.

METHODS

A systematic literature search was conducted by the author of this report (HM) using PubMed (between April 2023 and March 2024). The search used the keyword combination (functional dyspepsia) and (microbiome).

BASIC RESEARCH

Table 1 summarizes the basic studies published during this period that examined the relationship between functional dyspepsia and the microbiome. Interestingly, three papers were related to Massa Medicata Fermentata (MMF). MMF is mainly fermented using flour, wheat bran, *Vignae semen, Armeniacae Semen Amarum, Artemisia annua Herba, Polygonum hydropiper, and Xanthium sibiricum*, which is used in traditional Chinese medicine to treat functional dyspepsia[11].

TABLE 1. SUMMARY FINDINGS ON THE LINK BETWEEN FUNCTIONAL DYSPEPSIA AND MICROBIOME (BASIC RESEARCH).

References	Drugs or conditions evaluated	Method	Subjects	Major findings
Wang et al[11]	Massa Medicata Fermentata (MMF)	The gastric emptying rate and intestinal propulsion rate were calculated, serum gastrin concentration was measured. The 16S rRNA microbial detection was performed.	A mouse model	MMF improved the gastric emptying rate, intestinal propulsion rate, and gastrin concentration in the serum of model mice. MMF could increase *Bacteroidetes* and decrease Verrucomicrobia in the intestines of model mice.
Fan et al[12]	Massa Medicata Fermentata (MMF)	The histopathological evaluation and ghrelin levels were assessed (in blood and tissue). The 16S rDNA sequencing method was used.	A rat model	MMF improved the pathological tissue histological structure of FD rats and increased the levels of MTL and GAS hormones in serum and the levels of ghrelin in the gastric antrum, spleen, and duodenum. MMF can improve the composition and diversity of the gut microbiota.
Bai et al[13]	Massa Medicata Fermentata (MMF)	The sucrose preferences, gastric emptying, histological changes in the duodenum and serum levels of pro-inflammatory cytokines were evaluated. The 16S rDNA sequencing method was used	A rat model	MMF reduced the serum levels of TNF-α, and IFN-λ, ameliorated intestinal mucosal lamina propria injury, and the sucrose preference increased, and the gastric emptying rate decreased. MMF alleviated intestinal microflora disturbance and exerted a regulatory effect on *Bacteroidetes*, Proteobacteria, and *Firmicutes*
Chen et al[14]	Qi-Zhi-Wei-Tong	The proinflammatory cytokines in the stomach, colon tissues and blood, and the fecal bile acid composition were evaluated. The 16S rDNA sequencing method was used.	A mouse model	The inflammatory responses were reduced. Increasing the levels of the Akkermansia genus and decreasing the populations of the Desulfovibrio genus were observed. The alteration of gut microbiota was associated with gut bacteria bile acids metabolism.
Ammar et al[15]	STW 5-II	STW 5-II was incubated with human fecal microbiota in vitro. The pH, gas production, SCFAs production were evaluated. The 16S rDNA sequencing and UHPLCHRMS-based metabolite profiling were used.	In vitro (the SHIME® system)	STW 5-II led to consistent changes in pH and gas production and increased production of SCFAs. STW 5-II promoted the enrichment of *Bifidobacteriaceae*, *Lachnospiraceae*, *Ruminococcaceae*, *Erysipelotrichaceae*, and *Eggerthellaceae* and suppressed *Enterobacteriaceae*.
Liu et al[16]	Fucoidan and laminarin	The serum motilin, ghrelin, the total bile acid level, acetylcholine esterase levels, Immunohistochemical staining and qPCR were evaluated. The 16S rDNA sequencing method was used.	A mouse model	Fucoidan and laminarin reversed the dysfunction mainly through regulating motilin and ghrelin, the cholinergic pathway, the total bile acid level, c-kit protein expression, and gastric smooth muscle contraction-related gene expression. Fucoidan and laminarin altered richness of *Muribaculaceae*, *Lachnospiraceae*, and *Streptococcus*.

Wang et al[11] established a mouse model of spleen deficiency and food accumulation and used it to test the effect of MMF on gastric emptying rate, intestinal propulsion rate, serum gastrin concentration, and cholinesterase activity. Microbial 16S rRNA detection was performed in different groups of mouse feces. MMF improved gastric emptying rate, intestinal propulsion rate, and serum gastrin concentration. There was no significant difference in cholinesterase activity between the control and MMF-treated mice. 16S rRNA sequencing showed that MMF increased the abundance of *Bacteroidetes* and decreased that of *Verrucomicrobia* in the intestines of the model mice.

Fan et al[12] utilized an FD rat model created by intraperitoneal injection of reserpine into rats. MMF is administered transgastrically daily. After treatment, specimens of rats in the gastric antrum, spleen, and duodenum were evaluated with pathological staining and immunohistochemical detection of Ghrelin protein expression. Serum gastrointestinal hormone levels were also analyzed. MMF improved the histological structure of FD rats and increased the serum levels of motilin, gastrin, and ghrelin in the gastric antrum, spleen, and duodenum, while reducing substance P (SP), vasoactive intestinal polypeptide (VIP), and cholecystokinin (CCK). The 16S rDNA sequencing method was used to evaluate the gut microbiota of experimental rats. The diversity analysis showed that the MMF group was more similar to the normal group than the FD group, indicating that MMF could restore intestinal microbiota. At the phylum level, there were no significant differences in the dominant species of microbiota among the groups. Compared to the control group, the abundance of *Verrucomicrobiota* significantly increased in the FD group, and MMF alleviated this change. At the family level, compared to the FD group, MMF restored *Oscillospiraceae* and *Ruminococcus*.

Bai et al[13] used an FD rat model created using iodoacetamide and a water platform for sleep deprivation. After MMF treatment, the sucrose preference, gastric emptying rate, histological changes in the duodenum, and serum levels of pro-inflammatory cytokines were evaluated. The study showed that MMF reduced the serum levels of TNF-α and IFN-γ, improved the morphology of duodenal intestinal villi, and ameliorated intestinal mucosal lamina propria injury in FD rats, and the sucrose preference increased, and the gastric emptying rate decreased in FD rats. MMF did not significantly alter the type of intestinal flora in FD rats. Compared to the control group, the level of *Bacteroidetes* decreased, and the level of *Firmicutes* increased in the FD group. Compared with the FD group, the abundance of *Firmicutes* and *Proteobacteria* increased in the MMF group, whereas the level of *Bacteroidetes* decreased. Compared with the control group, the ratio of *Firmicutes/Bacteroidetes* was significantly reduced in the FD group, and compared with the FD group, the ratio of *Firmicutes/Bacteroides* was significantly increased in the MMF group. It is interesting to note that the behavior of *Bacteroides* in response to MMF was the opposite of that reported by Wang et al[11].

Chen et al[14] examined the effect of Qi-Zhi-Wei-Tong granules (QZWT) on proinflammatory cytokines in the stomach, colon tissues, and blood, and fecal bile acid composition using chronic restraint stress and an iodoacetamide-induced chronic non-atrophic gastritis mouse model. The 16S rDNA sequencing method was used to analyze the gut microbiota community in fecal samples. Behavioral testing showed that QZWT alleviated chronic restraint stress-induced anxiety- and depression-like behavior in mice. QZWT mitigated gastric mucosal inflammatory cell infiltration in model mice and suppressed the mRNA upregulation of proinflammatory cytokines in stomach tissues, including IL-1β and TNF-α. Compared with the control group, the augmented *Firmicutes/Bacteroidetes* (F/B) ratios were increased in the model mice group. The QZWT treatment failed to restore changes in the F/B ratio. QZWT increased the abundance of *Staphylococcus*, *Allobaculum*, *Turicibacter*, *Akkermansia,* and *Bifidobacterium*, whereas it decreased *Ruminococcus, Desulfovibrio, Clostridium*, and *Adlercreutzia*. The inflammatory response is also reduced. Increasing the levels of the *Akkermansia* genus and decreasing populations of the *Desulfovibrio* genus were observed. Alterations in gut microbiota are associated with gut bacterial bile acid metabolism. In terms of bile acid composition, the QZWT-treated mice were distinct from the gastritis model mice, supporting the possibility that QZWT regulates metabolism *via* the gut microbiota.

Ammar et al[15] demonstrated the impact of STW 5-II on pH, gas production, and short-chain fatty acid (SCFAs) production *in vitro* using the SHIME® system. The 16S rDNA sequencing and UH-PLC-HRMS-based metabolite profiling were also performed. STW 5-II is a multiherbal preparation of six medicinal plants: *Iberis amara, Menthae piperitae, Chamomilla recutita, Glycyrrhiza glabra, Carum carvi*, and *Melissa officinalis*. STW 5-II has been shown to be effective in several clinical trials involving patients with FD. STW 5-II led to consistent changes in pH and gas production and increased the production of SCFAs. STW 5-II promoted the enrichment of *Bifidobacteriaceae,*

Eggerthellaceae, Bacteroidaceae, Prevotellaceae, Erysipelotrichaceae, Lachnospiraceae, and *Ruminococcaceae,* and suppressed *Enterobacteriaceae*. The majority of STW 5-II constituents metabolized by fecal bacteria are flavonoids, chalcones, triterpene glycosides, and dihydroxycinnamic acid derivatives. They also showed that these derived final metabolites regulate intestinal epithelial barrier function and inflammation.

Liu et al[16] investigated the regulatory effects of fucoidan and laminarin on functional dyspepsia in mice induced by loperamide. Fucoidan and laminarin reversed this dysfunction mainly by regulating gastrointestinal hormones (motilin and ghrelin), the cholinergic pathway, total bile acid levels, c-kit protein expression, and gastric smooth muscle contraction-related gene expression (ANO1 and RYR3). Fucoidan and laminarin reverse loperamide-induced gut microbial abnormalities. At the phylum level, loperamide injection mainly reduced the abundance of *Bacteroidota, Actinobacteriota, Desulfobacterota, and Campylobacterota*. Treatment with fucoidan or laminarin reversed this effect. At the genus level, loperamide induced alterations in numerous genera, including *Muribaculum, Bacteroides, and Odoribacter*. Similarly, fucoidan and laminarin exhibited varying degrees of recovery. Changes in various bacterial flora were correlated with AChE, c-kit protein, and RYR3 gene expression.

In summary, the basic research reported here evaluated the long-term effects of medicinal herbs. Although the effects of traditional medicines have been known for thousands of years, their mechanism of action remains unclear in many cases. Future studies focusing on gut microbiota metabolism may reveal these mechanisms. However, mouse and rat models were all created using different methods, and whether they truly reflect the human pathogenesis of FD needs to be followed up with controlled clinical trials.

OBSERVATIONAL HUMAN STUDY

Table 2 summarizes the observational human studies published during this period that examined the relationship between functional dyspepsia and the microbiome.

Shanahan et al[17] compared the upper GI symptoms, gastric emptying, diet, and mucosa-associated microbiota (MAM) between patients and controls. The relative abundances of the predominant members of the *Firmicutes, Bacteroidota, and Fusobacteriota* phyla were linked to symptom burden in FD. Moreover, inverse relationships were also observed between the relative abundances of *Streptococcus* and *Prevotella*, and the relative abundance of *Veillonella spp.* with gastric emptying time. No significant differences in long-term nutrient intake or diet quality were found between the FD and control groups, and there appeared to be a limited association between habitual diet and duodenal MAM profiles. A Japanese study[18] showed that *Streptococcus* was significantly increased at all sites in the upper gut in patients with FD. *Streptococcus* and *Prevotella* are oral microbes, and the association between the oral environment and FD is of great interest.

Kovaleva et al[19] investigated the correlation between the biomarkers of intestinal barrier disorders and the severity of symptoms and gut microbiota in patients with overlapping FD and irritable bowel syndrome (IBS). The intraepithelial lymphocyte count in the duodenum of patients with FD/IBS was correlated with the abundance of *Klebsiella* and *Roseburia*. The eosinophil count in the duodenum correlated with the counts of *Atopobiaceae* and *Barnesiella*, while in the colon, it correlated with *Enterobacteriaceae* and *Tuzzerella*. The MUC-2 concentration level in the duodenum, which is used to evaluate the condition of the intestinal mucosal barrier in the pre-epithelial layer, correlated with the abundance of *Sellimonas*. In contrast, in the colon, it was correlated with the abundance of *Atopobiaceae, Enterococcaceae, Enterococcus, Hungatella, Lachnospiraceae, Lactococcus, Negativibacillus, Intestinibacter, Rhizobiaceae, Senegalimassilia*, and *Xanthomonadaceae*.

Kim et al[20] assessed dietary nutrients, gastrointestinal symptom severity, the immunological status of the duodenal mucosa, and microbiome composition in oral, duodenal, and fecal samples. Compared with the control group, *Streptococcus* increased in the duodenal mucosa. In stool samples, patients with FD had increased *Neisseria* and decreased *Faecalibacterium* and *Butyricicoccus* compared with controls. A strong inverse relationship was found between stool *Butyricicoccus* and the severity of FD symptoms. In addition, the relative abundance of stool *Butyricicoccus* showed the most significant association with intercellular proteins (ZO-1, occludin, and claudin-2).

TABLE 2. SUMMARY FINDINGS ON THE LINK BETWEEN FUNCTIONAL DYSPEPSIA AND MICROBIOME (OBSERVATIONAL STUDY).

References	Drugs or conditions evaluated	Method	Subjects	Major findings
Shanahan et al[17]	N/A	The upper GI symptoms, gastric emptying and dietary assessment were evaluated. The mucosa-associated microbiota (MAM) in the duodenum analyzed via 16S rRNA gene amplicon sequencing.	56 FD, 30 controls	The relative abundances of predominant members of the *Firmicutes, Bacteroidota* and *Fusobacteriota* phyla were linked to symptom burden in FD. Inverse relationships between the relative abundances of *Streptococcus* and *Prevotella*, and the relative abundance of *Veillonella spp.* with gastric emptying time, were also observed.
Kovaleva et al[19]	N/A	Biopsy of the duodenum and colon was performed to count intraepithelial lymphocytes (IELs) and mucosal eosinophils, assess fatty acid binding protein (FABP) level, and stain for mucin-2 (MUC-2). Composition of the gut microbiota was evaluated using 16S rRNA gene sequencing.	45 FD/IBS overlap, 16 controls	FD/IBS overlap exhibited an increase in biomarkers of intestinal barrier disorders. All biomarkers of intestinal barrier permeability were correlated with the abundance of some gut microbiota taxa.
Kim et al[20]	N/A	Dietary nutrients, gastrointestinal symptom, immunological status of the duodenum, and microbiome composition from oral, duodenal, and fecal samples were evaluated. Immunohistochemistry, real-time polymerase chain reaction, 16S rRNA sequencing were used.	12 FD, 16 controls	Duodenal mucosal inflammation and impaired expression of tight junction proteins were confirmed in patients with FD. The relative abundance of duodenal *Streptococcus* and reductions in stool *Butyricicoccus* were confirmed. These changes in the gut microbiota were both correlated with symptom severity.
Wang et al[21]	*H. pylori* eradication	The microbial variation induced by *H. pylori* infection and eradication treatment in FD patients, was evaluated.	98 FD patients (54 *H. pylori*-positive)	Gastric microbial abundance and diversity were significantly reduced in the *H. pylori*-infected FD patients. Eradication treatment increased alpha and beta diversity of gastric mucosa-colonizing microbes, and promoted the expansion of several probiotic microbes, such as *Leuconostoc mesenteroides.*

Wang et al[21] explored the microbial variation induced by *H. pylori* infection and eradication treatment in patients with FD. *Neisseria subflava* is a taxonomic biomarker of *H. pylori*-positive FD, while *Lactobacillus* and *Ochrobactrum* are taxonomic biomarkers of *H. pylori*-negative FD. *H. pylori* eradication markedly transforms the structure of the gastric mucosa-colonizing microbiota in patients with FD. The taxonomic biomarkers changed to *Lactobacillus, Leuconostoc, Muribaculum, Shewanella*, and *Pantoea*, indicating a complete alteration in the structure of the gastric microbiota after *H. pylori* eradication. Moreover, *H. pylori* eradication decreases the abundance of *Weissella* and *Prevotella*, both of which have pathogenic potential. The abundances of *Bifidobacterium* and *Lactobacillus* were not affected by *H. pylori* eradication. This study shows that the gastric microbiota in patients with FD is clearly different depending on the presence or absence of *H. pylori*. Furthermore, it provides evidence that *H. pylori*-related dyspepsia is different from FD without *H. pylori* infection[3,22-25].

INTERVENTIONAL HUMAN STUDY

Table 3 summarizes the prospective interventional trials published during this period examining the effects of therapeutic agents on FD, in which the microbiome was also evaluated.

Zhang et al[26] demonstrated the efficacy of *Bifidobacterium animalis subsp.* and *lactis* BL-99 (BL-99) against FD symptoms. BL-99 was isolated from the feces of healthy infants. BL-99 alleviated intestinal inflammation in mice with osteoporosis and colitis. After eight weeks of treatment, the clinical response rate (CRR) of the FD score was higher in the BL-99 group (90.0%) than in the placebo group (58.0%). The fecal microbiome was comparatively analyzed before and after the BL-99 intervention using high-throughput metagenomic shotgun sequencing. BL-99 increased the abundance of SCFA-producing bacteria (*Faecalibacterium prausnitzii* and *Roseburia intestinalis*) and the lactate-producing *Ligilactobacillus spp.* (*L. ruminis* and *L. salivarius*). In contrast, BL-99 decreased the abundance of some *Bacteroidetes species*, such as *Bacteroides uniformis, Bacteroides thetaiotaomicron, Phocaeicola vulgatus, Alistipes putredinis*, and *Alistipes shahii*.

Wang et al[27] examined the efficacy of Chaihu-Shugan-San (CSS). CSS is a classic traditional Chinese medicine (TCM) formula from the Ming Dynasty, as documented in "Jingyue's Complete Works"[27]. In China, it is prevalently used in the treatment of a wide range of ailments, with a particular emphasis on functional gastrointestinal disorders. After 4 weeks of treatment, the dyspepsia score significantly improved in the CSS group compared to the placebo. Bacterial diversity and abundance in patients were lower than those in healthy controls, which were restored by CSS treatment. Treatment with CSS reduced the abundance of *Blautia, Bifidobacterium*, and *Streptococcus* while concurrently increasing the abundance of *Bacteroides, Faecalibacterium, Agathobacter, Roseburia, Lachnospiraceae*_NK4A136_group, and *norank_f_Eubacterium_coprostanoligenes*_group.

Rebamipide has been widely prescribed as a gastric mucosal protective drug, mainly in Japan and South Korea, and its antioxidant and mucus-enhancing effects have been reported to be effective against gastric inflammation[28-30]. Rebamipide is effective in improving the pathology of dyspepsia. Kovaleva et al[31] showed the effects of rebamipide on the intestinal barrier, gut microbiota structure and function, and symptom severity associated with the overlap between FD and IBS. The authors compared trimebutine and rebamipide. The severity of digestive symptoms reduced in the rebamipide group to levels similar to those observed in the trimebutine group. Duodenal, sigmoidal lymphocytic, and sigmoidal eosinophilic infiltration decreased in the rebamipide group but not in the trimebutine group. Treatment with rebamipide increased the levels of *Romboutsia*, *Collinsella*, *Intestinimonas*, *Fusicatenibacter, Erysipelatoclostridium, Peptoniphilus*, and *Ezakiella*, but decreased the levels of *Corynebacterium, Lactobacillus*, *Vibrio*, *Olsenella,* and *Desulfovibrio*.

CONCLUSIONS

Recent scientific articles related to FD and gut microbiota have primarily focused on the pathogenesis of duodenal inflammation, particularly the activation of eosinophils and mast cells, which may have an important influence on the gut-brain relationship in FD. Notably, the oral microbi-

TABLE 3. THE PROSPECTIVE INTERVENTIONAL TRIALS PUBLISHED DURING THIS TIME PERIOD EXAMINING THE EFFECTS OF THERAPEUTIC AGENTS ON FD IN WHICH THE MICROBIOME.

References	Drugs or conditions evaluated	Method	Subjects	Major findings
Zhang et al[26]	*Bifidobacterium animalis subsp. lactis* BL-99	A randomized placebo-controlled clinical trial (partial double-blind)	200 FD patients	High dose BL-99 significantly improved dyspepsia symptoms compared to placebo. BL-99 promoted the accumulation of SCFA-producing microbiota and the increase of SCFA levels in stool and serum.
Wang et al[27]	Chaihu-Shugan-San	A randomized, double-blind, placebo-controlled trial	94 FD patients	Chaihu-Shugan-San significantly improved dyspepsia symptoms and gastric emptying compared to placebo. Chaihu-Shugan-San modulated of certain bacterial populations,
Kovaleva et al[31]	Trimebutine and rebamipide	A randomized, controlled, single-blind trial	60 FD/IBS overlap patients	Rebamipide improves the intestinal barrier condition and symptoms in FD/IBS overlap. Rebamipide induced more significant changes in the gut microbiome composition than treatment with trimebutine

ome, including *Streptococcus spp*. may play a role in gastric motility and duodenal inflammation. Additionally, the efficacy of traditional medicines worldwide is supported by changes in the intestinal microflora and its metabolites. In other words, both old and new evidence are being progressively revealed.

Conflict of Interest

Hidekazu Suzuki has received research funding from Tohso Company, Ltd., Biofermin Pharmaceutical Company, Ltd., and honorarium from Otsuka Pharmaceutical Company, Ltd., Takeda Pharmaceutical Company, Ltd. Other authors have no conflict of interest to declare.

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Authors' Contributions

HM, MS, and HS performed the research and wrote the article.

Ethics Statement

Note applicable due to the type of study.

AI Statement

Authors used ChatGPT for English proofreading.

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