

Study of the potential mechanism of acupuncture treatment for functional dyspepsia based on association rule mining and bioinformatics/network pharmacology approach

An-Lan Zhao^{1,2}, Ling-Yong Xiao^{1,2}, Hong-Yue Niu^{1,2}, Lian Liu³, Xiao-Yu Dai^{1,2*}

¹Department of Acupuncture, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300193, China. ²National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin 300381, China. ³College of Acupuncture and Massage, Tianjin University of Traditional Chinese Medicine, Tianjin 300000, China.

*Corresponding to: Xiao-Yu Dai, Department of Acupuncture, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, No. 88, Changling Road, Xiqing District, Tianjin 300193, China. E-mail: drdaixiaoyu@163.com.

Author contributions

This study was conceived by Anlan Zhao. Anlan Zhao and Lingyong Xiao drafted the manuscript. Anlan Zhao and Lian Liu were responsible for data screening and verification. Anlan Zhao, Xiaoyu Dai, Hongyue Niu participated in the design of the data synthesis analysis scheme. Dai Xiaoyu provided oversight, critical evaluation, and verification of the manuscript. All authors contributed to the article and approved the submitted version.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Peer review information

Gastroenterology & Hepatology Research thanks Li-Jiang Ji and other anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations

FD, Functional dyspepsia; CBM, China Biology Literature; CNKI, China National Knowledge Infrastructure; VIP, Chongqing VIP Chinese Science and Technology Periodical Database; PP, protein-protein interaction; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; RCT, Randomized Controlled Trial; TNF, Tumor necrosis factor; IL-1, Interleukin; NPY, Neuropeptide Y; AchE, acetylcholinesterase; ARM, association rule mining; DC, Degree Centrality; BC, Betweenness Centrality; BP, biological process; MM, molecular function; CC, cell composition.

Citation

Zhao AL, Xiao LY, Niu HY, Liu L, Dai XY. Study of the potential mechanism of acupuncture treatment for functional dyspepsia based on association rule mining and bioinformatics/network pharmacology approach. *Gastroenterol Hepatol Res*. 2023;5(2):7. doi: 10.53388/ghr2023-03-071.

Executive editor: Zi-Yao Feng.

Received: 07 June 2023; Accepted: 26 June 2023; Available online: 30 June 2023.

© 2023 By Author(s). Published by TMR Publishing Group Limited. This is an open access article under the CC-BY license. (<https://creativecommons.org/licenses/by/4.0/>)

Abstract

Objective: To explore the main acupoint prescription and mechanism of acupuncture in treating Functional dyspepsia (FD) by analyzing the clinical randomized controlled trial literature on acupoints and targets of acupuncture in the treatment of FD combined with association rule mining and bioinformatics/network pharmacology methods. **Methods:** Search relevant clinical randomized controlled trial literature on acupoints and therapeutic targets of acupuncture in the treatment of FD from eight databases from their inception to June 18th, 2022. We obtained acupuncture selection points, meridian, and therapeutic targets and established acupoints database for acupuncture treatment of FD. FD-related targets were collected from GeneCards, DisGeNET, OMIM, and DrugBank databases. We obtained the potential targets of acupuncture on FD by taking the intersection of acupuncture for FD therapeutic targets and FD-related targets. We performed the protein-protein interaction network, Gene Ontology (GO) analysis, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. **Results:** In this study, 26 Randomized Controlled Trials related to acupuncture treatment of FD were retrieved. We obtained 29 acupoints, 17 acupuncture for FD therapeutic targets, and 10 intersection targets. Tumor necrosis factor (TNF), Interleukin (IL)-1, and Neuropeptide Y (NPY) are key targets of acupuncture in the treatment of FD. **Conclusion:** ST36-CV12-PC6-LR3 is the main acupoint prescription for FD. Acupuncture may affect Neuroactive ligand-receptor interaction, Gastric acid secretion, and IL-17, TNF signaling pathways by regulating related key targets, and play a synergistic role in the treatment of FD by inhibiting gastric acid secretion, alleviating inflammatory response, regulating the brain-gut axis, improving mood and other aspects.

Keywords: acupuncture; functional dyspepsia; network acupuncture; mechanism

Introduction

Functional dyspepsia (FD) is a highly prevalent gastrointestinal disorder with one or more symptoms that can't be explained or identified by traditional diagnostic procedures, including persistent or recurrent post-prandial fullness, early satiation, epigastric pain, and burning in the epigastrium [1]. The global incidence of dyspepsia has increased rapidly at an annual rate of 1%–6% [2]. FD constitutes a major public health problem with considerable impacts on health economics and severely influences the quality of life in patients [2]. The first-line treatment of the routine western therapies [3] include gastric acid-secretion inhibitors, acetylcholinesterase (AChE) inhibitors (acotiamide, a prokinetic agent), anxiolytics /antidepressants, prokinetics (dopamine receptor antagonists, 5-HT₄ receptor agonists), etc. Although the use of gastric acid-secretion inhibitors can relieve the sensation of epigastric burning, long-term application may delay the gastric emptying rate [4]. FD drug treatment is the main means, but there are quite a number of FD patients with routine therapies that is invalid, and the long-term use of certain side effects, therefore, at the same time, need to pay attention to FD non-drug treatment [5]. Acupuncture has been widely used in China for the past 3,000 years and has been proven a valuable treatment for gastrointestinal symptoms [6]. A Systematic Review and Meta-Analysis [7] suggested that acupuncture combination with western medicine has the potential to improve the treatment of FD, and the efficacy is better than that of Western medicine alone. The mechanism of acupuncture for FD, however, remains incompletely undefined. Acupuncture involves multiple systems throughout the human body, and its therapeutic effect with multiple targets has been increasingly acknowledged [8]. In recent years, data mining has been used in acupuncture research [9]. Meanwhile, bioinformatics and network pharmacology approach have been applied to explore acupuncture mechanisms [8]. Therefore, this study intends to explore the effective acupuncture prescriptions and the main mechanism of acupuncture in the treatment of FD using association rule mining, bioinformatics, and network pharmacology approach, so as to provide the basis for the clinical treatment of FD and further explore the potential mechanism of acupuncture in the treatment of FD.

Materials and Methods

Data sources and search strategy

We comprehensively searched the eight electronic databases including PubMed, EBSCO, Cochrane Library, Web of Science, China Biology Literature (CBM), CNKI, VIP, and Wanfang Database from their inception to June 18th, 2022, for published studies on acupuncture in the treatment of FD with no language restrictions. Taking the search strategy of the Pubmed database as an example, shown in Table 1, the search strategy of other databases will be adjusted according to the characteristics of the database.

Inclusion criteria

(I) Participants: patients who met FD diagnostic criteria regardless of gender or age. (II) Interventions: acupuncture therapies alone or those combined with basic western medicine or traditional Chinese medicine were used. Acupuncture therapies included manual acupuncture, moxibustion, electroacupuncture, etc., as shown in the search strategy. Subsequently, this study referred to acupuncture as all therapies and was not subdivided unless a specific therapy was involved. (III) Comparisons: the patients were given conventional treatment, including domperidone, mosapride citrate, pantoprazole, etc. (IV) Outcomes: The outcome involved protein targets, the difference before and after protein target or within-group was statistically significant. (V) Study types: randomized controlled trials (RCTs)

Exclusion criteria

(I) Case reports, cross-sectional studies, editorials, cohort studies,

meta-analyses, animal experiments, and reviews. (II) Duplicate literature. (III) The full content is not available.

Study selection and Data extraction

Two independent investigators screened the eight databases for studies from their inception to June 18th, 2022 according to the inclusion and exclusion criteria. The investigators imported the retrieved studies into EndnoteX9 software to manage literatures and remove duplications. Two investigators completed the preliminary screening and downloaded the required literature by reviewing the title keywords and abstract. Then, we read carefully the full content to select standard literature that met the inclusion criteria. If disagreement occurred, a third investigator was invited to assess such literatures through discussion. A researcher entered the information of acupoint prescription and protein target into Microsoft Excel form to establish acupoint database for acupuncture treatment of FD.

Quality Assessment

To conduct the assessments of literature quality and risk of bias, two reviewers independently used RevMan software [10], which mainly included the generation of random sequences, allocation concealment, blinding of participants and personnel, blinding in outcome assessment, completeness of outcome data, selective reporting of research results and other sources of bias. We categorised the items as: low risk, high risk or unclear risk. All the disputes were discussed or solved by a third professional researcher.

Association rule mining

We recorded the relevant acupoints and meridians for further analysis through Microsoft Excel. Then we used SPSS Modeler 18.0 software to conduct association rule mining (ARM) of acupoints to explore the correlation between different acupoints. We proceeded by adopting the Apriori algorithm to perform quantitative analysis of the compatibility of acupoints. The strength of the association rule was measured in terms of its support, confidence, and lift [11]. The confidence was set at least 80% for ARM with 15% support in this study. It indicated that the combination of acupoints accounted for at least 15% of the total acupoint prescription, and the probability of selecting the combination of acupoints was at least 80%. In addition, Lift represents the correlation between two item sets. The higher Lift was, the higher the positive correlation was.

Network Analysis.

In the above literature search, we also obtained acupuncture for FD therapeutic targets. In order to accurately identify the potential target of acupuncture for the treatment of FD, we collected the FD-related targets, and then obtain the potential targets by taking the intersection of acupuncture for FD therapeutic targets and FD-related targets. We constructed protein-protein interaction (PPI) network and performed Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis.

Identification of FD-related targets. We collected the targets related to FD from the GeneCards database (<https://www.GeneCards.org/>), DisGeNET database (<https://www.disgenet.org/>), OMIM database (<https://www.omim.org/>) and DrugBank database (<https://go.drugbank.com/>) where Functional dyspepsia was used as the retrieval term to collect FD-related targets. Relevance score > 1 and Score GDA > 0.05 were used as criteria to screen targets more related to FD. We combined the results from the four databases and deleted the duplicates to obtain the final FD-related targets.

Collection of potential targets of acupuncture treatment on FD.

Venny 2.1 (<https://bioinfogp.cnb.csic.es/tools/venny/>) was used to analyze the intersection targets between acupuncture for FD therapeutic targets and FD-related targets while constructing Venn diagram. Then, the intersecting targets were selected as the relevant targets of acupuncture for treating FD, which might be the potential target of acupuncture for the treatment of FD.

Construction of PPI Network. The intersection targets were introduced into STRING (<https://string-db.org/>) to perform PPI

Table 1 The search strategy for Pubmed database

Number	Search terms
#1	Functional dyspepsia [Mesh]
#2	Functional dyspepsia [Title/Abstract] OR non-ulcer dyspepsia [Title/Abstract] OR indigestion [Title/Abstract]
#3	#1 OR #2
#4	Acupuncture [Mesh] OR Moxibustion [MeSH]
#5	Acupuncture [Title/Abstract] OR Moxibustion [title/abstract] OR Needle [Title/Abstract] OR Needling [Title/Abstract] OR Electroacupuncture [Title/Abstract] OR Cupping [title/abstract] OR Warm needle [title/abstract] OR Fire needle [title/abstract] OR Acupoint herbal patching [Title/Abstract]
#6	#4 OR #5
#7	Randomized controlled trial [Mesh] OR double-blind method [MeSH] OR single-blind method [MeSH]
#8	Randomized controlled trial [Title/Abstract] OR Controlled clinical trial [Title/Abstract] OR Randomized experiment [Title/Abstract] OR
#9	#7 OR #8
#10	#3 AND #6 AND #9

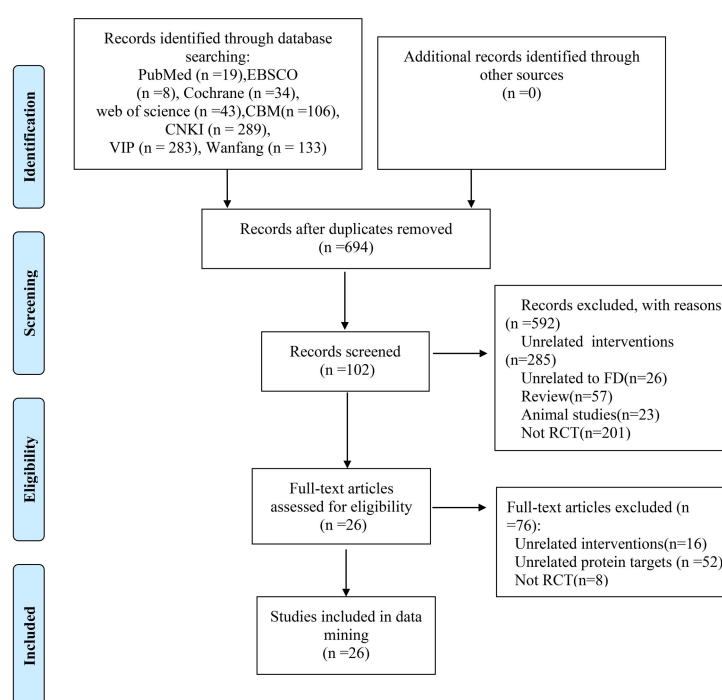


Figure 1 Flow chart of the Literature screening

analysis. Then, the PPI data was downloaded in TSV format and imported into Cytoscape 3.8.0 software. To explore the potential mechanisms of acupuncture treatment of FD, the PPI network was constructed and visualized using Cytoscape software plug-in BisoGenet [12] which included HPRD, BIND, DIP, MINT, INTACT, BIOGRID databases. The Cytoscape software plug-in CytoNCA was applied to compute the Degree Centrality, (DC) Betweenness Centrality (BC), and values of the nodes for topology analysis of the PPI network to obtain hub targets. In DC and BC values, nodes with high DC and BC were regarded as influential targets [13].

GO and KEGG Analysis. GO analysis and KEGG pathway enrichment analysis were widely used to study the features of gene, in which GO analysis included biological process (BP), molecular function (MF), and cell composition (CC). The top 10 functional categories in BP, MF, CC with $P < 0.05$ were chosen for visual presentation by R software as a histogram. The top 20 KEGG pathway enrichment analysis results with $P < 0.05$ were visualized by R software as a histogram.

Results

Description of Eligible literatures

A total of 915 literatures were collected via the initial search. 694 literatures remained after removing duplicates. We obtained 102 literatures by reading the title, keywords, and abstract and then determined the final 26 literatures by reading the full text. The details of literature screening was reported in Figure 1.

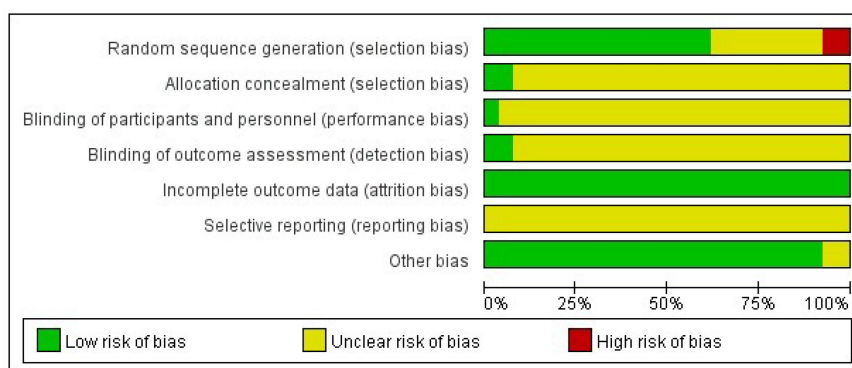
Risk of Bias Assessment

The risk of bias assessment for each study was described in Table 2. For example, 16 RCTs reported random sequence generation methods, while 8 other studies were rated as “uncertain risk” because they only mentioned “randomization” and 2 trials that did not mention “randomization” were rated as “high risk”. The risk of bias graph and risk of bias summary were shown in Figure 2 and Figure 3.

Acupoint and Meridians application analysis

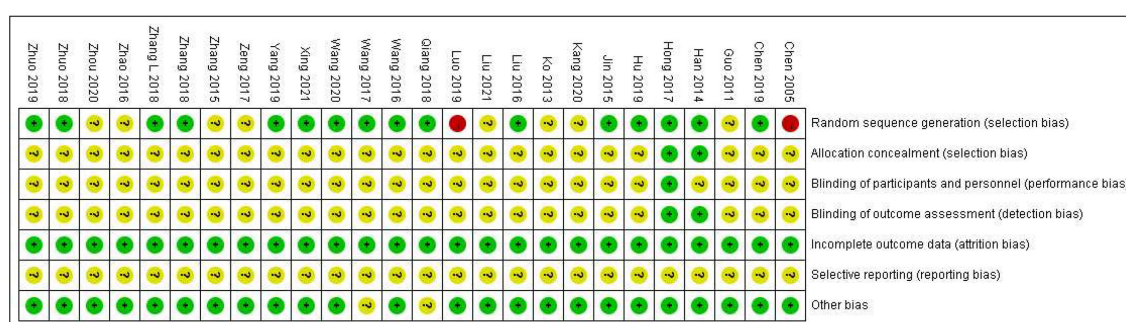
Table 2 Risk of bias of the included studies

Study	Generation of random sequences	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Liu [14] 2021	unclear risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Xing [15] 2021	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Zhou [16] 2020	unclear risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Wang [17] 2020	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Kang [18] 2020	unclear risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Zhuo [19] 2019	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Yang [20] 2019	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Luo [21] 2019	high risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Hu [22] 2019	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Chen [23] 2019	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Zhuo [24] 2018	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Zhang [25] 2018	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Zhang L [26] 2018	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Qiang [27] 2018	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Wang [28] 2017	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Zeng [29] 2017	unclear risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Hong [30] 2017	low risk	low risk	low risk	low risk	low risk	unclear risk	low risk
Zhao [31] 2016	unclear risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Wang [32] 2016	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Liu [33] 2016	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Jin [34] 2015	low risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Zhang [35] 2015	unclear risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Han [36] 2014	low risk	low risk	unclear risk	low risk	low risk	unclear risk	low risk
Xu [37] 2015	unclear risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Guo [38] 2011	unclear risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk
Chen [39] 2005	high risk	unclear risk	unclear risk	unclear risk	low risk	unclear risk	low risk



Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 2 Risk of bias graph



Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

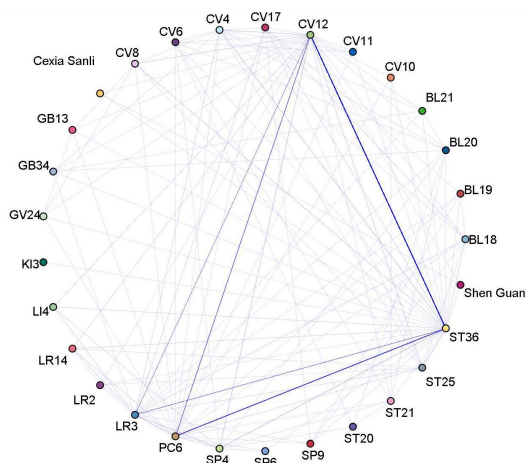
Figure 3 Risk of bias summary

Table 3 Frequency of acupoints

Number	Acupoints	Frequency	Percentage (%)
1	ST36	25	21.6
2	CV12	20	17.2
3	PC6	16	13.8
4	LR3	10	8.6
5	SP4	6	5.2
6	ST25	4	3.4
7	CV4	4	3.4
8	CV8	3	2.6
9	ST21	2	1.7
10	BL18	2	1.7
11	BL20	2	1.7
12	LR14	2	1.7
13	LI4	2	1.7
14	CV6	2	1.7
15	CV17	2	1.7
16	ST20	1	0.9
17	SP6	1	0.9
18	SP9	1	0.9
19	BL19	1	0.9
20	BL21	1	0.9

Number	Acupoints	Frequency	Percentage (%)
21	KI3	1	0.9
22	GB13	1	0.9
23	GB34	1	0.9
24	LR2	1	0.9
25	CV11	1	0.9
26	CV10	1	0.9
27	GV24	1	0.9
28	Cexia Sanli	1	0.9
29	Shen Guan	1	0.9
Total		116	100.0

Meridians	Frequency	Acupoints
Conception Vessel	33	CV12(20)、CV4(4)、CV8(3)、CV6(2)、CV17(2)、CV11(1)、CV10(1)
Stomach meridian of foot-yangming	32	ST36(25)、ST25(4)、ST21(2)、ST20(1)
Pericardium meridian of hand-jueyin	16	PC6(16)
Liver meridian of foot-jueyin	13	LR3(10)、LR14(2)、LR2(1)
Spleen meridian of foot-taiyin	8	SP4(6)、SP6(1)、SP9(1)
Bladder meridian of foot-taiyang	6	BL18(2)、BL20(2)、BL19(1)、BL21(1)
Gallbladder meridian of foot-shaoyang	2	GB13(1)、GB34(1)
Large intestine meridian of hand-yangming	2	LI4(2)
Kidney meridian of foot-shaoyin	1	KI3(1)
Governor Vessel	1	GV24(1)



There was a total of 29 acupoints, 27 of which were traditional acupoints, and 2 of which were experience acupoints that did not belong to any traditional meridians (Table 3). The top 5 points were ST36 (Zusanli), CV12 (Zhongwan), PC6 (Neiguan), LR3 (Taichong), and SP4(Gongsun). Among the 9 meridians included (Table 4), Conception Vessel and Stomach meridian of foot-yangming were most used with frequencies 33 (28.95%), 32 (28.07%) respectively, followed by Pericardium meridian of hand-jueyin with frequencies 16 (14.04%)

We analyzed the association rules of acupuncture prescriptions used in the included literature. We set parameters as support > 15%, confidence > 80%, and Lift > 1, and constructed the network (Figure

Through our literature search, 17 acupuncture for FD therapeutic targets were obtained. We identified 2244 FD-related targets via searching 4 databases and determined 10 intersectional targets by taking the intersection of the above two sets. 10 intersectional targets were taken as the potential target of acupuncture against FD (Figure 5).

To further clarify the potential mechanism of acupuncture against FD, the PPI network with 187 direct or indirect targets and 340 interrelationships were constructed (the 10 red nodes in the network were intersection targets) via Cytoscape and its plug-in BisoGenet (Figure 6(A)). We conducted topological analysis of the PPI network based on two parameters of DC and BC. Then we selected the target with DC and BC greater than the average as the hub gene. First, we screened 28 nodes ($DC > 5.34$, $BC > 421.47$) to construct the sub-network (Figure 6(B)). After the second screening, 17 nodes ($DC > 2.84$, $BC > 19.78$) were chosen to build the final network (Figure 6(C)). Through topological analyses, we obtained 17 hub genes, three of which belong to the direct potential targets of acupuncture for the treatment of FD. It indicated that tumor necrosis factor (TNF), Interleukin (IL)-1, and Neuropeptide Y (NPY) might be the most important targets for acupuncture against FD.

To investigate the biological information on acupuncture for the treatment of FD, GO and KEGG analysis of the 10 intersectional targets were performed. The GO analysis results revealed a total of 945 entries with $P < 0.05$. In BP enrichment analysis, the result revealed 919 entries, such as involving response to food, regulation of smooth

Table 5 Association rules of acupoints for FD

Number	Acupoints	Support (%)	Confidence (%)	Lift	Frequency
1	ST36、CV12	92.59	80	1.08	25
2	ST36、PC6	59.26	100	1.08	16
3	ST36、PC6、CV12	44.44	100	1.08	12
4	ST36、LR3	37.04	100	1.08	10
5	CV12、LR3	37.04	90	1.22	10
6	CV12、LR3、ST36	37.04	90	1.22	10
7	ST36、LR3、CV12	33.33	100	1.08	9
8	ST36、LR3、PC6	18.52	100	1.08	5
9	LR3、SP4、ST36	18.52	80	2.16	5
10	CV12、SP4、ST36	18.52	80	1.08	5
11	CV12、LR3、PC6	18.52	80	1.08	5

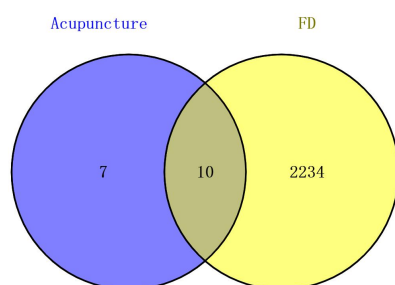


Figure 5 Venn diagram of acupuncture targets and FD targets

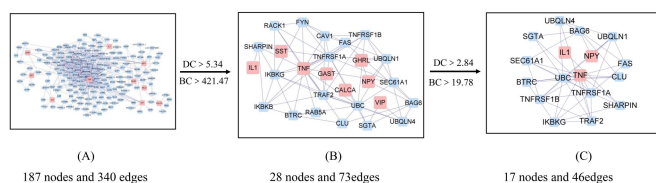


Figure 6 PPI network and topology analysis

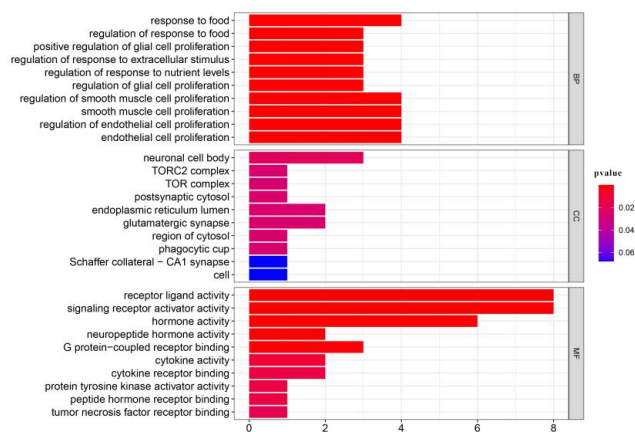


Figure 7 Bargraph of GO function analysis

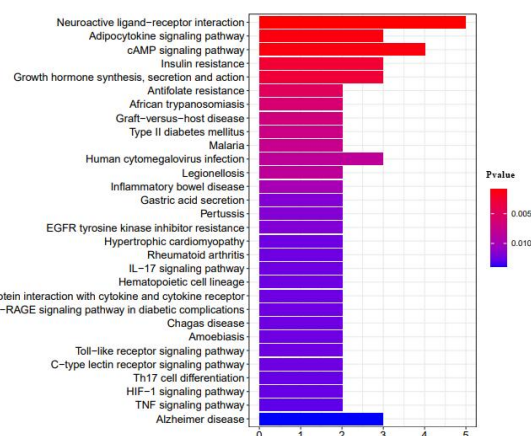


Figure 8 Bargraph of KEGG pathway enrichment analysis

muscle cell proliferation, regulation of endothelial cell proliferation, etc; In CC enrichment analysis, the result obtained 8 entries involved in neuronal cell body, endoplasmic reticulum lumen, glutamatergic synapse, etc; In MF enrichment analysis, the result obtained 18 entries enriched in receptor ligand activity, hormone activity, G protein-coupled receptor binding, etc. The top 10 terms (BP, CC, MF) were visualized in Figure 7 respectively. The KEGG analysis results revealed a total of 58 entries with $P < 0.05$. The top 30 significant pathways of KEGG analysis were shown in Figure 8. Among these pathways, Neuroactive ligand-receptor interaction, Gastric acid secretion, TNF signaling pathway may be involved in acupuncture for the treatment of FD.

Discussion

FD is a prevalent and complex symptom that arises in gastrointestinal tract, and its pathophysiology has not been fully clarified. It is generally agreed that the disordered communication between the gut and the brain is involved in the pathogenesis of FD, resulting in visceral hypersensitivity, motility disturbances, mucosal and immune function, alterations in gastrointestinal microbiota, and central nervous system processing [40]. Studies [41, 42] found that FD patients had low-grade inflammation, manifesting itself in mucosal mast cells and eosinophils infiltration increases, and the extent of the mucous membrane permeability increased and significant correlation between the severity of low-grade inflammation. The gut-brain axis is closely related to FD and is often bidirectionally regulated. The disorders of the immune system and gastrointestinal microbiota in FD can regulate gut-brain communication through the hypothalamus-pituitary-adrenal axis [40]. In addition, a variety of brain gut peptides regulate gastrointestinal contractility and modify gastrointestinal function [43]. Also worth mentioning is mental stress affecting gastrointestinal function through the gut-brain axis [44].

In this study, the acupoint prescription of acupuncture treatment of FD was explored through association rule analysis. ST36, CV12, PC6, LR3, and SP4 were used most often. The strong association rules of the top 5 were ST36-CV12, ST36-PC6, ST36-PC6-CV12, ST36-LR3, CV12-LR3. As indicated, the main acupoint prescription for FD was ST36-PC6-CV12-LR3. ST36, PC6, CV12, and LR3 have been reported to effectively improve the symptoms and quality of life of FD patients [33, 45] and their efficacy has been recognized by clinicians. A study [46] has shown that electroacupuncture at both ST36 and CV12 or at CV12 alone was effective in treating rapid gastric emptying. Acupuncture at PC6 could effectively improve gastric motility, promote motilin secretion and reduce visceral sensitivity [47].

In this study, we identified final a total of 26 RCTs and 10 intersection targets that were associated with FD and regulated by

acupuncture stimulation. The PPI network and topological analysis were performed to identify the hub targets. Through topological analysis, TNF, IL-1, and NPY were established as the most important targets for acupuncture against FD. TNF acts as a proinflammatory mediator stimulates the recruitment of inflammatory cells to the site of infection, which induces local inflammation. Anti-TNF therapy [48] is a new method, which can inhibit cytokines including the production of TNF and IL-1 β , preventing pro-inflammatory signal transduction, alleviating inflammation. IL-1 is a pro-inflammatory cytokine and comprises two distinct proteins, IL-1 α and IL-1 β [49]. IL-1 β and TNF- α , as classical pro-inflammatory factors, play an important role in mediating the immune response to chronic inflammation of the gastrointestinal tract [50]. NPY is recognized as an important gastrointestinal hormones for regulating food intake, gastric acid secretion, gastrointestinal motility, and exocrine function of the pancreas [51]. Notably, NPY has anti-anxiety effect [52].

The targets of acupuncture against FD were enriched in BP, CC, and MF through GO analysis. The result of BP suggested that acupuncture mainly regulated response to food, the regulation of response to nutrition level, the regulation of smooth muscle cell proliferation. Furthermore, it was shown to affect some CC and MF including neuronal cell body, receptor ligand activity and hormone activity. In the present study, 58 KEGG pathways including Neuroactive ligand-receptor interaction, Gastric acid secretion, TNF signaling pathway were significantly enriched. Receptor genes for Neuroactive ligand-receptor interaction are GHRL, MLN, NPY, SST, VIP. GHRL, MLN, SST and VIP are popular brain-gut peptides, which can regulate gastrointestinal motility and appetite control in FD patients [53]. FD patients on an empty stomach in the abdominal discomfort or pain, reduce after eating and acid treatment effective suppression prompt symptoms associated with gastric acid secretion [54]. KEGG results suggest that acupuncture may improve clinical acid-related symptoms by regulating gastric acid secretion. IL-17, one of the cytokines secreted by Th17 cells induces the production of a vast number of various inflammatory cytokines such as TNF- α and IL-1 β , inducing inflammation [55].

Conclusions

Based on data mining, our study revealed the main acupoint prescription was ST36-CV12-PC6-LR3. We systematically elucidated the mechanisms of acupuncture against FD via bioinformatics/network pharmacology approach. The hub target proteins are TNF, IL-1 and NPY. By participating in the regulation of response to food, hormone activity, cytokine activity and other responses. Through Neuroactive ligand-receptor interaction, gastric acid secretion, TNF signaling pathway, inhibiting gastric acid secretion, reducing inflammation, regulating brain-gut axis, improving mood, thus playing a therapeutic role.

Limitations

The quality of the original literature included in this study was not high, which had a certain impact on the data quality of this study. For accurate analysis, the target of the included literature was intersected with the FD-related target in the database to ensure the reliability of the conclusion, to the greatest extent. But there are still many unknown targets that need further study. This study provides a theoretical basis for further research on the mechanism of acupuncture treatment of FD. Despite the encouraging results, more rigorously designed clinical and basic studies are needed to further confirm the current findings.

References

1. Stanghellini V, Chan FKL, Hasler WL, et al. Gastrointestinal Disorders. *Gastroenterol* 2016;150(6):1380–92. Available at: <http://doi.org/10.1053/j.gastro.2016.02.011>
2. Tack J, Talley NJ. Functional dyspepsia—symptoms, definitions

- and validity of the Rome III criteria. *Nat Rev Gastroenterol Hepatol* 2013;10(3):134–41. Available at: <http://doi.org/10.1038/nrgastro.2013.14>
3. Miwa H, Nagahara A, Asakawa A, et al. Evidence-based clinical practice guidelines for functional dyspepsia 2021. *J Gastroenterol* 2022;57(2):47–61. Available at: <http://doi.org/10.1007/s00535-021-01843-7>
4. TOUGAS G, EARNEST DL, CHEN Y, VANDERKOY C, ROJAVIN M. Omeprazole delays gastric emptying in healthy volunteers: an effect prevented by tegaserod. *Aliment Pharmacol Ther* 2005;22(1):59–65. Available at: <http://doi.org/10.1111/j.1365-2036.2005.02528.x>
5. Zhu Y, Sun C, Chen J, et al. Research progress in pathogenesis and treatment of functional dyspepsia. *Chin J Dig Med Imageolog* 2020;10(6):272–278. Available at: <http://doi.org/10.3877/cma.j.issn.2095-2015.2020.06.008>
6. Zhang R, Lao L, Ren K, Berman BM. Mechanisms of Acupuncture–Electroacupuncture on Persistent Pain. *Anesthesiology* 2014;120(2):482–503. Available at: <http://doi.org/10.1097/ALN.0000000000000101>
7. Kwon C-Y, Ko S-J, Lee B, Cha JM, Yoon JY, Park J-W. Acupuncture as an Add-On Treatment for Functional Dyspepsia: A Systematic Review and Meta-Analysis. *Front Med* 2021;8. Available at: <http://doi.org/10.3389/fmed.2021.682783>
8. Han Z, Zhang Y, Wang P, Tang Q, Zhang K. Is acupuncture effective in the treatment of COVID-19 related symptoms? Based on bioinformatics/network topology strategy. *Brief Bioinform* 2021;22(5). Available at: <http://doi.org/10.1093/bib/bbab110>
9. Yu J, Jiang Y, Tu M, Liao B, Fang J. Investigating Prescriptions and Mechanisms of Acupuncture for Chronic Stable Angina Pectoris: An Association Rule Mining and Network Analysis Study. *Evidence-Based Complementary Altern Med* 2020;2020:1–11. Available at: <http://doi.org/10.1155/2020/1931839>
10. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343(oct182):d5928–d5928. Available at: <http://doi.org/10.1136/bmj.d5928>
11. Zheng W, Wu J, Gu J, et al. Modular Characteristics and Mechanism of Action of Herbs for Endometriosis Treatment in Chinese Medicine: A Data Mining and Network Pharmacology–Based Identification. *Front Pharmacol* 2020;11. Available at: <http://doi.org/10.3389/fphar.2020.00147>
12. Miryala SK, Anbarasu A, Ramaiah S. Discerning molecular interactions: A comprehensive review on biomolecular interaction databases and network analysis tools. *Gene* 2018;642:84–94. Available at: <http://doi.org/10.1016/j.gene.2017.11.028>
13. Liu W, Fan Y, Tian C, et al. Deciphering the Molecular Targets and Mechanisms of HGWD in the Treatment of Rheumatoid Arthritis via Network Pharmacology and Molecular Docking. *Evid Based Complement Alternat Med* 2020;2020:1–13. Available at: <http://doi.org/10.1155/2020/7151634>
14. Liu J, Du W, Chi X. Clinical Study on Warm Needling plus Xiang Sha Liu Jun Decoction for Functional Dyspepsia. *Shanghai J Acupunct Moxibust* 2021;40(4):394–399. Available at: <http://doi.org/10.13460/j.issn.1005-0957.2021.04.0394>
15. Xing F. Observation on Therapeutic Effect of Stomach Three-Needle Acupuncture Combined with Jianweishu Granule on Functional Dyspepsia of Spleen Deficiency and Qi Stagnation Type. *Liaoning J Tradit Chin Med* 2021;48(3):169–171. Available at: <http://doi.org/10.13192/j.issn.1000-1719.2021.03.047>
16. Zhou L, Wang D, Pan X, et al. Clinical effect of electroacupuncture in treating functional dyspepsia of liver and

- stomach disharmony syndrome and its effect on GAS and MTL. *J Practical Med* 2020;36(4):538–542. Available at: <http://doi.org/10.3969/j.issn.1006-5725.2020.04.024>
17. Wang J, Jiang B, Zhen Q. Effect of Shugan Hewei Needle Point Method Combined with Chinese Herb Medicine Acupoint Application on Traditional Chinese Medicine Syndromes Scores and Gastric Motility for Patients with Functional Dyspepsia. *J Sichuan Tradit Chin Med* 2020;38(06):188–191. Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLtIOAiTRKibYIV5Vjs7i0-kJR0HYBJ80QN9L51zrP5DD1vcEesrgdu3_piWU1rszh0VtLB0VDiHMRzqBE4yx&uniplatform=NZKPT
 18. Kang N, Ma W, Hong Y. Clinical Study on Chinese Medicine External Therapy for Functional Dyspepsia Overlapping with Diarrhea-predominant Irritable Bowel Syndrome of Deficiency Cold Type. *New Chin Med* 2020;52(05):81–83. Available at: <http://doi.org/10.13457/j.cnki.jncm.2020.05.024>
 19. Zhuo Z, Zhou D, Zhu L, et al. Effect of acupuncture and moxibustion on serum endothelin and HSP protein in patients with functional dyspepsia of Liver Stagnation and spleen deficiency. *Cardiovasc Dis Electron J Int Tradit Chin West Med* 2019;7(17):166–167. Available at: <http://doi.org/10.16282/j.cnki.cn11-9336/r.2019.17.133>
 20. Yang Y, Zhen W, Ma S, et al. Therapeutic effect of acupuncture combined with traditional Chinese medicine on children with functional dyspepsia. *J Xinjiang Med Univ* 2019;42(11):1474–1477. Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLtIOAiTRKibYIV5Vjs7i0-kJR0HYBJ80QN9L51zrP5DD1vcEesrgdu3_piWU1rszh0VtLB0VDiHMRzqBE4yx&uniplatform=NZKPT
 21. Luo Q. Clinical Observation of Acupuncture plus Chinese Medication for Functional Dyspepsia. *Shanghai J Acupunct Moxibust* 2019;38(2):151–155. Available at: <http://doi.org/10.13460/j.issn.1005-0957.2019.02.0151>
 22. Hu J, Jin R, Ye F. Observation on the curative effect of acupoint application combined with thunder fire moxibustion in the treatment of functional dyspepsia and its effect on serum PGI, PGI₂ and G-17. *Chin J Tradit Med Sci Technol* 2019;26(5):706–708. Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLtIOAiTRKibYIV5Vjs7i0-kJR0HYBJ80QN9L51zrP5DD1vcEesrgdu3_piWU1rszh0VtLB0VDiHMRzqBE4yx&uniplatform=NZKPT
 23. Chen F, Mu Y, Xu T, et al. Buqi Xiaopi Acupuncture Method in Treating Functional Dyspepsia and Effect on Serum Gastric Hormones. *J Shandong Univ Tradit Chin Med* 2019;43(6):577–580. Available at: <http://doi.org/10.16294/j.cnki.1007-659x.2019.06.011>
 24. Zhuo Z. Clinical effect of acupuncture on functional dyspepsia. *Chin J Mod Drug App* 2018;12(21):37–38. Available at: <http://doi.org/10.14164/j.cnki.cn11-5581/r.2018.21.019>
 25. Zhang W, Chen Y. Effect of Acupuncture on Psychological Factors and Serum Ghrelin Levels in Patients with Functional Dyspepsia. *Shanghai J Acupunct* 2018;37(01):37–41. Available at: <http://doi.org/10.13460/j.issn.1005-0957.2018.01.0037>
 26. Zhang L, Li XJ, Ma J, et al. Clinical effect of acupuncture combined with ShisanweiHezhongwan in the treatment of functional dyspepsia of hepatogastric disharmony type. *Chin J Int Tradit West Med Digest* 2018;26(10):834–839. Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLtIOAiTRKibYIV5Vjs7i0-kJR0HYBJ80QN9L51zrP3WPgQihSby t_jOjwBqD022T8xBFj-Hp3fmr5C_C5y1&uniplatform=NZKPT
 27. QIANG L, JIANG Y. Electroacupuncture for functional dyspepsia and the influence on serum Ghrelin, CGRP and GLP-1 levels. *World J Acupunct-Moxibust* 2018;28(2):86–90. Available at: <http://doi.org/10.1016/j.wjam.2018.06.004>
 28. Wang G. Clinical Observation of 62 Cases of Functional Dyspepsia Treated by Acupuncture and Moxibustion. *Mod Diagn Treat* 2017;28(20):3771–3773. Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLtIOAiTRKibYIV5Vjs7i0-kJR0HYBJ80QN9L51zrP5DD1vcEesrgdu3_piWU1rszh0VtLB0VDiHMRzqBE4yx&uniplatform=NZKPT
 29. Zeng L, Tuo L. Effect of Acupuncture on Dyspepsia with Sleep Disorders. *Liaoning J Tradit Chin Med* 2017;44(2):359–361. Available at: <http://doi.org/10.13192/j.issn.1000-1719.2017.02.048>
 30. Hong S, Ding S, Wu F, et al. Efficacy and safety of manual acupuncture manipulations with different frequencies on epigastric pain syndrome (EPS) in functional dyspepsia (FD) patients: study protocol for a randomized controlled trial. *Trials* 2017;18(1). Available at: <http://doi.org/10.1186/s13063-017-1845-3>
 31. Zhao Y. Clinical observation of Mosapride Citrate Tablets combined with acupuncture on the treatment of functional dyspepsia. *Hebei J Tradit Chin Med* 2016;38(7):1046–1050. Available at: <http://doi.org/10.3969/j.issn.1002-2619.2016.07.023>
 32. Wang S, Xu Y, Gao Y, et al. Observations on the Efficacy of Heat-sensitive Point Moxibustion in Treating Functional Dyspepsia. *Shanghai J Acupunct Moxibust* 2016;35(05):538–540. Available at: <http://doi.org/10.13460/j.issn.1005-0957.2016.05.0538>
 33. Liu WR. Effect of acupuncture on functional dyspepsia caused by Liver Qi and stomach syndrome and its effect on serum ghrelin. *Chin J Tradit Med Sci Technol* 2016;23(01):69–70. Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLtIOAiTRKibYIV5Vjs7i0-kJR0HYBJ80QN9L51zrP5DD1vcEesrgdu3_piWU1rszh0VtLB0VDiHMRzqBE4yx&uniplatform=NZKPT
 34. Jin Y, Zhao Q, Zhou K, et al. Acupuncture for Functional Dyspepsia: A Single Blinded, Randomized, Controlled Trial. *Evid Based Complement Alternat Med* 2015;2015:1–9. Available at: <http://doi.org/10.1155/2015/904926>
 35. Zhang C, Guo L. Dalitong Granule combined with electroacupuncture in the treatment of functional dyspepsia: A randomized controlled trial. *Chin J Integr Med* 2015;21(10):743–750. Available at: <http://doi.org/10.1007/s11655-015-2175-5>
 36. Han G, Ko SJ, Park JW, et al. Acupuncture for functional dyspepsia: study protocol for a two-center, randomized controlled trial. *Trials* 2014;15(1). Available at: <http://doi.org/10.1186/1745-6215-15-89>
 37. Xu F, Tan Y, Huang Z, et al. Ameliorating Effect of Transcutaneous Electroacupuncture on Impaired Gastric Accommodation in Patients with Postprandial Distress Syndrome-Predominant Functional Dyspepsia: A Pilot Study. *Evid Based Complement Alternat Med* 2015;2015:168252. Available at: <http://doi.org/10.1155/2015/168252>
 38. Guo LK, Zhang CX, Guo XF. Long-term efficacy and safety research on functional dyspepsia treated with electroacupuncture and ZhizhuKuanzhong capsule. *Chin Acupunct Moxibust* 2011;31(12):1071–1077. Available at: <http://doi.org/10.13703/j.0255-2930.2011.12.007>
 39. Chen J, Pan F, Xu J. Effects of Acupuncture on the Gastric Motility in Patients with Functional Dyspepsia. *Chin J Int Tradit West Med* 2005;10(10):880–882. Available at: <http://doi.org/10.7661/CJIM.2005.10.880>
 40. Ford AC, Mahadeva S, Carbone MF, Lacy BE, Talley NJ. Functional dyspepsia. *The Lancet* 2020;396(10263):1689–1702. Available at: [http://doi.org/10.1016/S0140-6736\(20\)30469-4](http://doi.org/10.1016/S0140-6736(20)30469-4)
 41. Vanheel H, Vicario M, Vanuytsel T, et al. Impaired duodenal mucosal integrity and low-grade inflammation in functional dyspepsia. *Gut* 2013;63(2):262–271. Available at: <http://doi.org/10.1136/gutjnl-2012-303857>

42. Walker MM, Aggarwal KR, Shim LS, et al. Duodenal eosinophilia and early satiety in functional dyspepsia: Confirmation of a positive association in an Australian cohort. *J Gastroenterol Hepatol* 2014;29(3):474–479. Available at: <http://doi.org/10.1111/jgh.12419>
43. Jiang S-M. Beneficial effects of antidepressant mirtazapine in functional dyspepsia patients with weight loss. *World J Gastroenterol* 2016;22(22):5260. Available at: <http://doi.org/10.3748/wjg.v22.i22.5260>
44. Padhy SK, Sahoo S, Mahajan S, Sinha SK. Irritable bowel syndrome: Is it “irritable brain” or “irritable bowel”? *J Neurosci Rural Pract* 2015;06(04):568–577. Available at: <http://doi.org/10.4103/0976-3147.169802>
45. Ma TT, Yu SY, Li Y, et al. Randomised clinical trial: an assessment of acupuncture on specific meridian or specific acupoint vs. sham acupuncture for treating functional dyspepsia. *Aliment Pharmacol Ther* 2012;35(05):552–561. Available at: <http://doi.org/10.1111/j.1365-2036.2011.04979.x>
46. Yue G, Yuan X, Ge X, et al. Effect of electroacupuncture at different acupoints in treating rapid gastric emptying: Zusanli (ST36) plus Zhongwan (CV12) versus Zhongwan (CV12) alone. *J Tradit Chin Med* 2021;41(2):326–330. Available at: <http://doi.org/10.19852/j.cnki.jtcm.2021.02.010>
47. Hong F. Therapeutic effect of electroacupuncture on functional dyspepsia at SP4 and PC6 points. *Shanghai J Acupunct Moxibust* 2016;35(01):38–40. Available at: <http://doi.org/10.13460/j.issn.1005-0957.2016.01.0038>
48. Berns M, Hommes DW. Anti-TNF- α therapies for the treatment of Crohn's disease: the past, present and future. *Expert Opin Invest Drugs* 2016;25(2):129–143. Available at: <http://doi.org/10.1517/13543784.2016.1126247>
49. Israel LP, Benharoch D, Gopas J, Goldbart AD. A Pro-Inflammatory Role for Nuclear Factor Kappa B in Childhood Obstructive Sleep Apnea Syndrome. *Sleep* 2013;36(12):1947–1955. Available at: <http://doi.org/10.5665/sleep.3236>
50. TAHARA T, SHIBATA T, OKUBO M, et al. Association between interleukin-1 β and tumor necrosis factor- α polymorphisms and symptoms of dyspepsia. *Mol Med Rep* 2015;11(5):3888–3893. Available at: <http://doi.org/10.3892/mmr.2015.3163>
51. Palus K, Całka J. Neurochemical Plasticity of the Coeliac-Superior Mesenteric Ganglion Complex Neurons Projecting to the Prepyloric Area of the Porcine Stomach following Hyperacidity. *Neural Plast* 2016;2016:1–9. Available at: <http://doi.org/10.1155/2016/8596214>
52. Zhou Z, Zhu G, Hariri AR, et al. Genetic variation in human NPY expression affects stress response and emotion. *Nat* 2008;452(7190):997–1001. Available at: <http://doi.org/10.1038/nature06858>
53. He LP, Mao H. Research progress of brain-gut peptide in functional dyspepsia. *Int J Dig Dis* 2013;33(05):315–318. Available at: <https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLtIOAiTRKgchrJ08w1e7xAZywCwkEEKhEZY-fSEsJ35CaBUh6fNrDx1oaTVvPz20m1YFeHENDR1GhocdTk0a&uniplatform=NZKPT>
54. Ke MY. Diagnosis and treatment of dyspepsia in China (2007 Dalian). *Chin J Gastroenterol* 2008;13(02):114–117. Available at: <https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLtIOAiTRKgchrJ08w1e7VSL-HJEdEx3ZyPRqZSipdNt3VUwy8vKrXVN59HTehv4Ick7zSa8U9H5oiNww9LXS&uniplatform=NZKPT>
55. Quintana FJ, Basso AS, Iglesias AH, et al. Control of Treg and TH17 cell differentiation by the aryl hydrocarbon receptor. *Nat* 2008;453(7191):65–71. Available at: <http://doi.org/10.1038/nature06880>