Version Date: (Version 3, 11/12/2024)

Hualien Tzu Chi Hospital - Internal Medical Technology Research Project Application Form

1. Basic Information

Application Number:_____

Project Category (Single Choice)	■Individual Research Project: Principal Investigator is a senior staff member of the hospital. ■Experimental Research (Up to NT$800,000) □Non-Experimental Research (Up to NT$400,000) □Holistic Care Department Project (Up to NT$800,000) (Limited to department supervisors) □New Staff Research Project (Up to NT$200,000) □University-Hospital Collaborative Research Project (Up to NT$400,000) □Ministry of Science and Technology Transferred In-Hospital Project (Up to NT$800,000) □Medical Education Research Project (Up to NT$400,000)				
Personnel Category (Single Choice)	■Physician □Non-Physician				
Project Title	Exploring Novel Therapeutic Approaches for Disorders of Gut-Liver-Brain Interaction: Impact on Gastrointestinal and Psychological Symptoms as well as Pathophysiological Alterations				
Principal Investigator's Name	Ming-Wun Wong	Position	Attending Physician	Applying Department	Gastroenterology Department
Project Duration	2025.01.01~2025.12.31				
Research Nature and Classification	□Basic Research ■Applied Research □Technology Development Innovation and Development Classification: ■(1) Clinical Research □(2) Translational Research □(3) Medical Engineering and Materials □(4) Information Technology □(5) Medical Assistance Operations □(6) Other, please specify. _____.				
Holistic Care (Please refer to the definition, multiple selections allowed)	Holistic Care Classification: (1) Patient-Centered Care（■Physical，■Psychological，■Environmental，□Spiritual） (2) Health Education(■Behavioral Change，□Health Promotion，■Disease Prevention，■Early Diagnosis，■Early Treatment) (3) Other, please specify_____.				

Has this in-hospital project been previously applied for the 2023 Ministry of Science and Technology Special Research Project? ■ No □ Yes.

Have you applied for various research projects funded by government agencies this year?

■ No □ Yes, a total of _____ projects.

The total number of in-hospital research projects applied for and led by you this year is 1 (jointly led projects are not included).

The priority ranking of this project is 1 position.

Does this project involve the following? ☐ Not Required ■ Human Experiment/Human Specimens (including human embryos/human embryonic stem cells) ☐ Animal Experiment ☐ Biosafety (including recombinant gene experiments/gene transfection field trials/level 2 or higher infectious biological materials) [Please check the appropriate box]

Project Contact Person	Name:Ming-Wun Wong Phone: (Office) (03)8561825#13224 (Home) 0982-098812 E-MAIL:hypertr42@gmail.com

2. Application for Subsidy Funds (The budget will be included in the review and scoring process, please avoid inflated estimates)

Based on the actual needs of the research project, subsidies can be applied for the costs required for the following items: For individual research projects, the subsidy is up to NT$800,000 for experimental research and up to NT$400,000 for non-experimental research. The total research funding for new staff research projects is capped at NT$200,000. The total research funding for university-hospital collaborative research projects is capped at NT$400,000. The subsidy for holistic care department projects is up to NT$800,000. The subsidy for Ministry of Science and Technology transferred in-hospital projects is up to NT$800,000.

Subsidy Items		Requested Amount
Operational Expenses	1. Research Personnel Costs	NT$ 49,980
	2. Experimental Animal Costs	
	3. Consumables, Materials, Books, and Miscellaneous Expenses	NT$ 750,020
Research Equipment Costs		NT$ 0
Total		NT$ 800,000

3. Equipment Configuration

The names of the main instruments required for this project, their locations, and the signature of the person responsible for approving their use.

Instrument Name	Location (Department)	Signature and Stamp of the Department Head Approving the Use of the Instrument

4. Project Team Members

1. Primary research on human resources

Category (Principal Investigator, Co-Principal Investigator, Collaborator, Research Assistant, etc.)	Name	Current Position	Specific Role, Tasks, and Scope of Work in This Research Project
Principal Investigator	Wong, Ming-Wun	Attending Physician in Gastroenterology	Project progress supervision, research implementation and planning, data analysis, and report writing.
Co-Principal Investigator	Chen, Chien-Lin	Director of Gastroenterology	Actual case handling in the project, such as conducting examinations and operations.
Co-Principal Investigator	Yi, Chih-Hsun	Attending Physician in Gastroenterology	Actual case handling in the project, such as conducting examinations and operations.
Co-Principal Investigator	Liu, Tso-Tsai	Director of Digestive Function Testing Department	Actual case handling in the project, such as conducting examinations and operations.
Co-Principal Investigator	Lei, Wei-Yi	Attending Physician in Gastroenterology	Actual case handling in the project, such as conducting examinations and operations.
Co-Principal Investigator	Hung, Jui-Sheng	Attending Physician in Gastroenterology	Actual case handling in the project, such as conducting examinations and operations.
Co-Principal Investigator	Cheng, Chiu-Hsuan	Director of Cytopathology Department	Actual case handling in the project, such as performing tissue pathology analysis.
Research Assistant	Chen,Yen-Jhu	Research Assistant	Organizing data, data analysis and statistics, and handling administrative tasks.
Research Assistant	Jian,Yu-xuan	Research Assistant	Organizing data, data analysis and statistics, and handling administrative tasks.

2. Research projects participated in by the Principal Investigator, Co-Principal Investigator, and Collaborating Researchers in the past three years.

姓 名	計 畫 名 稱	計畫內擔任之工作	起迄年月	補助機構
Wong, Ming-Wun	Clinical Applications of Diaphragmatic Breathing in Patients with Gut-Brain Axis Dysregulation: Exploring the Efficacy on Psychosomatic Symptoms and Autonomic Nervous System Effects.	Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Identifying the Pathophysiological Mechanisms of Gastroesophageal Reflux Disease (GERD) Patients Through Postprandial High-Resolution Impedance Esophageal Function Testing: Clinical Applications for Reflux Symptoms and Treatment Management.	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Exploring the Pathophysiological Mechanisms and Roles of Neuromodulators and Cognitive Behavioral Therapy in Regulating Visceral Hypersensitivity and Hypervigilance in Individuals with Gut-Brain Axis Communication Abnormalities.	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	The Efficacy of Jingsi Herbal Drink Concentrate on Psychosomatic Symptoms of Gut-Brain Axis Dysregulation: A Randomized Double-Blind Clinical Trial	Co-Principal Investigator	2024/01/01~ 2025/12/31	Tzu Chi Medical Corporation
Wong, Ming-Wun	Antireflux mucosal ablation for the treatment of PPI-dependent gastroesophageal reflux disease: treatment efficacy and physiological alteration	Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Exploring pathophysiological mechanisms of laryngopharyngeal reflux: utilization with artificial intelligence and clinical implication for precision diagnosis and personalized treatment strategies	Principal Investigator	2022/8/1~ 2025/07/31	Ministry of Science and Technology
Wong, Ming-Wun	Supervised Learning Artificial Intelligence in 24-h Impedance-pH: Technique Performance and Clinical Implications for Diagnosing GERD	Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	ing Si Herbal Tea in the treatment of dyspeptic symptoms and psychophysical burden in patients with disorders of long COVID gut brain interaction a doub le blind, randomized,placebo controlled study	Co-Principal Investigator	2023/01/01~ 2023/12/31	Tzu Chi Medical Corporation
Wong, Ming-Wun	Interaction among supragastric belching, psychologic distress and esophageal acid reflux: Implications for optimal management of GERD	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Relevance of esophageal hypervigilance, functional gastrointestinal disorders, and	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital

	psychological distress as pathophysiological mechanisms to esophageal symptoms			
Wong, Ming-Wun	Oropharyngeal swallowing physiology in patients with esophageal hypomotility: Studies with HRPM	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Exploring capsaicin sensitization, sensorimotor function, psychophyiological reflux characteristics in human esophagus: therapeutic implications for esophageal dysfunction and gastroesophageal reflux disease	Co-Principal Investigator	2023/8/1~ 2026/07/31	Ministry of Science and Technology
Wong, Ming-Wun	Utility of high resolution pharyngeal manometry and Sydney Swallow Questionnaire for evaluation of oropharyngeal dysphagia and voice disorder	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Application of Artificial Intelligence in High-resolution Esophageal Function Testing: A Study on Unsupervised Deep Learning Algorithms	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Impact of regulating diet and exercise on clinical characteristics and intestinal microbiota in patients with metabolic-related fatty liver	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Wong, Ming-Wun	Jing Si Herbal Tea in the treatment of dyspeptic symptoms and psychophysical burden	Co-Principal Investigator	2022/1/1~ 2022/12/31	Tzu Chi Medical Corporation
Wong, Ming-Wun	Diagnosis and establishment of indications for proton pump inhibitors in the improvement of laryngopharyngeal reflux based on nighttime average basal impedance values of the proximal esophagus	Principal Investigator	2020/8/1~ 2022/07/31	Ministry of Science and Technology
Wong, Ming-Wun	Interrelationships among esophageal peristalsis, mucosa integrity, and mucosa afferent innervation: mechanisms for esophageal dysfunction and gastroesophageal reflux	Co-Principal Investigator	2020/8/1~ 2023/07/31	Ministry of Science and Technology
Chen, Chien-Lin	Identifying the Pathophysiological Mechanisms of Gastroesophageal Reflux Disease (GERD) Patients Through Postprandial High-Resolution Impedance Esophageal Function Testing: Clinical Applications for Reflux Symptoms and Treatment Management	Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Exploring the Pathophysiological Mechanisms and Roles of Neuromodulators and Cognitive Behavioral Therapy in Regulating Visceral Hypersensitivity and Hypervigilance in Individuals with Gut-Brain Axis Communication Abnormalities	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital

Chen, Chien-Lin	Clinical Applications of Diaphragmatic Breathing in Patients with Gut-Brain Axis Dysregulation: Exploring the Efficacy on Psychosomatic Symptoms and Autonomic Nervous System Effects.	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Exploring the Prevalence, Pathophysiology, and Clinical Features of Gastrointestinal Diseases in Taiwanese Adults with Metabolic Dysfunction-Associated Fatty Liver Disease	Principal Investigator	2024/01/01~ 2026/12/31	Tzu Chi Medical Corporation
Chen, Chien-Lin	The Efficacy of Jingsi Herbal Drink Concentrate on Psychosomatic Symptoms of Gut-Brain Axis Dysregulation: A Randomized Double-Blind Clinical Trial.	Principal Investigator	2024/01/01~ 2025/12/31	Tzu Chi Medical Corporation
Chen, Chien-Lin	Jing Si Herbal Tea in the treatment of dyspeptic symptoms and psychophysical burden in patients with disorders of long COVID gut brain interaction a doub le blind, randomized,placebo controlled study	Principal Investigator	2023/01/01~ 2023/12/31	Tzu Chi Medical Corporation
Chen, Chien-Lin	Interaction among supragastric belching, psychologic distress and esophageal acid reflux: Implications for optimal management of GERD	Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Exploring capsaicin sensitization, sensorimotor function, psychophyiological reflux characteristics in human esophagus: therapeutic implications for esophageal dysfunction and gastroesophageal reflux disease	Principal Investigator	2023/8/1~ 2026/07/31	Ministry of Science and Technology
Chen, Chien-Lin	Jing Si Herbal Tea in the treatment of dyspeptic symptoms and psychophysical burden	Principal Investigator	2022/1/1~ 2022/12/31	Tzu Chi Medical Corporation
Chen, Chien-Lin	Exploration of esophageal reflux clearance, mucosa integrity, and psychological characteristics: pathophysiological and therapeutic implications for gastroesophageal reflux disease	Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Relevance of esophageal hypervigilance, functional gastrointestinal disorders, and psychological distress as pathophysiological mechanisms to esophageal symptoms	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Antireflux mucosal ablation for the treatment of PPI-dependent gastroesophageal reflux disease: treatment efficacy and physiological alteration	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Oropharyngeal swallowing physiology in patients with esophageal hypomotility: Studies with HRPM	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Exploring pathophysiological mechanisms of laryngopharyngeal reflux: utilization with artificial intelligence and clinical	Co-Principal Investigator	2022/8/1~ 2025/07/31	Ministry of Science and Technology

	implication for precision diagnosis and personalized treatment strategies			
Chen, Chien-Lin	Relationships among mucosal afferent innervation, esophageal peristalsis and pharmacological modulation in the human esophagus: implications for pathophysiology and management in patients with GERD	Co-Principal Investigator	2022/8/1~ 2025/07/31	Ministry of Science and Technology
Chen, Chien-Lin	Impact of opioids on esophageal peristalsis and acid reflux characteristics:relevance for esophageal pathophysiology and therapeutic implications	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Supervised Learning Artificial Intelligence in 24-h Impedance-pH: Technique Performance and Clinical Implications for Diagnosing GERD	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Utility of high resolution pharyngeal manometry and Sydney Swallow Questionnaire for evaluation of oropharyngeal dysphagia and voice disorder	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Application of Artificial Intelligence in High-resolution Esophageal Function Testing: A Study on Unsupervised Deep Learning Algorithms	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Impact of regulating diet and exercise on clinical characteristics and intestinal microbiota in patients with metabolic-related fatty liver	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Chen, Chien-Lin	Exploring the Pathophysiological Role of Esophageal Mucosal Afferent Nerve Distribution in Gastroesophageal Reflux Disease with Esophageal Motility Dysfunction.	Co-Principal Investigator	2020/8/1~ 2022/07/31	Ministry of Science and Technology
Chen, Chien-Lin	Improving the Diagnosis of Laryngopharyngeal Reflux by the Nighttime Average Baseline Mucosal Impedance Value in the Proximal Esophagus and Establishing the Indication for Proton Pump Inhibitors.	Co-Principal Investigator	2020/8/1~ 2022/07/31	Ministry of Science and Technology
Chen, Chien-Lin	Interrelationships among esophageal peristalsis, mucosa integrity, and mucosa afferent innervation: mechanisms for esophageal dysfunction and gastroesophageal reflux	Principal Investigator	2020/8/1~ 2023/07/31	Ministry of Science and Technology
Yi, Chih-Hsun	Identifying the Pathophysiological Mechanisms of Gastroesophageal Reflux Disease (GERD) Patients Through Postprandial High-Resolution Impedance Esophageal Function Testing: Clinical Applications for Reflux Symptoms and Treatment Management.	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital

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Yi, Chih-Hsun	The Efficacy of Jingsi Herbal Drink Concentrate on Psychosomatic Symptoms of Gut-Brain Axis Dysregulation: A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2024/01/01~ 2025/12/31	Tzu Chi Medical Corporation
Yi, Chih-Hsun	The Efficacy of Jingsi Herbal Drink Concentrate on Psychosomatic Symptoms of Long COVID - Gut-Brain Axis Dysregulation: A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Tzu Chi Medical Corporation
Yi, Chih-Hsun	Exploring the Interrelationship Between Belching, Psychosomatic Symptoms, and Esophageal Acid Reflux: Clinical Applications for Optimizing Gastroesophageal Reflux Disease Treatment.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Yi, Chih-Hsun	Exploring the Pathophysiological Mechanisms and Interrelationship Between Esophageal Hypervigilance, Psychological Distress, and Functional Gastrointestinal Disorders in Esophageal Symptom Patients.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Yi, Chih-Hsun	Exploring the Efficacy and Physiological Changes of Anti-Reflux Mucosal Ablation Therapy in Proton Pump Inhibitor-Dependent Gastroesophageal Reflux Disease.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Yi, Chih-Hsun	Analyzing the Pharyngeal Swallowing Physiology and Dynamics in Esophageal Ineffective Motility Patients Using High-Resolution Pharyngeal Function Testing.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Yi, Chih-Hsun	Exploring the Relationship Between Esophageal Capsaicin Sensitivity, Motility Sensory Function, and Psychophysiological Reflux Characteristics: Clinical Implications and Treatment Guidelines for Esophageal Dysfunction and Gastroesophageal Reflux Disease.	Co-Principal Investigator	2023/8/1~ 2026/07/31	Ministry of Science and Technology
Yi, Chih-Hsun	Exploring the Pathophysiological Mechanisms of Gastroesophageal Reflux Disease Through Esophageal Reflux Clearance Ability, Mucosal Integrity, and Psychosomatic Characteristics:	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital

	Establishing a Basis for Precise Diagnosis and Treatment.			
Yi, Chih-Hsun	Impact of opioids on esophageal peristalsis and acid reflux characteristics:relevance for esophageal pathophysiology and therapeutic implications	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Yi, Chih-Hsun	Utility of high resolution pharyngeal manometry and Sydney Swallow Questionnaire for evaluation of oropharyngeal dysphagia and voice disorder	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
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Yi, Chih-Hsun	Impact of regulating diet and exercise on clinical characteristics and intestinal microbiota in patients with metabolic-related fatty liver	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Yi, Chih-Hsun	The Efficacy of Jingsi Herbal Drink on Psychosomatic Symptoms of Functional Dyspepsia: A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2022/1/1~ 2022/12/31	Tzu Chi Medical Corporation
Yi, Chih-Hsun	探討食道酸敏感度、食道二度收縮與胃食道逆流亞型的相互關係及致病機轉	Principal Investigator	2021/1/1~ 2021/12/31	Hualien Tzu Chi Hospital
Yi, Chih-Hsun	探討食道微生物菌相在胃食道逆流症之新型阻抗參數、臨床分型以及過度敏感所扮演的角色	Co-Principal Investigator	2021/1/1~ 2021/12/31	Hualien Tzu Chi Hospital
Yi, Chih-Hsun	以高解析度阻抗咽部功能檢查探討咽部吞嚥困難及藥物反應之臨床應用	Co-Principal Investigator	2021/1/1~ 2021/12/31	Hualien Tzu Chi Hospital
Yi, Chih-Hsun	Interrelationships among esophageal peristalsis, mucosa integrity, and mucosa afferent innervation: mechanisms for esophageal dysfunction and gastroesophageal reflux	Co-Principal Investigator	2020/8/1~ 2023/07/31	Ministry of Science and Technology
Liu, Tso-Tsai	Identifying the Pathophysiological Mechanisms of Gastroesophageal Reflux Disease (GERD) Patients Through Postprandial High-Resolution Impedance Esophageal Function Testing: Clinical Applications for Reflux Symptoms and Treatment Management.	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Liu, Tso-Tsai	Exploring the Pathophysiological Mechanisms and Roles of Neuromodulators and Cognitive Behavioral Therapy in Regulating Visceral Hypersensitivity and Hypervigilance in Individuals with Gut-Brain Axis Communication Abnormalities.	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital

Liu, Tso-Tsai	Clinical Application of Diaphragmatic Breathing in Patients with Gut-Brain Axis Dysregulation: Exploring the Efficacy on Psychosomatic Symptoms and the Impact on the Autonomic Nervous System.	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
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Liu, Tso-Tsai	The Efficacy of Jingsi Herbal Drink Concentrate on Psychosomatic Symptoms of Gut-Brain Axis Dysregulation: A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2024/01/01~ 2025/12/31	Tzu Chi Medical Corporation
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Liu, Tso-Tsai	The Efficacy of Jingsi Herbal Drink Concentrate on Psychosomatic Symptoms of Long COVID - Gut-Brain Axis Dysregulation: A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Tzu Chi Medical Corporation
Liu, Tso-Tsai	Exploring the Interrelationship Between Belching, Psychosomatic Symptoms, and Esophageal Acid Reflux: Clinical Applications for Optimizing Gastroesophageal Reflux Disease Treatment.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Liu, Tso-Tsai	Exploring the Pathophysiological Mechanisms and Interrelationship Between Esophageal Hypervigilance, Psychological Distress, and Functional Gastrointestinal Disorders in Esophageal Symptom Patients.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Liu, Tso-Tsai	Analyzing the Pharyngeal Swallowing Physiology and Dynamics in Esophageal Ineffective Motility Patients Using High-Resolution Pharyngeal Function Testing.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Liu, Tso-Tsai	Exploring the Efficacy and Physiological Changes of Anti-Reflux Mucosal Ablation Therapy in Proton Pump Inhibitor-Dependent Gastroesophageal Reflux Disease.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Liu, Tso-Tsai	Exploring the Relationship Between Esophageal Capsaicin Sensitivity, Motility Sensory Function, and Psychophysiological Reflux Characteristics: Clinical Implications and Treatment Guidelines for Esophageal Dysfunction and Gastroesophageal Reflux Disease.	Co-Principal Investigator	2023/8/1~ 2026/07/31	Ministry of Science and Technology
Liu, Tso-Tsai	Exploring the Pathophysiological Mechanisms of Gastroesophageal Reflux	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital

	Disease Through Esophageal Reflux Clearance Ability, Mucosal Integrity, and Psychosomatic Characteristics: Establishing a Basis for Precise Diagnosis and Treatment.			
Liu, Tso-Tsai	Impact of opioids on esophageal peristalsis and acid reflux characteristics:relevance for esophageal pathophysiology and therapeutic implications	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Liu, Tso-Tsai	Utility of high resolution pharyngeal manometry and Sydney Swallow Questionnaire for evaluation of oropharyngeal dysphagia and voice disorder	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Liu, Tso-Tsai	Supervised Learning Artificial Intelligence in 24-h Impedance-pH: Technique Performance and Clinical Implications for Diagnosing GERD	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Liu, Tso-Tsai	Application of Artificial Intelligence in High-resolution Esophageal Function Testing: A Study on Unsupervised Deep Learning Algorithms	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Liu, Tso-Tsai	The Efficacy of Jingsi Herbal Drink on Psychosomatic Symptoms of Functional Dyspepsia: A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2022/1/1~ 2022/12/31	Tzu Chi Medical Corporation
Liu, Tso-Tsai	Interrelationships among esophageal peristalsis, mucosa integrity, and mucosa afferent innervation: mechanisms for esophageal dysfunction and gastroesophageal reflux	Co-Principal Investigator	2020/8/1~ 2023/07/31	Ministry of Science and Technology
Lei, Wei-Yi	Exploring the Pathophysiological Mechanisms and Roles of Neuromodulators and Cognitive Behavioral Therapy in Regulating Visceral Hypersensitivity and Hypervigilance in Individuals with Gut-Brain Axis Communication Abnormalities.	Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Lei, Wei-Yi	Clinical Application of Diaphragmatic Breathing in Patients with Gut-Brain Axis Dysregulation: Exploring the Efficacy on Psychosomatic Symptoms and the Impact on the Autonomic Nervous System.	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Lei, Wei-Yi	Identifying the Pathophysiological Mechanisms of Gastroesophageal Reflux Disease (GERD) Patients Through Postprandial High-Resolution Impedance Esophageal Function Testing: Clinical Applications for Reflux Symptoms and Treatment Management.	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
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Lei, Wei-Yi	Exploring the Relationship Between Esophageal Capsaicin Sensitivity, Motility Sensory Function, and Psychophysiological Reflux Characteristics: Clinical Implications and Treatment Guidelines for Esophageal Dysfunction and Gastroesophageal Reflux Disease.	Co-Principal Investigator	2023/8/1~ 2026/07/31	Ministry of Science and Technology
Lei, Wei-Yi	Exploring the Pathophysiological Mechanisms of Gastroesophageal Reflux Disease Through Esophageal Reflux Clearance Ability, Mucosal Integrity, and Psychosomatic Characteristics: Establishing a Basis for Precise Diagnosis and Treatment.	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Lei, Wei-Yi	Utility of high resolution pharyngeal manometry and Sydney Swallow Questionnaire for evaluation of oropharyngeal dysphagia and voice disorder	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Lei, Wei-Yi	Application of Artificial Intelligence in High-resolution Esophageal Function Testing: A Study on Unsupervised Deep Learning Algorithms	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Lei, Wei-Yi	Supervised Learning Artificial Intelligence in 24-h Impedance-pH: Technique Performance and Clinical Implications for Diagnosing GERD	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital

Lei, Wei-Yi	Impact of regulating diet and exercise on clinical characteristics and intestinal microbiota in patients with metabolic-related fatty liver	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Lei, Wei-Yi	The Efficacy of Jingsi Herbal Drink on Psychosomatic Symptoms of Functional Dyspepsia: A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2022/1/1~ 2022/12/31	Tzu Chi Medical Corporation
Lei, Wei-Yi	Exploring the Pathophysiological Role of Esophageal Mucosal Afferent Nerve Distribution in Gastroesophageal Reflux Disease with Esophageal Motility Dysfunction.	Principal Investigator	2020/8/1~ 2022/07/31	Ministry of Science and Technology
Lei, Wei-Yi	Interrelationships among esophageal peristalsis, mucosa integrity, and mucosa afferent innervation: mechanisms for esophageal dysfunction and gastroesophageal reflux	Co-Principal Investigator	2020/8/1~ 2023/07/31	Ministry of Science and Technology
Hung, Jui-Sheng	Identifying the Pathophysiological Mechanisms of Gastroesophageal Reflux Disease (GERD) Patients Through Postprandial High-Resolution Impedance Esophageal Function Testing: Clinical Applications for Reflux Symptoms and Treatment Management.	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Hung, Jui-Sheng	Exploring the Pathophysiological Mechanisms and Roles of Neuromodulators and Cognitive Behavioral Therapy in Regulating Visceral Hypersensitivity and Hypervigilance in Individuals with Gut-Brain Axis Communication Abnormalities.	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Hung, Jui-Sheng	Clinical Application of Diaphragmatic Breathing in Patients with Gut-Brain Axis Dysregulation: Exploring the Efficacy on Psychosomatic Symptoms and the Impact on the Autonomic Nervous System.	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Hung, Jui-Sheng	The Efficacy of Jingsi Herbal Drink Concentrate on Psychosomatic Symptoms of Gut-Brain Axis Dysregulation: A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2024/01/01~ 2025/12/31	Tzu Chi Medical Corporation
Hung, Jui-Sheng	Analyzing the Pharyngeal Swallowing Physiology and Dynamics in Esophageal Ineffective Motility Patients Using High-Resolution Pharyngeal Function Testing.	Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Hung, Jui-Sheng	Utility of high resolution pharyngeal manometry and Sydney Swallow Questionnaire for evaluation of oropharyngeal dysphagia and voice disorder	Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Hung, Jui-Sheng	The Efficacy of Jingsi Herbal Drink Concentrate on Psychosomatic Symptoms of Long COVID - Gut-Brain Axis Dysregulation: A Randomized Double-	Co-Principal Investigator	2023/01/01~ 2023/12/31	Tzu Chi Medical Corporation

	Blind Clinical Trial.			
Hung, Jui-Sheng	Exploring the Interrelationship Between Belching, Psychosomatic Symptoms, and Esophageal Acid Reflux: Clinical Applications for Optimizing Gastroesophageal Reflux Disease Treatment.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Hung, Jui-Sheng	Exploring the Pathophysiological Mechanisms and Interrelationship Between Esophageal Hypervigilance, Psychological Distress, and Functional Gastrointestinal Disorders in Esophageal Symptom Patients.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Hung, Jui-Sheng	Exploring the Efficacy and Physiological Changes of Anti-Reflux Mucosal Ablation Therapy in Proton Pump Inhibitor-Dependent Gastroesophageal Reflux Disease.	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Hung, Jui-Sheng	Exploring the Relationship Between Esophageal Capsaicin Sensitivity, Motility Sensory Function, and Psychophysiological Reflux Characteristics: Clinical Implications and Treatment Guidelines for Esophageal Dysfunction and Gastroesophageal Reflux Disease.	Co-Principal Investigator	2023/8/1~ 2026/07/31	Ministry of Science and Technology
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Hung, Jui-Sheng	Impact of opioids on esophageal peristalsis and acid reflux characteristics:relevance for esophageal pathophysiology and therapeutic implications	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Hung, Jui-Sheng	Supervised Learning Artificial Intelligence in 24-h Impedance-pH: Technique Performance and Clinical Implications for Diagnosing GERD	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
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Hung, Jui-Sheng	Impact of regulating diet and exercise on clinical characteristics and intestinal microbiota in patients with metabolic-related fatty liver	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
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Hung, Jui-Sheng	Interrelationships among esophageal peristalsis, mucosa integrity, and mucosa afferent innervation: mechanisms for esophageal dysfunction and gastroesophageal reflux	Co-Principal Investigator	2020/8/1~ 2023/07/31	Ministry of Science and Technology
Cheng, Chiu-Hsuan	A Basic Research Program on the Clinical Characteristics and Tumor Microenvironment of Endometrial Cancer.	Co-Principal Investigator	2022/1/1~ 2026/12/31	Hualien Tzu Chi Hospital

5.Research-related Expenses

Item Name		Description	Unit Price	Quantity	Total Price	Remarks
1. Operational Expenses	1. Research Personnel Costs (For related insurance fees, please consult the Human Resources Department)	(1) Full-time Staff (Applicable only for individual research project applications): Work remuneration (including year-end bonus reserve) Employer contribution for labor and health insurance Employer contribution for labor pension (6% of insured salary)				
		(2) Part-time Staff (Must be a current student): Work Remuneration ☐Undergraduate Student ☐Master's Student ☐Other: Employer Contribution for Labor and Health Insurance Employer Contribution for Labor Pension (6% of Insured Salary)				
		(3) Temporary Worker: Work Remuneration Employer Contribution for Labor and Health Insurance Employer Contribution for Labor Pension (6% of Insured Salary)	1,900 933 26 1,196 110	12 12 12 12 12		Hourly Wage: 190 10 hours per month (The minimum hourly wage will be increased to NT $190 starting January 1, 2025) Subtotal: 49,980
				Subtotal:	49,980	
	2.Experimental Animal Costs					
				Subtotal:		
	3. Consumables, Materials, Books, and Miscellaneous Expenses	Participant Compensation (Study 1)	1,000	345	345,000	
		Participant Compensation (Study 2)	6,000	45	270,000	
		Autonomic Nervous System Testing Equipment Rental	11,000	12	132,000	
		Computer Peripheral Consumables: Toner cartridges, ink cartridges, printer photoconductors/drums, specialized printer paper, etc.	2,000	1	2,000	
		Miscellaneous: Postage, printing costs, photocopy paper, photocopying fees, binding fees,	1,020	1	1,020	

		stationery, poster production costs, computer data statistics, computer data analysis, manuscript submission fees, publication fees, sectioning, embedding, and staining/immunostaining costs.				
				Subtotal:	750,020	
2. Research Equipment Costs (According to regulations, books, computers, and peripheral devices are not included in the subsidy. Medium and large-scale equipment may be applied for as necessary, and requests should be submitted collectively by the research department for shared use.)						
				Subtotal:	0	
Total					800,000	

6. Project Summary

Patients with gut-brain axis disorders often exhibit bothersome gastrointestinal symptoms despite having no significant abnormalities in routine examinations. These symptoms severely impact the patients' physical and mental health. Recently, the concept of the gut-liver-brain axis has been proposed, suggesting that dysbiosis of the gut microbiota is associated with brain and liver diseases. The connection between the gut and liver relies on the gut barrier, thereby creating mutual influences among the gut, liver, and brain. Gut-brain axis disorders encompass conditions such as laryngopharyngeal reflux, functional dyspepsia, and irritable bowel syndrome, where patients often exhibit an imbalance in autonomic nervous system function. In functional dyspepsia, an inflammatory response caused by eosinophils and mast cells releasing histamine increases intestinal mucosal permeability, which is a critical pathogenic mechanism. In studies on fatty liver, brain signals can regulate the secretion of very-low-density lipoprotein triglycerides via the vagus nerve and reduce liver fat content. Diaphragmatic breathing helps enhance parasympathetic nerve activity and suppress sympathetic nerve activity, making it a recommended adjunct therapy for relieving gastroesophageal reflux symptoms, especially those accompanied by belching.

This study aims to investigate the effects of diaphragmatic breathing on patients with gut-brain axis disorders accompanied by belching, assessing changes in physical and mental symptoms, autonomic nervous system function, and fatty liver before and after treatment. For functional dyspepsia, a randomized controlled trial will be conducted to explore the efficacy and pathological changes of antihistamine drugs in treating functional dyspepsia symptoms.

Keywords: gut-liver-brain axis, belching, diaphragmatic breathing, physical and mental symptoms, autonomic nervous system, gut-brain axis disorders, fatty liver, antihistamines

7. Background and Objectives of the Research Project

Please provide a detailed description of the background, objectives, significance, and relevant research both domestically and internationally related to this project. Additionally, include a review of important reference literature.

Research Background

Disorders of Gut-Brain Interaction, DGBI

Functional gastrointestinal disorders, now referred to as gut-brain axis dysregulation, occur when patients experience gastrointestinal symptoms, but no organic cause can be found upon examination, leaving them still significantly distressed (Figure 1).[1] These symptoms are diverse, involving the esophagus, stomach, small intestine, and large intestine, with complex origins such as gut microbiota imbalance, changes in mucosal immune function, abnormal gut signaling, and dysregulation of the central nervous system's control over gut signals and motility. [2] If the upper digestive tract is affected, it may lead to upper abdominal pain and bloating, termed functional dyspepsia; if the lower digestive tract is affected, it may cause abdominal pain, diarrhea, constipation, and other issues, referred to as irritable bowel syndrome (IBS). [2] Our recent research shows that among patients with gastroesophageal reflux disease, approximately 20% of those with laryngopharyngeal reflux symptoms have pathological reflux evidence, and their esophageal hypersensitivity and anxiety levels are significantly higher than those without laryngopharyngeal reflux symptoms.[3] These gut-brain axis dysregulation patients often respond poorly to conventional gastrointestinal drug treatments, and thus may sometimes require the addition of neuromodulatory drugs for management.[4]

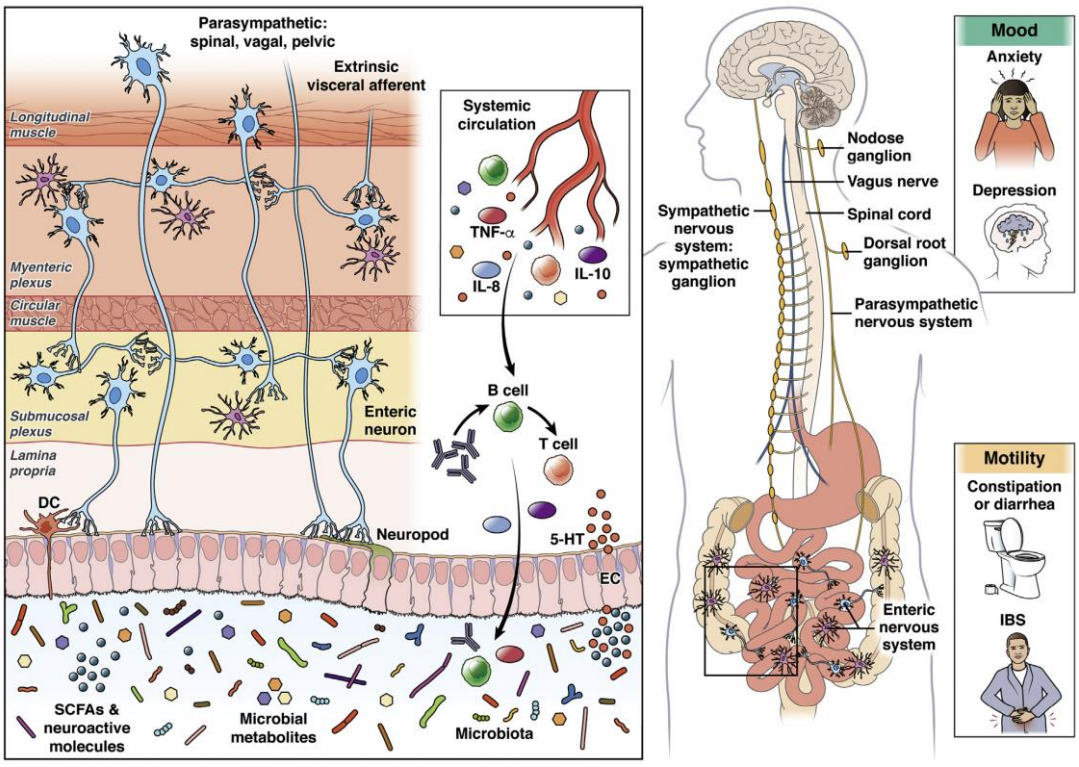


Figure 1. Possible causes of gut-brain axis dysregulation (DGBI) include: gut microbiota imbalance, abnormalities in mucosal immune function, changes in peripheral gut signaling, and dysregulation of the central nervous system's control over gut signaling and motility. The autonomic nervous system plays a crucial role as a communication bridge between the brain (central) and the gastrointestinal tract (peripheral).[1]

For functional dyspepsia, the inflammatory response triggered by the release of histamine from eosinophils and mast cells leads to increased intestinal mucosal permeability, which is an important pathogenic mechanism.[5-7] Meta-analysis studies have shown that H2 antihistamines are comparable in effectiveness to proton pump inhibitors (PPIs) in the treatment of functional dyspepsia (FD),[8] while H1 antihistamines can achieve a therapeutic efficacy of up to 79%.[9] However, there are currently no studies comparing the treatment effects and pathological changes of H1/H2 combination antagonists versus H1 antagonists alone for the treatment of functional dyspepsia.

Recent studies have shown that fatty liver and irritable bowel syndrome share common comorbid factors, including obesity, gut microbiota, dietary factors, and immune-mediated causes.[10, 11] Therefore, the coexistence of these two conditions in patient populations has sparked interest. Additionally, compared to global prevalence studies, the incidence of irritable bowel syndrome is higher in patients with fatty liver.[12] Recent studies have found that up to 55.6% of patients with fatty liver also suffer from irritable bowel syndrome. The research further indicates that individuals with both fatty liver and irritable bowel syndrome have a lower quality of life and more severe physical and mental symptoms.[13]

Concept of Gut liver brain axis

In recent years, the importance of the liver-brain axis in maintaining human health has received widespread attention. Research shows that gut microbiota imbalance is associated with both brain and liver diseases. In other words, the pathophysiology of liver and brain disorders is often closely linked to gastrointestinal issues. The phenomenon of leaky gut is associated with liver diseases such as non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), and hepatocellular carcinoma (HCC).[14-19] In addition, dysbiosis of the gut microbiota has been found in various brain-related psychiatric and neurological disorders, such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), autism, stroke, depression, and substance addiction.[20-26] Liver diseases can also cause neurological disorders through the liver-brain axis, such as hepatic encephalopathy. In 1998, Marshall proposed the concept of the gut-liver axis.[27] Ten years ago, the impact of the gut-liver-brain axis on human health was first revealed.[28] Therefore, the reciprocal communication between the gut, liver, and brain has gradually been recognized and depicted (Figure 2).[29]

The connection between the gut and liver relies on the intestinal barrier. Once compromised, more bacteria or their metabolites can enter the liver, thereby promoting or exacerbating various liver

diseases.[30-32] The various hormones and metabolites produced in the gut during nutrient absorption and metabolism can influence neural signals from the gut to the brain. Once these signals enter the bloodstream, they act on local vagus nerves, spinal afferent neurons, and the brain, which then feedback to the liver through the vagus nerve.[33] The inter-organ communication between the liver and brain is primarily mediated through the nervous and circulatory systems. The mechanisms of the liver-brain axis mainly include blood-brain barrier permeability, vagus nerve signaling, epigenetic regulation, toxic metabolites, β-amyloid protein metabolism, and immune responses.[34]

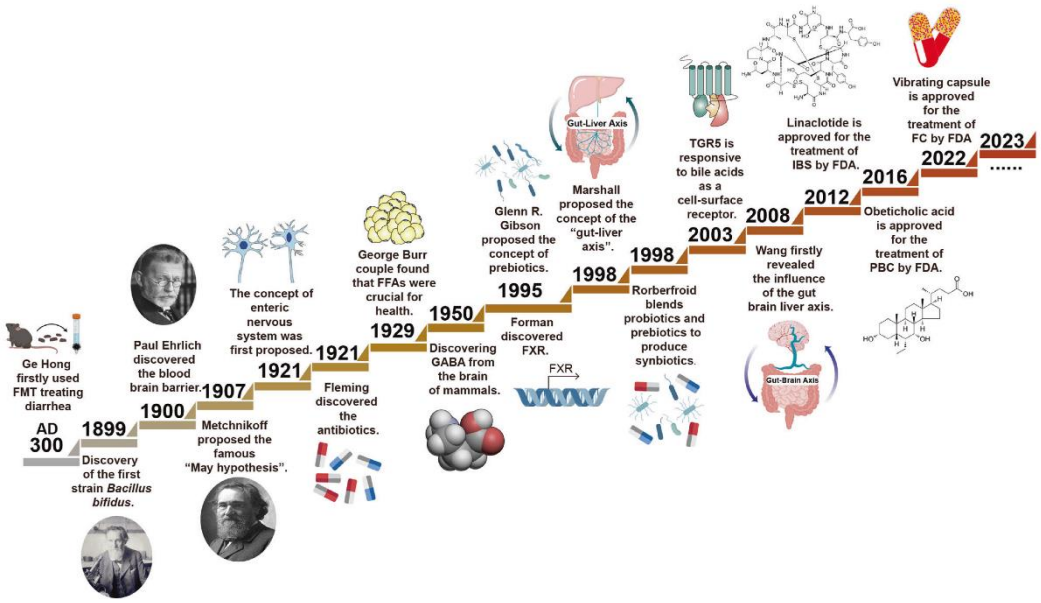


Figure 2: Timeline of Key Milestones in the Gut-Liver-Brain Axis.

Figure 2 shows that in the 3rd to 4th century, Ge Hong collected folk remedies and published Elbow-back Emergency Formula (肘後備急方), where he first used fecal liquid to treat food poisoning and severe diarrhea. In 1899, Henry Tissier in France isolated the first strain of *Bifidobacterium* from the feces of healthy breastfed infants. In 1900, German bacteriologist Paul Ehrlich discovered the blood-brain barrier. In 1907, Metchnikoff proposed the famous "Theory of Longevity," stating that the gut microbiota and its interaction with the host are crucial for health. In 1921, the concept of the enteric nervous system (ENS) was first proposed, focusing on the neuroanatomy, function, and pathophysiology of the gut-brain interaction. Six years later, Wieland was awarded the Nobel Prize in Chemistry for his discovery of bile acids and their chemical structure. In 1929, George Burr and his wife discovered that fatty acids are crucial for health. In 1950, gamma-aminobutyric acid (GABA) was first discovered in the brain of mammals. In 1995, Glenn R. Gibson, the "father of prebiotics," proposed the concept of prebiotics. In the same year, Forman and colleagues first discovered the Farnesoid X receptor (FXR). In 1998, Marshall introduced the concept of the "gut-liver axis." At the same time, Roberfroid further combined probiotics and prebiotics to create a product called synbiotics. In 2003, the Takeda G protein-coupled receptor 5 (TGR5), a receptor on the surface of bile acid-responsive cells, was discovered for the first time. In 2008, Wang first revealed the impact of the gut-brain-liver axis on human health. In 2012, the first drug related to the gut-brain axis, Linaclotide, was approved by the FDA for the treatment of irritable bowel syndrome

(IBS). In 2016, the first drug related to the gut-liver axis, Obeticholic acid, was approved by the FDA for the treatment of primary biliary cirrhosis. In 2022, a drug associated with the gut-brain axis, Vibrating capsule, was approved by the FDA for the treatment of functional constipation.[35]

The relationship between the autonomic nervous system and the gut liver brain axis

The gastrointestinal tract is controlled by the enteric nervous system (ENS) and the autonomic nervous system (ANS).[1] The enteric nervous system can automatically regulate gastrointestinal function, while the central nervous system regulates gastrointestinal function through the interaction between the autonomic nervous system and the enteric nervous system. [2] Abnormal function of either or both the parasympathetic and sympathetic nervous systems may lead to obstruction of communication between the intestine and the brain, thus causing disorders of the gut-liver-brain axis. [36] The parasympathetic nerves of the upper gastrointestinal tract are innervated by the vagus nerve, while the lower gastrointestinal tract is innervated by the sacral neurons of the spinal cord. [2] Most studies have found that patients with gut-liver-brain axis disorders have weakened parasympathetic activity and dominant sympathetic activity, which is consistent with the autonomic control of gastrointestinal motility: parasympathetic activity enhances gastrointestinal motility, while sympathetic activity inhibits gastrointestinal motility. [36]

To put it further, the vagus nerve is an important two-way highway that connects the brain and the gut.[37] It is closely connected to the enteric nervous system (ENS) and has the ability to influence brain behavior, such as stress response, anxiety, depression, social behavior, and cognitive function.[38-40] The afferent fibers of the vagus nerve originate from the smooth muscles of the gut and transmit gut information to the central nervous system.[41, 42] In addition, the vagus nerve can detect microbial signals from the central nervous system and then feedback to the gut, releasing bacterial-derived metabolites such as short-chain fatty acids (SCFAs), gamma-aminobutyric acid (GABA), and serotonin (5-HT), or gut hormones like glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and cholecystokinin (CCK), all of which are influenced by enteroendocrine cells and enterochromaffin cells in the gut.[32, 43, 44]

Additionally, the vagal afferent nerves of the liver are responsible for indirectly sensing the liver microenvironment and transmitting sensory input to the solitary nucleus in the central nervous system, which then provides feedback to the liver through the vagal parasympathetic nerve.[45, 46] Recent studies have indicated that signals from the brain can regulate the secretion of very low-density lipoprotein (VLDL) triglycerides through the vagus nerve and reduce liver fat content.[47] In addition, exogenous vagal reflex activity connects the vagal sensory input from the liver, the brainstem, vagal efferent nerves, and intestinal neurons.[46]

Diaphragmatic breathing (Northwestem Medicine)

Breathing is closely linked to the function of the autonomic nervous system because the phrenic nerve, which controls the diaphragm, is connected to the vagus nerve.[48] The respiratory cycle reflects the balance between the parasympathetic and sympathetic nervous systems and can be observed through heart rate variability (HRV). When you inhale, the autonomic nervous system switches from parasympathetic to sympathetic; when you exhale, it switches from sympathetic to parasympathetic. In HRV, an increase in heart rate indicates increased sympathetic nerve activity during inhalation, while a decrease in heart rate indicates increased parasympathetic nerve activity during exhalation.[49]

Abdominal breathing promotes parasympathetic nervous system activity and inhibits sympathetic nervous system activity by reducing respiratory rate.[50, 51] When tidal volume is increased, the Hering-Breur reflex is activated, reducing chemoreceptor reflex sensitivity and enhancing baroreceptor reflexes, further inhibiting sympathetic activity.[52] The steps of abdominal breathing are as follows (Figure 3): inhale through the nose for about 4 seconds, feeling the expansion of the abdomen; hold your breath for 4 seconds; then exhale slowly through the mouth for about 6 seconds (Northwestem Medicine Diaphragmatic Breathing for GI Health)。

Abdominal breathing has been recommended as an adjunctive therapy to relieve symptoms of gastroesophageal reflux.[53] In addition to the fact that abdominal breathing has been shown to be effective in reducing the number of reflux episodes in randomized controlled trials,[54] in prospective studies of patients with gastroesophageal reflux For patients with belching who have failed treatment with hydrogen ion pump blockers, abdominal breathing has also been shown to improve gastroesophageal reflux symptoms and effectively improve the quality of life of these patients. [55]

According to the ROME IV international consensus definition, belching is troublesome hiccups that occur more than 3 days a week for at least 6 months, either from the esophagus or the stomach.[56] Although abdominal breathing can improve the symptoms of belching in patients with gastroesophageal reflux disease,55 the efficacy of abdominal breathing in patients with gut-liver-brain axis disorder and belching remains to be studied. The effect of abdominal breathing on fatty liver has not yet been studied. There are research explanations.

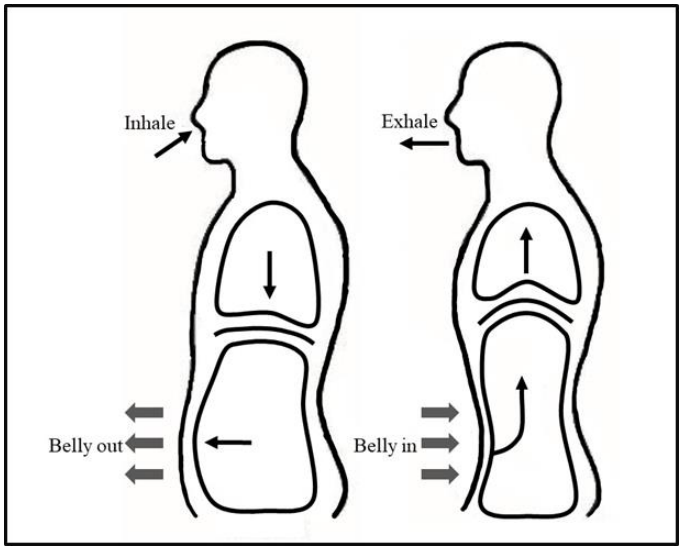


Figure 3. Abdominal breathing: When inhaling in the left picture, the diaphragm descends and the abdomen bulges; when exhaling in the right picture, the diaphragm rises and the abdomen returns to a flat state

Research objectives and hypotheses

Objective 1: To explore the therapeutic effect of abdominal breathing on patients with gut-liver-brain axis disorder combined with belching and fatty liver

Hypothesis 1-1: According to the Rome IV criteria, patients with gut-liver-brain axis disorder and belching may present with more obvious autonomic nervous system imbalance.

Hypothesis 1-2: Patients with gut-liver-brain axis disorder and belching may respond better to abdominal breathing training than patients without belching.

Hypothesis 1-3: Abdominal breathing training may help improve fatty liver and fibrosis in patients with gut-liver-brain axis disorder.

Objective 2: The efficacy and pathological changes of antihistamines on functional dyspepsia symptoms

Hypothesis 2-1: H1 blockers will provide better symptom relief than placebo, and the combination of H1 and H2 blockers will be more effective than H1 blockers alone.

Hypothesis 2-2: H1 blockers will be more effective than placebo in reducing the number of eosinophils in duodenal pathological sections, and the combination of H1 and H2 blockers will be more effective than H1 blockers alone .

8. Research Methods, Procedures and Implementation Progress

1.Please describe in detail the research methods and reasons adopted in this project.
2. Anticipated difficulties and solutions
3. Anticipate the difficulties that may be encountered and how to resolve them.
4.If it is a continuous project, the previous year's research progress report or primary data should also be attached.

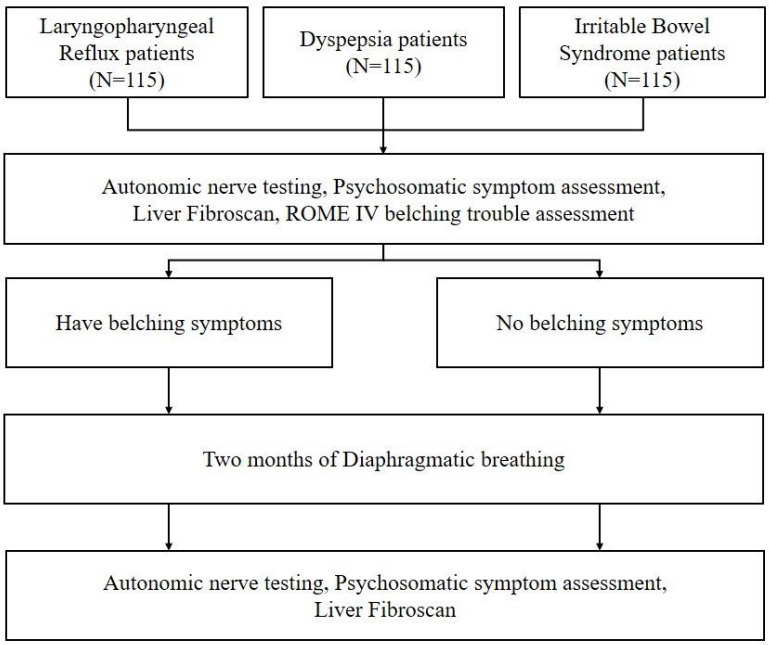
Research Methods

This study was conducted in two parts:

Study 1: The therapeutic effect of abdominal breathing on patients with gut-liver-brain axis disorder and belching

This trial is expected to last for 1 year. Patients will be recruited from the gastroenterology and hepatobiliary outpatient clinic. A total of 115 patients with laryngopharyngeal reflux disease, 115 patients with dyspepsia, and 115 patients with irritable bowel syndrome will be recruited. Subjects who meet the enrollment criteria will undergo autonomic nervous system assessment, physical and mental symptom assessment, ROME IV belching trouble assessment, and liver fibroscan assessment to investigate the prevalence of belching trouble in patients. If the patient is willing to undergo abdominal breathing test, the researcher will guide the patient to do abdominal breathing twice a day for two months, and then the patient will undergo autonomic nerve assessment, physical and mental symptom assessment, ROME IV belching assessment and liver function assessment. Fiber Scanner Evaluation.

Research flow chart



Subjects

This study is planned to last for 1 year. Patients will be recruited from the Gastroenterology and Hepatology outpatient clinic. A total of 115 patients with laryngopharyngeal reflux, 115 patients with dyspepsia, and 115 patients with irritable bowel syndrome will be enrolled.

Laryngopharyngeal Reflux (LPR) patients

Inclusion Criteria for Participants:

1. Age between 18 and 75 years, conscious, and willing to sign the informed consent form.
2. Laryngopharyngeal reflux is defined as having symptoms for more than three months (such as hoarseness, foreign body sensation in the throat, chronic cough, and frequent throat clearing) occurring at least once a week. The standard Laryngopharyngeal Reflux assessment tool, the Reflux Symptom Index (RSI), includes nine reflux-related symptoms. Each symptom is rated from 0 (no symptoms) to 5 (most severe). A total score exceeding 13 points meets the inclusion criteria for LPR patients.

Exclusion Criteria for Participants:

1. Intubated within the past two months.
2. Currently using antibiotics for an infectious disease.
3. Pregnant or breastfeeding women.
4. Individuals with myocardial ischemia or recent myocardial infarction.
5. Uncooperative participants.

Dyspepsia patients

Inclusion Criteria for Participants:

1. Age between 18 and 75 years, conscious, and willing to sign the informed consent form.
2. Meets the definition of functional dyspepsia: Functional dyspepsia is characterized by chronic upper gastrointestinal symptoms (at least once a week, lasting for at least three months, with the first occurrence of symptoms at least six months ago) including any of the following: postprandial bloating, early satiety, upper abdominal pain, or upper abdominal burning sensation, without gastrointestinal bleeding symptoms or significant weight loss. Upper gastrointestinal endoscopy shows no abnormalities.

Exclusion Criteria for Participants:

1. Underwent upper gastrointestinal surgery within the past two months.
2. Currently using antibiotics for an infectious disease.

3. Pregnant or breastfeeding women.

4. Individuals with myocardial ischemia or recent myocardial infarction.

5. Uncooperative participants.

Irritable Bowel Syndrome (IBS) patients

Inclusion Criteria for Participants:

1. Age between 18 and 75 years, conscious, and willing to sign the informed consent form.
2. Meets the definition of Irritable Bowel Syndrome (IBS): IBS is characterized by chronic lower gastrointestinal symptoms (at least once a week, lasting for at least three months) including abdominal pain associated with diarrhea or constipation, with no abnormalities found upon colonoscopy.

Exclusion Criteria for Participants:

1. Underwent lower gastrointestinal surgery within the past two months.
2. Currently using antibiotics for an infectious disease.
3. Pregnant or breastfeeding women.
4. Individuals with myocardial ischemia or recent myocardial infarction.
5. Uncooperative participants.

Diaphragmatic breathing (Michigan Medicine)

1. Sit in a comfortable chair and close your eyes.
2. Place one hand on your chest and the other on your abdomen to practice abdominal breathing: When you perform abdominal breathing, the hand on your abdomen will rise as you inhale and return to its original position when you exhale, while the hand on your chest should Stay still.
3. Inhale slowly through your nose for about 4 seconds, feeling your abdomen expand. (You may feel a little nervous when you first inhale.)
4. Hold your breath for 4 seconds.
5. Exhale slowly and steadily through your mouth for about 6 seconds, with your lips relaxed.
6. Continue this breathing cycle for five minutes.

Stress autonomic nerve test

The Autonomic Neuro-Activation Test is a standardized and measured method for assessing the baseline state of the Autonomic Neuro-Activation system and its response to activation. The test consists of three phases: a rest period (5 minutes), a stress test (3 minutes), and a recovery period (5 minutes), measured by heart rate variability (HRV). The stress test was in the form of mental arithmetic, where the subjects had to continuously subtract 7 from a random four-digit number

without using paper and pen. If they made a mistake, they had to start over. The whole process lasted three minutes.[57]

Autonomic nervous system measurement steps:

1. Confirm that the status indicator shows that the measurement is possible (LED color: green), and then wear the electrode patch.:
    - R (red buckle point): Stick to the inside of the right wrist
    - L (yellow buckle): Stick to the inside of the left wrist
    - F(Green buckle point): Attach to the inside of the left wrist
2. Press the measurement key on the device to start the measurement.
3. Before the formal measurement, the device will first detect the signal quality. Please keep still and avoid talking.
4. When the measurement officially begins, ask the subject to remain still and avoid talking for three to five minutes until the measurement is completed.
5. After the measurement is completed, the device will display the measurement result.

The heart rate variability indicators for evaluating the autonomic nervous system are as follows:[58]

1. Time domain indicators
    - Root mean square of the squared differences between normal heart beats (RMSSD): Assess parasympathetic nerve activity
2. Frequency domain indicators
    - Low frequency power (LF): Assesses sympathetic nerve activity
    - High Frequency Power (HF): Assess parasympathetic activity
    - Low frequency/high frequency power ratio (LF/HF ratio):Assesses the balance between sympathetic and parasympathetic nerves

Fibroscan

The liver fibrosis scanner assesses the stiffness of the liver by measuring the changes in the speed of ultrasound waves passing through different materials: ultrasound waves travel faster when passing through hard materials and slower when passing through elastic materials, so it can be used to measure The degree of liver fibrosis. In addition, the controlled attenuation parameter (CAP) can assess liver fat content and thus grade the severity of fatty liver.

Liver fibrosis grading [59]

- No liver fibrosis (F0): < 7.0 kPa
- Mild liver fibrosis (F1~2): > 7.0 kPa
- Significant liver fibrosis (F2~3): > 8.7 kPa

- Cirrhosis (F4): > 10.3 kPa

Fatty Liver Grading[60]

- No Fatty Liver (S0) (≤ 10%): CAP < 215 dB/m
- Mild Fatty Liver (S1) (11 ~ 33%): CAP > 215 dB/m
- Moderate Fatty Liver (S2) (34 ~ 66%): CAP > 252 dB/m
- Severe Fatty Liver (S3) (≥ 67%): CAP > 296 dB/m

Questionnaire Assessment Tool

Disease Questionnaire Assessment:

- Gastroesophageal Reflux Disease Questionnaire (GERDQ): A score above 12 points indicates a high likelihood of having GERD.[61]
- Reflux Symptom Index (RSI): The nine reflux-related symptoms are scored from 0 (no symptoms) to 5 (most severe). A total score above 13 points indicates a higher likelihood of having laryngopharyngeal reflux.[62]
- Functional Dyspepsia Questionnaire (FD): The subjective evaluation focuses on symptoms and quality of life, primarily including postprandial bloating, early satiety, upper abdominal pain, and other dyspeptic symptoms. Each item is scored from 0 to 6, with 0 indicating no symptoms and 6 indicating very severe symptoms. The total score ranges from 0 to 52, with higher scores indicating more severe symptoms.[63]
- Irritable Bowel Syndrome Questionnaire (IBS): The diagnostic criteria are based on Rome IV. The primary symptoms must have started at least six months ago, with recurrent abdominal pain occurring at least once per week on average over the past three months. Additionally, at least two of the following symptoms must be present: abdominal pain related to bowel movements, changes in stool frequency, and changes in stool appearance or form.[63]
- Irritable Bowel Syndrome Severity Scoring System (IBS-SSS): This tool records the frequency and severity of abdominal pain and bloating, as well as the patient's satisfaction with their bowel condition and its impact on daily life. The scoring range is <150, 150–300, and >300 (with a maximum score of 500), commonly used to classify IBS symptoms as mild, moderate, or severe.[64]
- Gastrointestinal Symptom Rating Scale (GSRS): This questionnaire is used to measure gastrointestinal symptoms in the general population and assess treatment effectiveness. It uses a 4-point Likert scale, with higher scores indicating more severe symptoms and lower scores indicating better health.[65]
- Belching Self-Assessment Visual Analogue Scale (VAS): The participant is asked to mark their level of discomfort on a 10 cm horizontal line, where the far left represents "no pain" and the far right represents "unbearable pain."[66]

Psychosomatic and Stress Questionnaire Assessment:

- Pittsburgh Sleep Quality Index (PSQI): In addition to evaluating sleep quality in patients with sleep disorders and psychiatric conditions, it is also used for assessing sleep quality in the general population. The index consists of 18 items grouped into 7 components, with each component scored on a scale from 0 to 3. The total score ranges from 0 to 21, with higher scores indicating poorer sleep quality.[67]
- Taiwan Depression Questionnaire (TDQ): This questionnaire includes three sections: emotional, cognitive, and physical aspect, with a total of 18 items. The scale uses a 4-point rating system, with each item scored from 0 to 3. The total score ranges from 0 to 54, with a score above 18 indicating depressive symptoms.[67] Patients with gut-liver-brain axis dysregulation often experience emotional disorders, such as anxiety and depression, which significantly impact the severity of gastrointestinal symptoms. The use of the Taiwan Depression Questionnaire (TDQ) can systematically assess the level of depression in participants and cross-analyze it with gastrointestinal symptoms and treatment outcomes. This allows for a more accurate evaluation of the role psychological factors play in gut-liver-brain axis dysregulation. Literature indicates a close relationship between the gut microbiome, mood, and the autonomic nervous system, which further underscores the importance of TDQ assessment. The gut microbiome is associated with various factors such as mood, gastrointestinal motility, and immune responses, highlighting the complex interactions of the microbiome-gut-brain axis. These interactions are closely linked to emotional disorders like anxiety and depression (Figure 1).[1]
- State-Trait Anxiety Inventory (STAI): The STAI consists of two subscales: State Anxiety and Trait Anxiety. The minimum score is 20, and the maximum score is 80. A higher score indicates the presence of anxiety symptoms.[68]
- Perceived Stress Scale (PSS-10): The PSS-10 is designed to assess the level of perceived stress in an individual's life situation. A higher score indicates greater stress.[69]
- Esophageal Hypervigilance and Anxiety Scale (EHAS): Esophageal hypervigilance and anxiety can trigger symptoms in patients with chronic esophageal diseases, including gastroesophageal reflux, esophageal motility disorders, and functional esophageal diseases. The questionnaire consists of 15 items and is divided into two main sections: esophageal hypervigilance symptoms and esophageal anxiety symptoms. This questionnaire not only assesses sensory system symptoms related to any esophageal condition but also helps in diagnosing functional esophageal diseases.[65]
- Laryngopharyngeal Hypervigilance and Anxiety Scale (LHAS): Laryngopharyngeal hypervigilance and anxiety can trigger symptoms in patients with chronic esophageal diseases. The questionnaire consists of 15 items and is divided into two main sections: laryngopharyngeal hypervigilance symptoms and laryngopharyngeal anxiety symptoms. This questionnaire not only assesses sensory system symptoms related to any esophageal condition but also helps in diagnosing functional esophageal diseases.[70]

- Visceral Sensitivity Index (VSI): The VSI measures gastrointestinal-specific anxiety. It consists of 15 items, with each item scored from 0 to 5. The total score ranges from a minimum of 0 to a maximum of 75.[71]

Lifestyle Habit Assessment:

The use of tobacco, alcohol, coffee, and tea may affect the autonomic nervous system function, potentially influencing the results of autonomic nervous system measurements in this study. For instance, nicotine and caffeine stimulate the sympathetic nervous system, which can lead to an increased heart rate and blood pressure, thus affecting the accuracy of autonomic nervous function assessments. Similarly, alcohol may influence both sympathetic and parasympathetic nervous activity, with long-term alcohol consumption potentially leading to dysregulation of nervous function. These factors could impact the autonomic nervous activity of participants, thus affecting the internal validity of the study. Therefore, collecting data on the use of tobacco, alcohol, coffee, and tea helps control these potential confounding variables, improving the accuracy and reliability of the research findings.

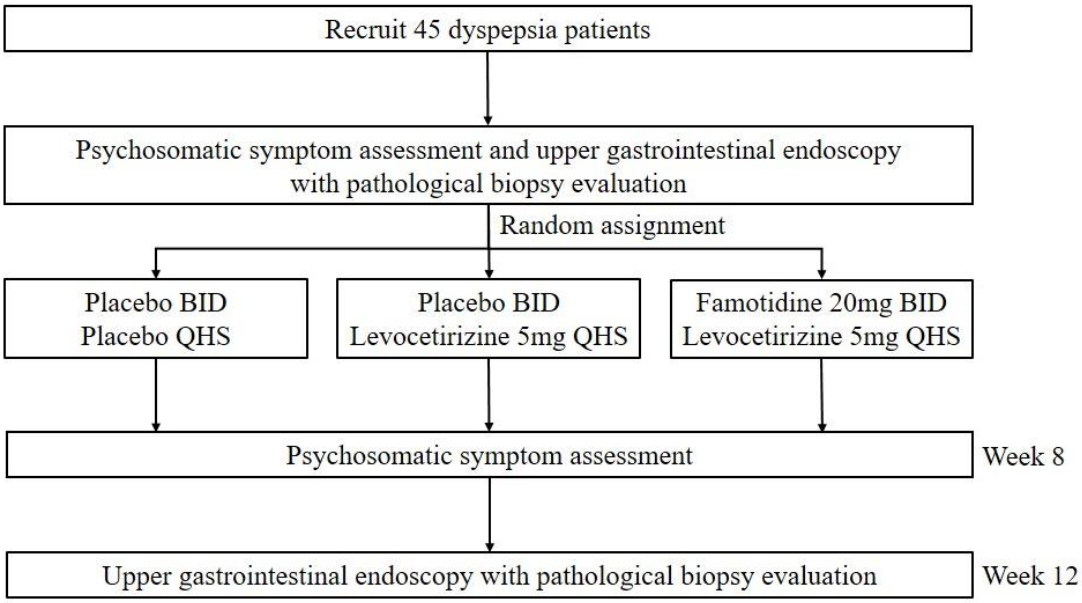
Statistical Analysis:

For continuous variables, if the distribution is normal, the mean and standard deviation will be used; if the distribution is non-normal, the median and interquartile range will be reported. The treatment effect will be presented as the percentage improvement in pre- and post-treatment scores of the Sleep Habit Questionnaire, Depression Questionnaire, Anxiety Questionnaire, Stress Questionnaire, Gastrointestinal Symptom Questionnaire, and Irritable Bowel Syndrome Questionnaire. The efficacy of abdominal breathing in the two groups (with or without accompanying belching symptoms) will be compared using the Chi-squared test. Liver fibrosis and fatty liver severity values will be compared before and after abdominal breathing using the Paired-Sample t Test. A P-value less than 0.05 will be considered statistically significant. The statistical software used for analysis is SPSS 19 (SPSS, Inc, Chicago, IL, USA).

Study 2: The Efficacy and Pathological Changes of Antihistamine Drugs in Treating Functional Dyspepsia Symptoms

This study is planned to last for one year, and patients will be recruited from the Gastroenterology and Hepatology outpatient clinic. A total of 45 dyspepsia patients will be enrolled. Eligible participants will undergo a psychosomatic symptom assessment and upper gastrointestinal endoscopy with pathological biopsy evaluation. Subsequently, participants will be randomly assigned to one of three treatment groups: H1/H2 combination antagonists: Levocetirizine 5mg qhs + Famotidine 20mg bid, H1 antagonist alone: Levocetirizine 5mg qhs + placebo bid, or the control group: placebo qhs + placebo bid. After eight weeks of treatment, psychosomatic symptom assessments will be conducted again, and an upper gastrointestinal endoscopy with biopsy evaluation will be performed at week 12.

Study Flowchart



Participants

Participants who agree to participate in this study must first sign the informed consent form and obtain approval from the Research Ethics Committee of Hualien Tzu Chi Hospital. This study is planned to last for one year, and patients will be recruited from the Gastroenterology and Hepatology outpatient clinic. A total of 45 dyspepsia patients will be enrolled. The inclusion and exclusion criteria for participants are as follows:

Inclusion criteria for participants:

1. Aged between 18 and 64 years, with clear consciousness and willing to sign the informed consent form.
2. Meets the definition of functional dyspepsia: Functional dyspepsia is characterized by chronic (at least once a week, lasting for at least three months, with the first symptom occurring at least six months ago) upper gastrointestinal symptoms (any of the following): postprandial bloating, early satiety, upper abdominal pain, or upper abdominal burning sensation, with no abnormalities found on upper gastrointestinal endoscopy.

Exclusion criteria for participants:

1. Underwent upper gastrointestinal surgery within the past two months.
2. Currently using antibiotics for infectious diseases.
3. Pregnant or breastfeeding women.

4. Individuals with myocardial ischemia or who have recently experienced a myocardial infarction.
5. Unable to cooperate.

Upper gastrointestinal endoscopy evaluation (routine examination)

We use standard upper gastrointestinal endoscopy for evaluation as the basis for diagnosing functional dyspepsia, and three biopsy samples are taken from the duodenum for eosinophil count analysis.

Questionnaire Assessment Tool

Disease Questionnaire Assessment:

- Functional Dyspepsia Questionnaire (FD): The subjective evaluation focuses on symptoms and quality of life, primarily including postprandial bloating, early satiety, upper abdominal pain, and other dyspeptic symptoms. Each item is scored from 0 to 6, wi[63]Gastrointestinal Symptom Rating Scale (GSRS): This questionnaire is used to measure gastrointestinal symptoms in the general population and assess treatment effectiveness. It uses a 4-point Likert scale, with higher scores indicating more severe symptom[65]

Psychosomatic and Stress Questionnaire Assessment:

- Pittsburgh Sleep Quality Index (PSQI): In addition to evaluating sleep quality in patients with sleep disorders and psychiatric conditions, it is also used for assessing sleep quality in the general population. The index consists of 18 items grouped int[67]
- The Taiwanese Depression Questionnaire (TDQ) consists of 18 items, covering emotional, cognitive, and physical aspects. It uses a four-point scale, with each item scored from 0 to 3. The total score ranges from 0 to 54, and a score greater than 18 indicates the presence of depressive symptoms.[67]
- State-Trait Anxiety Inventory (STAI): The STAI consists of two subscales: State Anxiety and Trait Anxiety. The minimum score is 20, and the maximum score is 80. A higher score indicates the presence of anxiety symptoms.[68]
- Perceived Stress Scale (PSS-10): The PSS-10 is designed to assess the level of perceived stress in an individual's life situation. A higher score indicates greater stress.[69]
- Visceral Sensitivity Index (VSI): The VSI measures gastrointestinal-specific anxiety. It consists of 15 items, with each item scored from 0 to 5. The total score ranges from a minimum of 0 to a maximum of 75.[71]

Statistical analysis

All data will be checked for normal distribution using the Kolmogorov-Smirnov test. For continuous variables, if normally distributed, the data will be presented as mean ± standard deviation; if not normally distributed, the data will be presented as median and interquartile range. For comparisons among three groups, if the data is continuous and normally distributed, Independent ANOVA will be used; if the data is continuous and not normally distributed, the Kruskal-Wallis test will be used; for categorical variables, Pearson Chi-square test will be used. Statistical analysis will be performed using SPSS 19 for Windows (SPSS, Inc., Chicago, IL, USA).

The clinical significance and originality of this study

This study will be the first to extensively apply diaphragmatic breathing to patients with gut-liver-brain axis dysregulation, specifically targeting those with functional dyspepsia, irritable bowel syndrome, laryngopharyngeal reflux with bloating, and fatty liver. The research not only evaluates gastrointestinal symptoms but also includes a multi-dimensional assessment of psychological symptoms, sleep quality, stress indicators, and visceral sensitivity. This study aims to comprehensively investigate the efficacy and mechanisms of non-invasive, non-pharmacological diaphragmatic breathing for patients with gut-liver-brain axis dysregulation. Additionally, the study will use heart rate variability to assess changes in autonomic nervous function and liver stiffness measurement to evaluate the degree of fatty liver and liver fibrosis. Regarding functional dyspepsia, this study will be the first to investigate the effects of antihistamine drugs on symptoms and pathological changes through a randomized controlled trial.

The relevance between the two parts of the study lies in their shared research focus—functional dyspepsia (FD). While the first part focuses on the effects of diaphragmatic breathing for patients with gut-liver-brain axis dysregulation and bloating symptoms, the second part investigates the efficacy of antihistamine drugs in functional dyspepsia patients. Both studies involve the management of the autonomic nervous system and gastrointestinal symptoms. Together, these two research parts provide different therapeutic approaches, exploring how both non-pharmacological and pharmacological methods can alleviate the symptoms of functional dyspepsia.

9.Expected tasks and specific outcomes

1. Expected tasks to be completed

(1) Evaluate the therapeutic effect of abdominal breathing on patients with gut-liver-brain axis dysregulation combined with belching symptoms.
(2) Investigate whether abdominal breathing training improves the degree of fatty liver and liver fibrosis in patients with gut-liver-brain axis dysregulation.
(3) Further study the therapeutic effect of antihistamine drugs on functional dyspepsia symptoms and associated pathological changes.

2. Expected contributions to academic research, national development, and other applications

(1) This study will verify the therapeutic effects of abdominal breathing on patients with gut-liver-brain axis dysregulation, accompanied by bloating symptoms and fatty liver, and explore the efficacy and pathological changes of antihistamine drugs in functional dyspepsia symptoms. The findings will provide important references for both domestic and international research and clinical applications.
(2) As the concept of gut-liver-brain axis dysregulation gains increasing attention, this study will introduce novel treatments for patients with bloating and fatty liver, potentially leading to breakthroughs in the current treatment of gastroesophageal reflux disease.

3. Expected training for the participating staff

(1) Basic research training (such as experimental design and implementation, result analysis and statistics, chart creation, oral presentations, paper writing, and submission).

(2) Participants will learn additional experimental techniques and skills through diverse tasks, including standard procedures for questionnaire validation, autonomic nervous system measurements, and operation of liver fibrosis scanning devices.

10. References

1. Margolis KG, Cryan JF, Mayer EA. The Microbiota-Gut-Brain Axis: From Motility to Mood. Gastroenterology 2021;160:1486-1501.
2. Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. Gastroenterology 2016;150:1257-61.
3. Wong MW, Hsiao SH, Wang JH, et al. Esophageal Hypervigilance and Visceral Anxiety Contribute to Symptom Severity of Laryngopharyngeal Reflux. Am J Gastroenterol 2023;118:786-793.
4. Drossman DA, Tack J, Ford AC, et al. Neuromodulators for Functional Gastrointestinal Disorders (Disorders of Gut-Brain Interaction): A Rome Foundation Working Team Report. Gastroenterology 2018;154:1140-1171 e1.
5. Talley NJ, Walker MM, Aro P, et al. Non-ulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. Clin Gastroenterol Hepatol 2007;5:1175-83.
6. Vanheel H, Vicario M, Vanuytsel T, et al. Impaired duodenal mucosal integrity and low-grade inflammation in functional dyspepsia. Gut 2014;63:262-71.
7. Cirillo C, Bessissow T, Desmet AS, et al. Evidence for neuronal and structural changes in submucous ganglia of patients with functional dyspepsia. Am J Gastroenterol 2015;110:1205-15.
8. Moayyedi P, Lacy BE, Andrews CN, et al. ACG and CAG Clinical Guideline: Management of Dyspepsia. Am J Gastroenterol 2017;112:988-1013.
9. Matter SE, Bhatia PS, Miner PB, Jr. Evaluation of antral mast cells in nonulcer dyspepsia. Dig Dis Sci 1990;35:1358-63.
10. Purssell H, Whorwell PJ, Athwal VS, et al. Non-alcoholic fatty liver disease in irritable bowel syndrome: More than a coincidence? World J Hepatol 2021;13:1816-1827.
11. Scalera A, Di Minno MN, Tarantino G. What does irritable bowel syndrome share with non-alcoholic fatty liver disease? World J Gastroenterol 2013;19:5402-20.
12. Singh SP, Kar SK, Panigrahi MK, et al. Profile of patients with incidentally detected nonalcoholic fatty liver disease (IDNAFLD) in coastal eastern India. Trop Gastroenterol 2013;34:144-52.
13. Purssell H, Bennett L, Street O, et al. The prevalence and burden of Rome IV bowel disorders of gut brain interaction in patients with non-alcoholic fatty liver disease: a cross-sectional study. Sci Rep 2023;13:8769.
14. Leung C, Rivera L, Furness JB, et al. The role of the gut microbiota in NAFLD. Nat Rev Gastroenterol Hepatol 2016;13:412-25.
15. Bajaj JS. Alcohol, liver disease and the gut microbiota. Nat Rev Gastroenterol Hepatol 2019;16:235-246.
16. Marra F, Svegliati-Baroni G. Lipotoxicity and the gut-liver axis in NASH pathogenesis. J Hepatol 2018;68:280-295.

17. Park JW, Kim SE, Lee NY, et al. Role of Microbiota-Derived Metabolites in Alcoholic and Non-Alcoholic Fatty Liver Diseases. Int J Mol Sci 2021;23.
18. Kang Y, Cai Y, Yang Y. The Gut Microbiome and Hepatocellular Carcinoma: Implications for Early Diagnostic Biomarkers and Novel Therapies. Liver Cancer 2022;11:113-125.
19. Bence KK, Birnbaum MJ. Metabolic drivers of non-alcoholic fatty liver disease. Mol Metab 2021;50:101143.
20. Tan AH, Lim SY, Lang AE. The microbiome-gut-brain axis in Parkinson disease - from basic research to the clinic. Nat Rev Neurol 2022;18:476-495.
21. Doifode T, Giridharan VV, Generoso JS, et al. The impact of the microbiota-gut-brain axis on Alzheimer's disease pathophysiology. Pharmacol Res 2021;164:105314.
22. Mao XY, Yin XX, Guan QW, et al. Dietary nutrition for neurological disease therapy: Current status and future directions. Pharmacol Ther 2021;226:107861.
23. Yu Y, Zhao F. Microbiota-gut-brain axis in autism spectrum disorder. J Genet Genomics 2021;48:755-762.
24. Honarpisheh P, Bryan RM, McCullough LD. Aging Microbiota-Gut-Brain Axis in Stroke Risk and Outcome. Circ Res 2022;130:1112-1144.
25. Simpson CA, Diaz-Arteche C, Eliby D, et al. The gut microbiota in anxiety and depression - A systematic review. Clin Psychol Rev 2021;83:101943.
26. Wang SC, Chen YC, Chen SJ, et al. Alcohol Addiction, Gut Microbiota, and Alcoholism Treatment: A Review. Int J Mol Sci 2020;21.
27. Dai X, Wang B. Role of gut barrier function in the pathogenesis of nonalcoholic Fatty liver disease. Gastroenterol Res Pract 2015;2015:287348.
28. Wang PY, Caspi L, Lam CK, et al. Upper intestinal lipids trigger a gut-brain-liver axis to regulate glucose production. Nature 2008;452:1012-6.
29. Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. Nat Rev Gastroenterol Hepatol 2019;16:35-56.
30. Bauer KC, Littlejohn PT, Ayala V, et al. Nonalcoholic Fatty Liver Disease and the Gut-Liver Axis: Exploring an Undernutrition Perspective. Gastroenterology 2022;162:1858-1875 e2.
31. Bajaj JS, Ng SC, Schnabl B. Promises of microbiome-based therapies. J Hepatol 2022;76:1379-1391.
32. Brescia P, Rescigno M. The gut vascular barrier: a new player in the gut-liver-brain axis. Trends Mol Med 2021;27:844-855.
33. Socala K, Doboszewska U, Szopa A, et al. The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. Pharmacol Res 2021;172:105840.
34. Smith ML, Wade JB, Wolstenholme J, et al. Gut microbiome-brain-cirrhosis axis. Hepatology 2024;80:465-485.
35. Yan M, Man S, Sun B, et al. Gut liver brain axis in diseases: the implications for therapeutic interventions. Signal Transduct Target Ther 2023;8:443.
36. Ali MK, Chen JDZ. Roles of Heart Rate Variability in Assessing Autonomic Nervous System in Functional Gastrointestinal Disorders: A Systematic Review. Diagnostics (Basel) 2023;13.

37. Prescott SL, Liberles SD. Internal senses of the vagus nerve. Neuron 2022;110:579-599.
38. Berthoud HR, Albaugh VL, Neuhuber WL. Gut-brain communication and obesity: understanding functions of the vagus nerve. J Clin Invest 2021;131.
39. Mendez-Hernandez R, Escobar C, Buijs RM. Suprachiasmatic Nucleus-Arcuate Nucleus Axis: Interaction Between Time and Metabolism Essential for Health. Obesity (Silver Spring) 2020;28 Suppl 1:S10-S17.
40. Jais A, Bruning JC. Arcuate Nucleus-Dependent Regulation of Metabolism-Pathways to Obesity and Diabetes Mellitus. Endocr Rev 2022;43:314-328.
41. Bonaz B, Sinniger V, Pellissier S. Vagus Nerve Stimulation at the Interface of Brain-Gut Interactions. Cold Spring Harb Perspect Med 2019;9.
42. Xie Z, Zhang X, Zhao M, et al. The gut-to-brain axis for toxin-induced defensive responses. Cell 2022;185:4298-4316 e21.
43. Bonaz B, Sinniger V, Pellissier S. Vagus nerve stimulation: a new promising therapeutic tool in inflammatory bowel disease. J Intern Med 2017;282:46-63.
44. Bravo JA, Forsythe P, Chew MV, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A 2011;108:16050-5.
45. Coulter AA, Rebello CJ, Greenway FL. Centrally Acting Agents for Obesity: Past, Present, and Future. Drugs 2018;78:1113-1132.
46. Patterson TT, Nicholson S, Wallace D, et al. Complex Feed-Forward and Feedback Mechanisms Underlie the Relationship Between Traumatic Brain Injury and the Gut-Microbiota-Brain Axis. Shock 2019;52:318-325.
47. Metz M, Beghini M, Wolf P, et al. Leptin increases hepatic triglyceride export via a vagal mechanism in humans. Cell Metab 2022;34:1719-1731 e5.
48. Kocjan J, Adamek M, Gzik-Zroska B, et al. Network of breathing. Multifunctional role of the diaphragm: a review. Adv Respir Med 2017;85:224-232.
49. Stauss HM. Heart rate variability. Am J Physiol Regul Integr Comp Physiol 2003;285:R927-31.
50. Ambrosino N, Paggiaro PL, Macchi M, et al. A study of short-term effect of rehabilitative therapy in chronic obstructive pulmonary disease. Respiration 1981;41:40-4.
51. Montano N, Cogliati C, Porta A, et al. Central vagotonic effects of atropine modulate spectral oscillations of sympathetic nerve activity. Circulation 1998;98:1394-9.
52. Bernardi L, Gabutti A, Porta C, et al. Slow breathing reduces chemoreflex response to hypoxia and hypercapnia, and increases baroreflex sensitivity. J Hypertens 2001;19:2221-9.
53. Yadlapati R, Gyawali CP, Pandolfino JE, et al. AGA Clinical Practice Update on the Personalized Approach to the Evaluation and Management of GERD: Expert Review. Clin Gastroenterol Hepatol 2022;20:984-994 e1.
54. Halland M, Bharucha AE, Crowell MD, et al. Effects of Diaphragmatic Breathing on the Pathophysiology and Treatment of Upright Gastroesophageal Reflux: A Randomized Controlled Trial. Am J Gastroenterol 2021;116:86-94.

55. Ong AM, Chua LT, Khor CJ, et al. Diaphragmatic Breathing Reduces Belching and Proton Pump Inhibitor Refractory Gastroesophageal Reflux Symptoms. Clin Gastroenterol Hepatol 2018;16:407-416 e2.
56. Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal Disorders. Gastroenterology 2016;150:1380-92.
57. Naliboff BD, Benton D, Solomon GF, et al. Immunological changes in young and old adults during brief laboratory stress. Psychosom Med 1991;53:121-32.
58. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health 2017;5:258.
59. Wong VW, Vergniol J, Wong GL, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology 2010;51:454-62.
60. de Ledinghen V, Vergniol J, Foucher J, et al. Non-invasive diagnosis of liver steatosis using controlled attenuation parameter (CAP) and transient elastography. Liver Int 2012;32:911-8.
61. Jones R, Junghard O, Dent J, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. Aliment Pharmacol Ther 2009;30:1030-8.
62. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice 2002;16:274-7.
63. Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV. Gastroenterology 2016.
64. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997;11:395-402.
65. Revicki DA, Wood M, Wiklund I, et al. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. Qual Life Res 1998;7:75-83.
66. Ten Cate L, Herregods TVK, Dejonckere PH, et al. Speech Therapy as Treatment for Supragastric Belching. Dysphagia 2018;33:707-715.
67. Taft TH, Triggs JR, Carlson DA, et al. Validation of the oesophageal hypervigilance and anxiety scale for chronic oesophageal disease. Aliment Pharmacol Ther 2018;47:1270-1277.
68. Lee Y, Yang MJ, Lai TJ, et al. Development of the Taiwanese Depression Questionnaire. Chang Gung Med J 2000;23:688-94.
69. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S467-72.
70. Krause AJ, Taft T, Greytak M, et al. Validation of the Laryngeal Cognitive-Affective Tool. Clin Gastroenterol Hepatol 2024;22:1395-1403 e3.
71. Taylor JM. Psychometric analysis of the Ten-Item Perceived Stress Scale. Psychol Assess 2015;27:90-101.