Association of Acupuncture with Vagus Nerve: A Bibliometric Analysis

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Abstract

Background: The vagus nerve serves as a critical conduit between the central nervous system and visceral organs, integrating sensory inputs, maintaining physiological homeostasis, and playing a role in the pathogenesis and treatment of various disorders. Recent years have witnessed growing interest in the clinical and mechanistic aspects of acupuncture and acupressure in modulating vagal activity.

Objective: This study aimed to conduct a bibliometric visualization analysis to outline the evolution, current landscape, research hotspots, and emerging trends in studies on the association of acupuncture with the vagus nerve, thereby offering insights for future investigations.

Methods: We retrieved publications from the Web of Science core database from its inception until April 6, 2024. Using CiteSpace, we analyzed publication outputs, authorship, institutional and national contributions, journal and subject distributions, co-citation networks, and keyword trends.

Results: Research in this field commenced in 1991 and has exhibited a fluctuating yet overall upward trajectory. China leads in publication volume, followed by the United States, with prominent institutions predominantly located in China. The research demonstrates strong interdisciplinary characteristics, particularly integrating complementary and Western medicine. Current hotspots focus on mechanisms and therapeutic applications related to inflammation, gastrointestinal motility, pain management, and depression.

Conclusion: Acupuncture-mediated vagus nerve regulation represents a promising area of research. Future efforts should prioritize elucidating underlying mechanisms, refining acupuncture protocols, and fostering international collaboration to advance the field.

Keywords: Acupuncture; Vagus nerve; CiteSpace; Visual analysis

The vagus nerve is the tenth pair of cranial nerves in the human body and is also the longest nerve[1]. It distributes to organs such as the heart, lungs, esophagus, stomach, intestines, liver, pancreas, and kidneys, with its terminal branches extending as far as the distal one-third of the colon. As a major component of the parasympathetic nervous system, it contains four types of fibers: somatic motor, visceral motor, visceral sensory, and somatic sensory. Together with the sympathetic nervous system, it participates in regulating and influencing the transmission of information and physiological states between the brain and the body[2].Unlike the sympathetic

nervous system, which mobilizes organ potential to help the body adapt to drastic changes in the environment, the primary function of the vagus nerve is to protect the body, promote digestion, and store energy to maintain physiological balance in a state of rest. Its most important role is to transmit information from the visceral organs (such as the intestines, liver, heart, and lungs) to the brain.Afferent fibers of the vagus nerve are integrated at the level of the nucleus of the solitary tract within the brainstem, and then project to other parts of the central nervous system (including the parabranchial nucleus, the dorsal raphe nucleus, the locus coeruleus, the hypothalamus, the thalamus, the amygdala, and the hippocampus)[3,4]. Recent studies indicate that the vagus nerve serves as a crucial link through which the brain perceives the body's immune responses[5].A substantial body of high-quality clinical evidence demonstrates that vagus nerve stimulation is an effective method for treating various diseases, including Alzheimer's disease, Parkinson's disease, depression, stroke, tinnitus, arrhythmias, heart failure, myocardial infarction, obesity, etc[6-19].

Acupuncture and Acupressure is a non-pharmacological therapy originating from China, which refers to the specific process of treating diseases through the insertion of needles and the pressing of acupuncture points on the body[20,21]. Acupuncture and acupressure, as ancient therapies, have been extensively validated by clinical research as effective methods for treating various conditions, including stress urinary incontinence, migraines, epilepsy, angina, cancer-related pain, urticaria, postoperative bowel obstruction, constipation, and substance addiction[22-33]. The therapeutic effects of Acupuncture and Acupressure exhibit characteristics that are multi-systematic, multi-faceted, multi-step, multi-level, and multi-targeted[34], Among them, the activation of the vagus nerve is an important mechanism of effect. Current clinical and basic experimental research indicates that Acupuncture and Acupressure can exert their effects by modulating the function of the vagus nerve. An article published in Nature in 2021 indicated that electroacupuncture can activate the vagus nerve-adrenal axis through the key nerve fibers $NEFH^{high}PROKR2^{adv}$ to exert systemic anti-inflammatory effects[35]. Research published in the same year indicates that electroacupuncture can inhibit GABAA receptors in DMV neurons, activating the vagus nerve-α7nAChR-mediated JAK2/STAT3 signaling pathway to suppress inflammatory responses[36]. In myocardial ischemia-reperfusion injury, electroacupuncture alleviates inflammation and myocardial damage by activating the vagus nerve-α7nAChR pathway to inhibit the release of HMGB1 from myocardial cells[37].

CiteSpace software is an emerging research tool widely used for bibliometric analysis. It visualizes the textual data of literature by drawing scientific knowledge maps, exploring and organizing the research hotspots, cutting-edge themes, and their evolutionary trends in specific disciplines or fields, providing a necessary analytical foundation for academic research[38,39]. Currently, research has explored the role of the vagus nerve in Acupuncture and Acupressure from the perspective of individual literature review, including its effects on the treatment of inflammation, infectious diseases, gastrointestinal disorders, and neuropsychiatric diseases[40-43]. However, currently there is no research that elucidates the relationship between Acupuncture and Acupressure and the vagus nerve from the perspective of macro scientific literature metrics and the visualization of knowledge graphs. Therefore, this study systematically reviews the research literature related to Acupuncture and Acupressure in connection with the vagus nerve using CiteSpace software[44]. This analysis examines multiple dimensions including authors, countries, institutions, journals, subject classifications, highly cited papers, and keywords, aiming to explore the current research status, areas of focus, and future development trends. It is intended to provide valuable reference and guidance for the clinical applications and further research of Acupuncture and Acupressure related to vagus nerve studies in the future.

1. Information and methodology

1.1 Literature search

Data source: Web of Science (WOS-E) Core Collection database Acupuncture and Acupressure and vagus nerve related literature. Search terms: Acupuncture Therapy, Acupuncture treatment, Acupotomy, Acupuncture, Electroacupuncture, Moxibustion, Acupuncture, Aear, Acupuncture, auricular, Manual Acupuncture, Acupoint, Acupuncture Point, Acupoint Massage, Acupuncture Massage, Acupuncture Massage, Acupressure, Transcutaneous Electrical Acupoint Stimulation, TEAS, Transcutaneous Auricular Vagus Nerve Stimulation, Vagus Nerve, Nerve, Vagus Nerve, Vagus Nerve, Vagus Nerve, Vagus Nerve, Vagus Nerve, Vagus Nerve, Vagus Nerve, Vagus Nerve, Cranial Nerve, Vagus Nerve Tracheal Nerve, Tracheogastric Nerve, Tenth Cranial Nerve, Vagus Nerve, Vagus Nerve Literature Type: article and review; Index=SCIEXPANED; Time Span =1991 to 2024, Retrieval Date: 6/4/2024.

1.2 Literature inclusion and exclusion criteria

Inclusion Criteria: ① The content of the literature was clearly the study of the relationship between Acupuncture and Acupressure and the vagus nerve; ② The language was English; ③ The literature information was complete and the full text was available, such as information about the country, the research organization, and the authors.

Exclusion criteria: ① other types of literature, such as conference papers, books, minutes, news reports (interviews), notices and messages, etc.; ② duplicated publications, only one with the most recent year of publication and more complete information was included; ③ withdrawn literature, inaccessible full text and incomplete data.

1.3 Literature Screening

Literature was screened independently by two researchers, and any disagreement was resolved through consultation and discussion. A total of 675 articles were excluded from the search, including duplicate publications, incomplete information and low quality literature, as well as conference papers, books, proceedings, news reports (interviews), notices and news, and retractions; 223 articles not related to the research topic of "Acupuncture and Acupressure and the Vagus Nerve" were excluded from the search through the reading of abstracts and the full-text content of the articles; and 223 articles were confirmed not to be duplicates through the de-duplication function of CiteSpace. By reading the abstracts and full-text content of the articles, we eliminated 223 articles that were not related to the research topic of "Acupuncture and Acupressure and Vagus Nerve"; then we confirmed that there were no duplicates by using the de-duplication function of CiteSpace, and finally we obtained 269 articles related to the research on the relationship between the vagus nerve and acupuncture.

1.4 Methods

In this study, the full records of retrieved data and cited references were exported in plain text format, saved as "download_.txt", processed by CiteSpace (version advanced 6.1.R6) software, and analyzed for relevant information. The time period was adjusted to 1991-2024, and the corresponding time partition was adjusted to 5a, based on "authors", "co-cited authors", "country", "Institution", "Keyword Co-occurrence", "Journal Co-citation" and "Literature Co-citation". The knowledge maps and tables were drawn and analyzed.

2. Results

2.1 Analysis of the literature situation and number of publications

Based on the search results of the WOS Core Collection, a total of 269 research papers on Acupuncture and Acupressure related to the vagus nerve were obtained. The studies in this field exhibited a large span in time distribution, with an overall trend of significant fluctuating growth (Figure 1).

It can be divided into the following two phases: the first phase was 1991-2006, during which little progress was made in the research of Acupuncture and Acupressure related to the vagus nerve. Since 1991, no more than three articles have been published each year, reflecting the fact that although research in this field started early, it has received little academic attention and is in the embryonic stage of exploration. In the second phase, from 2007 to 2023, the number of articles published in this field fluctuates but shows an upward trend, and reaches a peak in 2023 (34 articles) , which signifies that the research intensity in this field continues to increase. It predicts that the research related to vagus nerve in the field of Acupuncture and Acupressure has gradually matured and still has great potential for future development in a fluctuating upward period. Since the time search was limited to 2024-04-06, the statistics for 2024 are not yet complete.

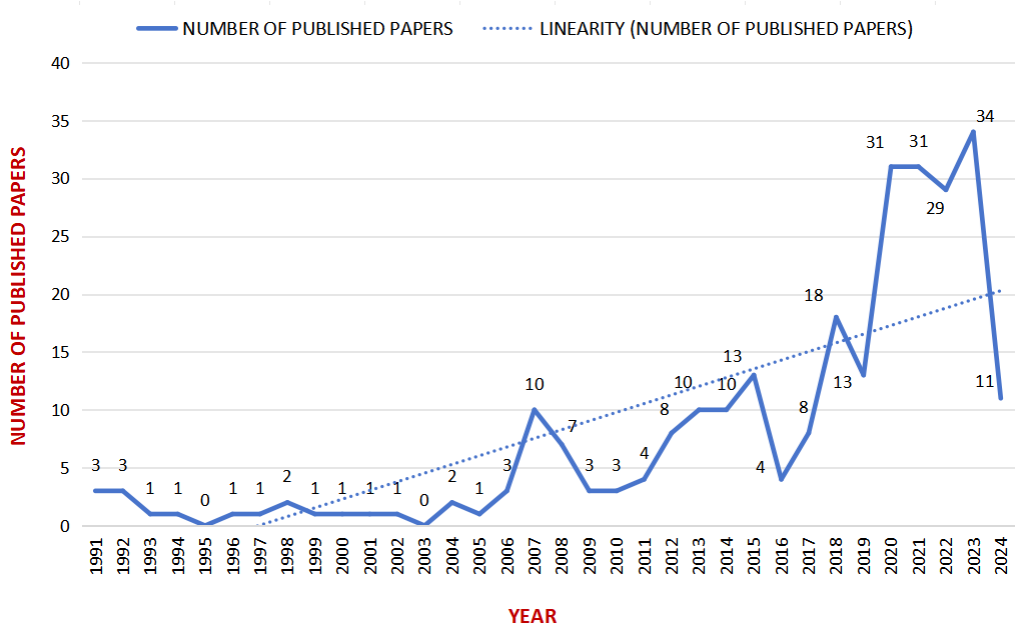

Figure 1. Trends in Literature Publication in the Field of Acupuncture and Vagus Nerve Research

2.2 Author postings and visualization analysis

As a powerful tool, author visualization mapping can dig deeper into the multiple connections between authors, including author publications, collaborations, and co-citation relationships, visualizing the impact of the research team, information about potential collaborators, and thus helping scholars to build closer collaborative relationships.

Using "Author" as the node and the threshold value set to TOP=50, we obtained a collaborative map of authors who published articles related to the vagus nerve in the field of Acupuncture and Acupressure (Figure 2) . Among them, N represents the nodes appearing, each node represents an author, the size of the node is proportional to the amount of articles published by the author, the color of the node indicates the year of the author's publication, and the line between the nodes indicates that there is a collaborative relationship between the authors, and the thicker the line means that authors collaborate with each other more frequently. The core authors with more than 10 publications are Rong, Beijing (18) , Wang, Yu (16) , Chen, Jiande D Z (13) and Zhu, Bing (10) (Table 1) . In

terms of the collaborative relationship (see Figure 2), the overall presentation was characterized by multi-team collaboration, with a core research team formed around four core authors, while presenting the status quo of the development of multiple small collaborative networks.

Author co-citation map (Figure 3) is a statistical data based on the number of citations of their published articles, which can accurately reflect the academic status of the author in this field. The higher the number of citations, the higher the centrality of the article, indicating that the author has more influence in the field. The top 3 total citations were HE W (45 times) , PEUKER ET (43 times) and BOROVIKOVA LV (40 times) . Among them, BOROVIKOVA LV is at the forefront in the citation frequency and centrality of published literature (see Table 2) , and is a representative figure with significant influence in this research field. BOROVIKOVA LV's Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin published in May 2002 has been cited 3574 times, It indicates that the mechanism of vagus nerve in reducing inflammatory response is the basis and direction of subsequent research[45].

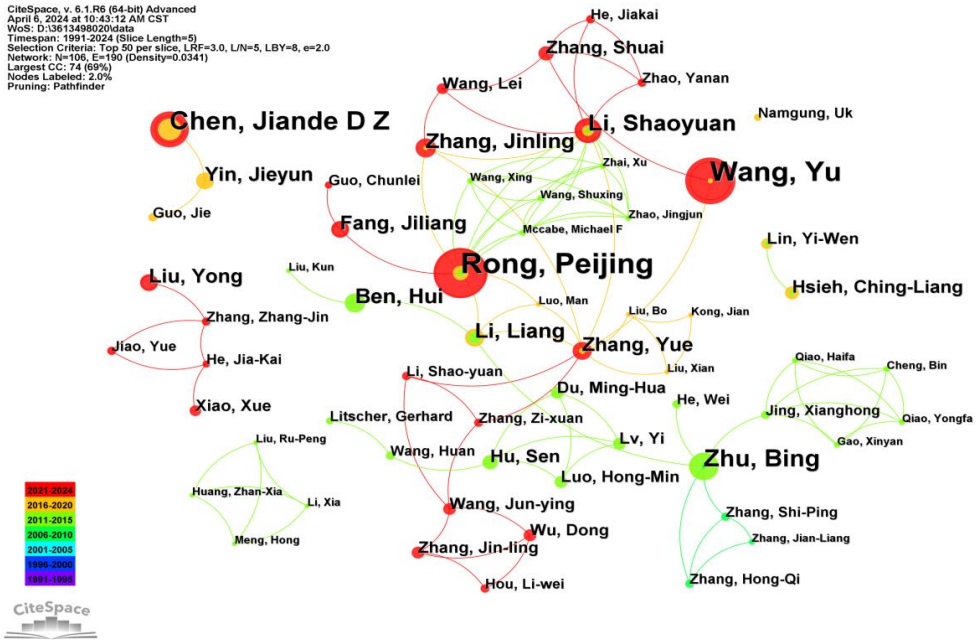

Figure 2. Collaboration map of authors in the research field of acupuncture and the vagus nerve

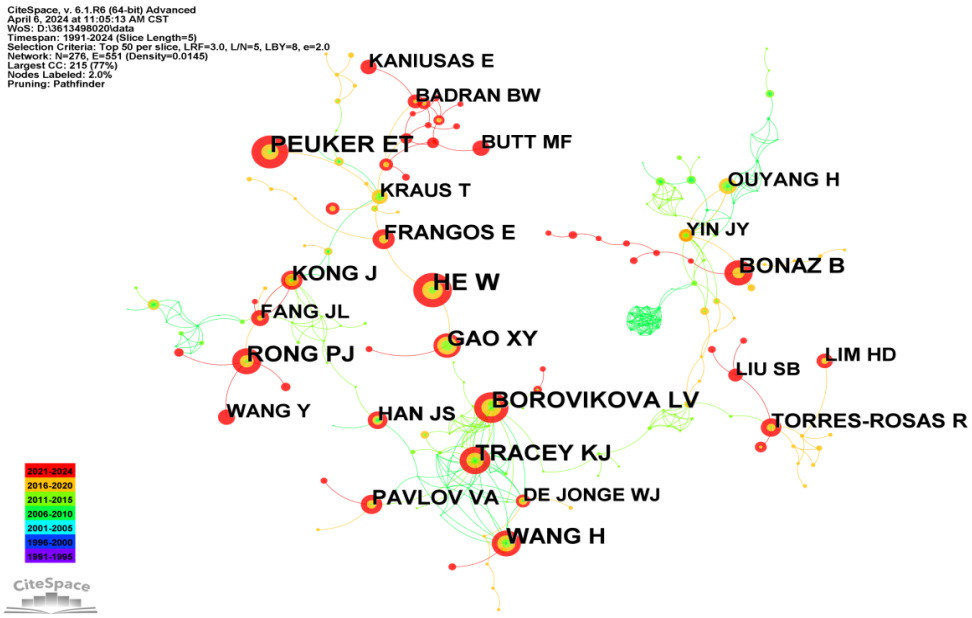

Figure 3. The authors of the published papers in the field of acupuncture and vagus nerve were co-cited

Table 1. The main authors of the research field of acupuncture and vagus nerve

Rank	Author	Count(%)	Institution
1	Rong, Peijing	18(5.50%)	China Academy of Chinese Medical Sciences
2	Wang, Yu	16(4.89%)	China Academy of Chinese Medical Sciences
3	Chen, Jiande D Z	13(3.98%)	Johns Hopkins University School of Medicine
4	Zhu, Bing	10(3.06%)	China Academy of Chinese Medical Sciences
5	Li, Shaoyuan	9(2.75%)	China Academy of Chinese Medical Sciences

Table 2. Co-cited authors in the field of acupuncture and vagus nerve research

Rank	Cited Author	Citations	Centrality	Institution
1	HE W	45	0.02	China Academy of Chinese Medical Sciences
2	PEUKER ET	43	0	Westfalian Wilhelms-University
3	BOROVIKOVA LV	40	0.63	The Picower Institute for Medical Research
4	TRACEY KJ	36	0.22	The Feinstein Institute for Medical Research
5	WANG H	34	0.19	North Shore Long Island Jewish Research Institute

2.3 Volume and Visualization of National and Regional Publications

The visual analysis of the global issuing countries helps to identify the countries that are important in the research field related to Vagus Nerve and Acupuncture and Acupressure and to explore the collaborative relationship between the countries. As shown in Table 3, China, as the birthplace of Acupuncture and Acupressure, has the largest number of articles in this field (156) , followed closely by the United States (65) and Germany (13) , indicating that these countries occupy a central position in this field and lead its development. The co-occurrence mapping of issuing countries (Figure 4) shows that this research field is geographically characterized by two major clusters, Asia and Europe and the United States. The Asian cluster is represented by countries such as China, Japan and South Korea. The European and American clusters, on the other hand, are represented by countries such as the United States and Germany. In addition, countries such as Canada, the United Kingdom and Germany show certain exchange and cooperation dynamics, while China maintains close cooperation with the United States, Austria, Vietnam and other countries. However, most of the countries still have fewer cooperative exchanges, so research cooperation between countries should be further expanded in the future.

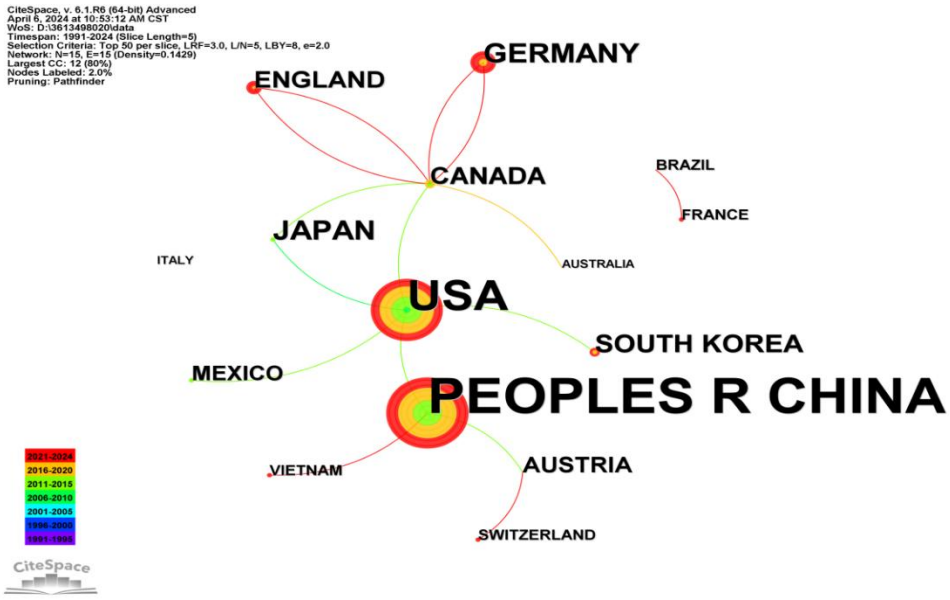

Figure 4. National co-occurrence map of acupuncture and vagus nerve research

Table 3. Major countries and regions in the field of acupuncture and vagus nerve research

Rank	Country	Publications	Centrality
1	PEOPLES R CHINA	156	0.57
2	USA	65	0.86
3	GERMANY	13	0
4	JAPAN	13	0
5	SOUTH KOREA	10	0
6	CANADA	9	0.59
7	ENGLAND	8	0
8	AUSTRIA	7	0.22
9	MEXICO	6	0
10	VIETNAM	3	0

2.4 Volume of institutional publications and visualization analysis

The visualization and analysis of issuing institutions is of great significance for analyzing inter-institutional communication and cooperation and parsing the research cooperation network. Among the top 10 institutions in terms of the number of articles (see Table 4) , 8 institutions are from China and 2 institutions are from the United States. Among them, China Academy of Traditional Chinese Medicine (41 articles), Capital Medical University (13 articles) and China Medical University (10 articles) are the top 3 institutions in terms of the number of articles. By analyzing the institutional co-occurrence map (see Figure 5) , it was found that the initial cooperation among research institutions has been carried out, but the overall cooperation is mostly limited to the national scope, and the transnational cooperation is still insufficient.

Figure 5. Co-occurrence map of institutions in the field of acupuncture and vagus nerve research

Table 4. Major publications in the field of acupuncture and vagus nerve research

Rank	Institution	Publications	Centrality
1	China Acad Chinese Med Sci	41	0.52
2	Capital Med Univ	13	0
3	China Med Univ	10	0
4	Beijing Univ Chinese Med	8	0.47
5	Nanjing Univ Chinese Med	8	0
6	Univ Hong Kong	7	0.27
7	Guangzhou Univ Chinese Med	7	0.04
8	Univ Michigan	7	0.04
9	Nanjing Med Univ	6	0.36
10	Harvard Med Sch	6	0.46

2.5 Journal publication volume and visualization analysis

Journal co-citation mapping is used to reflect the degree of relationship between journals by visualizing the changes in the relationship between different journals within a field, which can thereby reveal the trend and evolution of the discipline. When articles from two or more journals are simultaneously cited in one or more subsequent papers, these journals constitute a co-citation relationship. Co-citation intensity reflects the number of papers that cite articles from these journals at the same time, i.e., the frequency with which they are cited. Among the top ten most co-cited journals, nine journals were cited more than 70 times, with the top three being EVID-BASED COMPL ALT (141 times) , followed by BRAIN RES (101 times) and PLOS ONE (98 times) (see Table 5). In the journal co-citation map (see Figure 6) , there are 121 nodes with 150 connecting lines. large nodes such as EVID-BASED COMPL ALT, NATURE, BRAIN RES, and NEUROSCI LETT show a relatively dense distribution, suggesting that journals represented by these nodes have a high frequency of citations in the field of acupuncture and vagus nerve research, and include important research references in this important research references in the field.

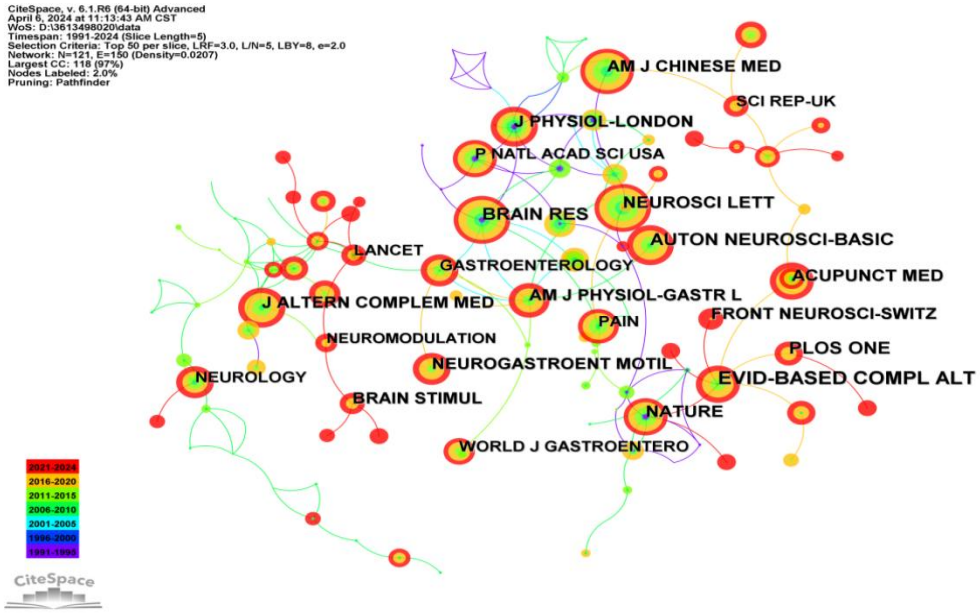

Figure 6. Journals in the field of acupuncture and vagus nerve research were cited together

Table 5. Major cited journals in the field of acupuncture and vagus nerve research

Rank	Institution	Frequency of citations	Centrality
1	EVID-BASED COMPL ALT	141	0.24
2	BRAIN RES	101	0.95
3	PLOS ONE	98	0.03
4	AUTON NEUROSCI-BASIC	95	0
5	NATURE	87	0.35

2.6 Keywords

2.6.1 Keyword Frequency Analysis

Keywords are a comprehensive condensation of research topics, and frequency analysis can effectively reveal the current research focus and future development trend of a specific academic field. Using CiteSpace software, we set "keyword" as the node to construct the keyword map. High-frequency keywords usually represent the research

hotspots in the field, and Table 6 lists the top 20 keywords in terms of frequency, among which electroacupuncture has the highest centrality index (52, 0.37) , indicating that it is widely used in the field. In the keyword mapping (see Figure 7) , a total of 139 nodes and 212 connecting lines appeared, with an overall density of 0.0221. A collation of the main keywords revealed that the techniques mainly involved in the research on acupuncture and the vagus nerve include electroacupuncture and auricular acupuncture; the stimulation of the vagus nerve by acupuncture involves the The mechanisms involved in acupuncture stimulation of the vagus nerve are the focus of attention; studies on the regulation of heart rate variability, gastric motility, inflammation, and pain are predominant; and related studies are mainly focused on animal experiments.

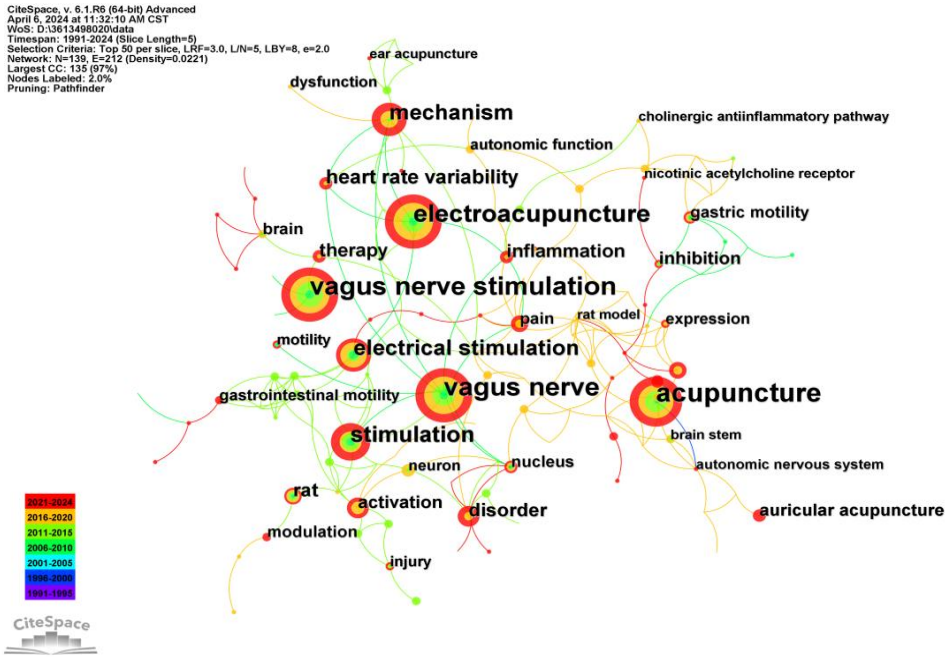

Figure 7. Keyword map in the field of acupuncture and vagus nerve research

Table 6. Main keywords in the field of acupuncture and vagus nerve research

Rank	Keywords	Frequency	Centrality	Rank	Keyword	Frequency	Centrality
1	acupuncture	74	0	11	inflammation	17	0.2
2	vagus nerve stimulation	69	0.06	12	therapy	17	0.24
3	vagus nerve	65	0.06	13	inhibition	14	0.03
4	electroacupuncture	52	0.37	14	activation	14	0.27
5	stimulation	34	0.02	15	auricular acupuncture	13	0
6	mechanism	33	0.27	16	gastric motility	12	0.03
7	electrical stimulation	32	0.27	17	nucleus	12	0.29

8	heart rate variability	21	0.15	18	brain	11	0.11
9	disorder	19	0.16	19	modulation	11	0.06
10	rat	19	0.08	20	pain	11	0.08

2.6.2 Keyword clustering analysis

In the keyword clustering analysis, the LLR model was chosen as the analyzing tool, and 13 clusters were extracted and the cluster mapping was drawn accordingly (see Figure 8) . The Q-value of this atlas is 0.7836 > 0.3 and the S-value is 0.9046 > 0.7, which indicates that the clustering structure is significant and credible. The main clusters and the keywords they contain are shown in Table 7. By combing the 13 clusters obtained and eliminating the research themes, it was found that the cluster mapping of gastric motility, in vitro, major depressive disorder, hemorrhagic shock, lower back pain are clustered to reflect the current major research in the field of acupuncture and vagus nerve.

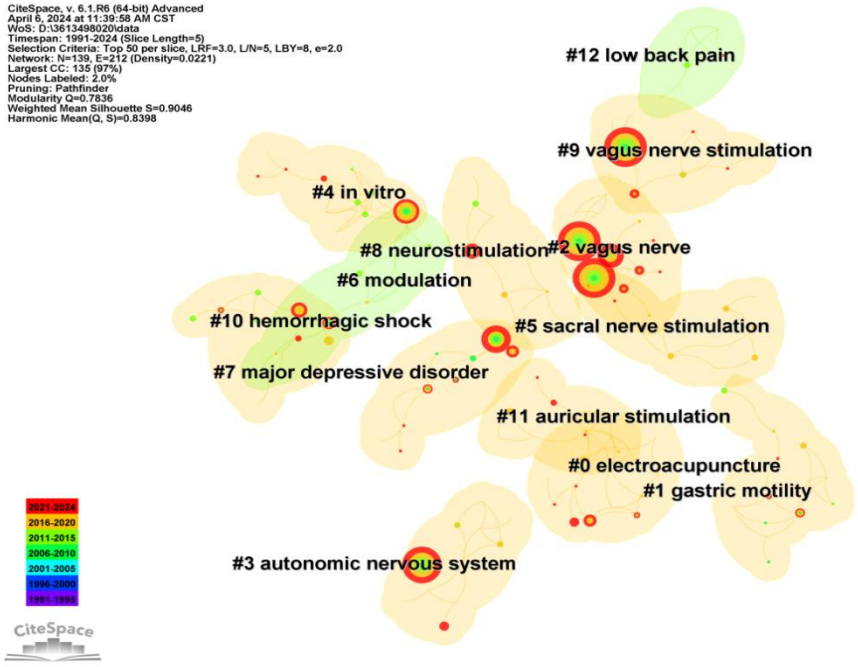

Figure 8. Keyword clustering map in the field of acupuncture and vagus nerve research

Table 7. Clustering of main keywords in the field of acupuncture and vagus nerve research

Rank	Size	S	Year	Cluster analysis（LLR algorithm）
0	15	0.938	2017	electroacupuncture (ea) (12.06，0.001); sympathetic nerve (12.06，0.001); dysmenorrhea (6.01，0.05); gastrointestinal surgery (6.01，0.05); epileptogenesis (6.01，0.05)
1	14	0.834	2011	gastric motility (12.85，0.001); septic shock (10.95，0.001); duodenal motility (10.95，0.001); cholinergic antiinflammatory pathway (7.27，0.01); intensity of acupuncture stimulation (5.46，0.05)

2	12	0.921	2010	vagus nerve (11.16, 0.001); pituitary (6.29, 0.05); autonomic nervous system (4.19, 0.05); heart rate variability (3.36, 0.1); gastric motility (3.24, 0.1)
3	11	0.982	2012	autonomic nervous system (12.55, 0.001); cranial nerves (7.64, 0.01); heart rate variability (hrv) (3.81, 0.1); vagus nerve (3.81, 0.1); chronic stress (3.81, 0.1)
4	11	0.941	2011	in vitro (10.29, 0.005); acupuncture point (10.29, 0.005); gaba(a) (10.29, 0.005); gastrointestinal motility (8.13, 0.005); secretion (6.63, 0.05)
5	11	0.801	2018	sacral nerve stimulation (10.91, 0.001); autonomic function (9.63, 0.005); inflammatory bowel disease (9.24, 0.005); inflammatory bowel diseases (8.1, 0.005); brain functional connectivity (7.3, 0.01)
6	11	0.963	2011	modulation (9.46, 0.005); glutamate (5.23, 0.05); bl21 (5.23, 0.05); vagovagal reflex (5.23, 0.05); dorsal vagal complex (5.23, 0.05)
7	10	0.816	2012	major depressive disorder (10.66, 0.005); functional connectivity (10.42, 0.005); shangchuhsu (9.8, 0.005); tsusanli (9.8, 0.005); non-inferiority trial (9.8, 0.005)
8	9	0.738	2015	neurostimulation (13.38, 0.001); depression (9.91, 0.005); trial (9.63, 0.005); treatment (6.66, 0.01); hpa axis (6.66, 0.01)
9	9	1	2014	vagus nerve stimulation (19.97, 1.0E-4); cholinergic anti-inflammatory pathway (11.99, 0.001); therapy (11.99, 0.001); acupressure (8.34, 0.005); anxiety (4.78, 0.05)
10	9	1	2014	hemorrhagic shock (8.05, 0.005); activation (6.43, 0.05); injury (6.43, 0.05); agonist (5.86, 0.05); zusanli (5.86, 0.05)
11	8	0.924	2017	auricular stimulation (9.39, 0.005); systematic review (8.25, 0.005); randomized controlled trial (7.38, 0.01); nonspecific effect (7.38, 0.01); hemodialysis (7.38, 0.01)
12	5	0.917	2013	low back pain (15.35, 1.0E-4); obese women (15.35, 1.0E-4); epilepsy [therapy] (7.63, 0.01); mentally disabled persons [psychology] (7.63, 0.01); humans (7.63, 0.01)

2.6.3 Keyword Time Zone Map Analysis

By analyzing the time zone map, the evolution of research topics in the field of acupuncture in the vagus nerve as well as the current research hotspots can be clearly understood. As shown in Figure 9, each keyword is presented as a node, with the horizontal axis indicating the time interval and the vertical axis indicating the research content, and these nodes accurately mark the specific time points in each year when the keywords were highlighted. Early studies focused on the role of acupuncture and the vagus nerve in the digestive, respiratory, and endocrine systems. Between 2006 and 2010, the mechanism of acupuncture's action on pathophysiological processes, such as inflammation, HRV, and pain, through the modulation of the vagus nerve became a hot topic of research.Between

2011 and 2015, the direction of the research shifted, and the studies began to focus on the effect of acupuncture on the vagus nerve in the area of mental health After 2016, the application of acupuncture in the field of vagus nerve regulation has been deepened, and its application has been expanded to include the evaluation and treatment of bowel disease, major depressive disorder, Parkinson's disease, and many other diseases. It also plays an important role in the assessment and management of pain symptoms, and has made significant progress in the study of key mechanisms such as the "cholinergic anti-inflammatory pathway". The emergence of these keywords indicates that they may become major research hotspots in this field in the future.

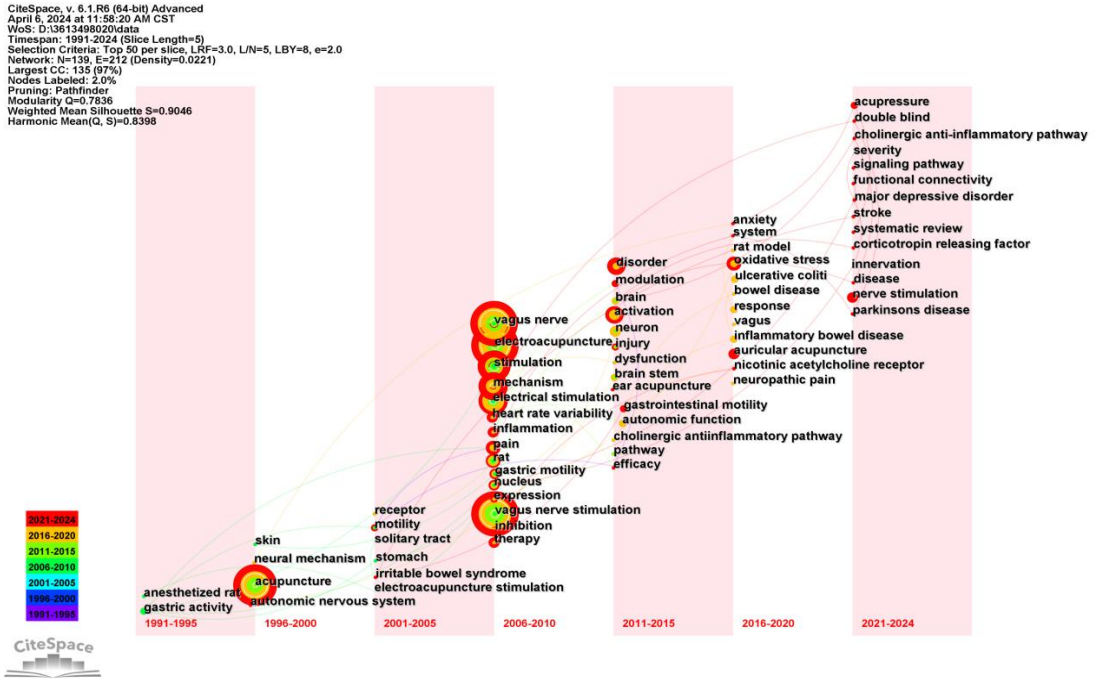

Figure 9. Time zone diagram of keywords in the field of acupuncture and vagus nerve research

2.5 Literature co-citation analysis

Through systematic analysis of the co-citation network visualization, the structure comprises 300 nodes and 599 edges, yielding a graph density of 0.0134 (Figure 10) . Node diameter corresponds to citation frequency. Table 8 presents the ten most cited documents (citation counts ≥ 13), revealing distinct research clusters: seven publications emphasize therapeutic applications of acupuncture-mediated vagus nerve stimulation, whereas the remaining three investigate physiological modulation mechanisms of vagal pathways and neural regulatory processes.

Frangos E et al.[46] published a seminal article in *Brain Stimulation* entitled "*Non-invasive Access to the Vagus Nerve Central Projections via Electrical Stimulation of the External Ear: fMRI Evidence in Humans*," which has been cited 20 times. This study provides robust functional magnetic resonance imaging (fMRI) evidence supporting non-invasive access to central vagus nerve projections via transcutaneous auricular electrical stimulation. Another highly cited work by Fang, JL et al.[47], a randomized controlled clinical trial ranking first in citation count, demonstrated that transcutaneous vagus nerve stimulation (tVNS) significantly modulates functional connectivity within the default mode network in patients with major depressive disorder. Notably, studies ranked 5th and 8th similarly investigated transcutaneous vagus nerve stimulation for depression treatment [48], collectively suggesting that neuromodulation approaches targeting the vagus nerve remain a prominent research focus in depression therapeutics.

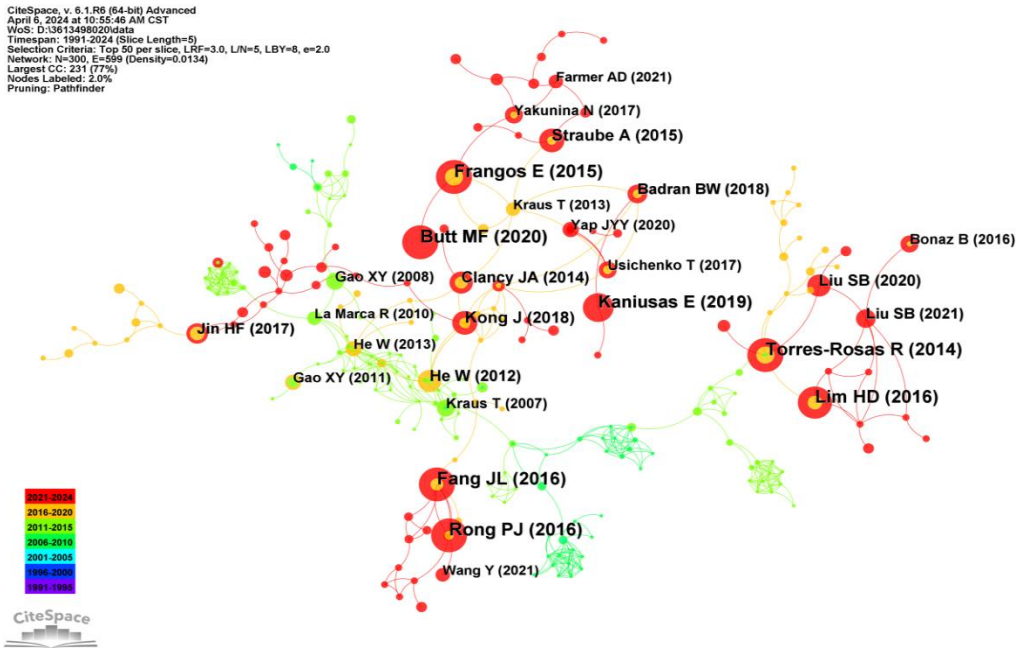

Figure 10. Literature in the field of acupuncture and vagus nerve research was co-cited

Table 8. Main cited literature in the field of acupuncture and vagus nerve research

Rank	Title	First Author	Year	Frequency of citations	Centrality
1	Non-invasive Access to the Vagus Nerve Central Projections via Electrical Stimulation of the External Ear: fMRI Evidence in Humans	Frangos, E	2015	20	0.07
2	Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder	Fang, JL	2016	20	0.12
3	Dopamine mediates vagal modulation of the immune system by electroacupuncture	Torres-Rosas, R	2014	20	0.24
4	The anatomical basis for transcutaneous auricular vagus nerve stimulation	Butt, MF	2020	20	0
5	Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: A	Rong, PJ	2016	20	0.04

	nonrandomized controlled pilot study				
6	Anti-Inflammatory Effects of Acupuncture Stimulation via the Vagus Nerve	Lim, HD	2016	19	0.05
7	Current Directions in the Auricular Vagus Nerve Stimulation I - A Physiological Perspective	Kaniusas, E	2019	17	0.01
8	Treating Depression with Transcutaneous Auricular Vagus Nerve Stimulation: State of the Art and Future Perspectives	Kong, J	2018	14	0.25
9	Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): a randomized, monocentric clinical trial	Straube, A	2015	14	0.05
10	Somatotopic Organization and Intensity Dependence in Driving Distinct NPY-Expressing Sympathetic Pathways by Electroacupuncture	Liu, SB	2020	13	0.04

3. Discussion

3.1 Current Research Landscape in Acupuncture and Vagus Nerve Studies

The investigation of vagus nerve-related acupuncture therapy originated in 1991, with publication outputs demonstrating a fluctuating growth pattern. Prominent contributors in this domain include Rong P, Wang Y, Chen JD, Zhu B et al., who have significantly advanced research progress through multi-institutional collaborations. Notably, publications by *Borovikova LV* rank among the global top 10 in both citation frequency and centrality metrics, establishing this researcher as a seminal figure in the field. A strong positive correlation exists between national publication outputs and institutional productivity, with Chinese institutions dominating Asian research contributions - all top five productive institutions are China-based. Currently, while major research institutions have established preliminary collaborative networks, these partnerships remain predominantly intra-national, highlighting the need for enhanced international cooperation to accelerate disciplinary advancement. Temporal keyword analysis identified current research priorities focusing on acupuncture's regulatory mechanisms affecting vagal nerve activity and their clinical therapeutic applications.

3.2 Applications and Hotspot Analysis in Acupuncture and Vagus Nerve Research

A systematic review of literature on acupuncture applications in vagus nerve research from 1991 to 2024 was conducted. Through bibliometric analysis using CiteSpace, including keyword frequency analysis, cluster identification, and time-zone mapping, the analysis revealed that current research hotspots focus on acupuncture-mediated vagus nerve modulation for: (a) inflammation regulation, (b) gastric motility enhancement, (c) pain management, and (d) depression therapy.

3.2.1 Acupuncture modulates the role of the vagus nerve in inflammatory responses

Keyword co-occurrence and time zone map analyses have revealed that the neuroimmune mechanisms underlying acupuncture-mediated modulation of inflammatory responses via the vagus nerve have become a focus of recent investigations. While inflammation represents a physiological defense mechanism against tissue injury, its excessive activation under pathological conditions may induce secondary tissue damage and exacerbate chronic disease progression. This process is maintained through a dynamic equilibrium between proinflammatory factors (e.g., TNF-α, IL-6) and anti-inflammatory mediators (e.g., IL-10, IL-12). Current evidence (as summarized in Table 9) demonstrates that acupuncture establishes a dual-pathway regulatory network via neural activation of the vagus nerve: the cholinergic anti-inflammatory pathway (CAP) and the hypothalamic-pituitary-adrenal (HPA) axis pathway.

The cholinergic anti-inflammatory pathway (CAP) mediates anti-inflammatory effects primarily via the intestinal-splenic dual-axis pathway. In the intestinal axis, acupuncture stimulates vagal afferent fibers that, following brainstem integration, release acetylcholine (ACh) via intestinal neuron-macrophage synapses. This subsequently activates α7 nicotinic acetylcholine receptor (α7nAChR)-dependent signal transduction and inhibits proinflammatory factor release, including tumor necrosis factor-alpha (TNF-α). Animal studies demonstrate that electroacupuncture at ST36 significantly attenuates plasma levels of TNF-α, IL-6, and other proinflammatory factors in intestinal inflammation models via intestinal cholinergic pathway activation[50,51]. Mechanistic investigations revealed that ST36 electroacupuncture preserves intestinal barrier integrity post-ischemia by maintaining tight junction protein ZO-1 localization, thereby attenuating systemic inflammation[52,53].The splenic pathway activates the splenic nerve through the efferent fibers of the vagus nerve, promotes Norepinephrine (NE) to trigger the synthesis of ACh by lymphocytes through β2 adrenergic receptors, and ultimately inhibits the secretion of TNF-α by splenic macrophages. In cecal ligation and puncture (CLP) -induced sepsis models, electroacupuncture at ST36, LI11, and ST25 significantly decreased serum TNF-α, IL-10, and D-lactate levels - an effect abolished by splenectomy, confirming splenic dependency[54]. Furthermore, acupuncture-mediated regulation of the vagal cholinergic anti-inflammatory pathway exerts anti-inflammatory effects by suppressing NF-κB nuclear translocation and activating α7nAChR-dependent JAK2-STAT3 signaling, as demonstrated in endotoxemia, chronic obstructive pulmonary disease (COPD), and hepatitis models[55].

Regarding the vagus nerve-adrenal axis pathway, acupuncture stimulates vagal afferent fibers and activates cholinergic neurons in the dorsal motor nucleus of the vagus (DMV). Subsequent activation of DMV neurons triggers adrenal medulla catecholamine release (e.g., epinephrine, norepinephrine, dopamine), which reduces proinflammatory cytokine (TNF-α, IL-6) production through inhibition of the monocyte/macrophage NF-κB pathway, thereby exerting anti-inflammatory effects. In a lipopolysaccharide (LPS) -induced murine sepsis model, electroacupuncture at Zusanli (ST36) was shown to activate the vagus-adrenal medulla-dopamine pathway, resulting in significant suppression of serum TNF-α and IL-6 levels[58]. Clinical studies have demonstrated that

acupuncture significantly ameliorates low-grade inflammation and intestinal ischemia-reperfusion injury (I/R) in functional dyspepsia (FD) through vagus nerve-adrenal axis activation[59,60]. Furthermore, research conducted by Professor Qiufu Ma's team revealed that low-intensity electroacupuncture (0.5 mA) at Zusanli (ST36) specifically activates PROKR2-Cre-labeled dorsal root ganglion neurons, reducing serum TNF-α levels in septic mice through the HPA axis. In contrast, stimulation of the abdominal acupoint Tianshu (ST25) lacked this effect, while high-intensity electroacupuncture primarily engaged sympathetic neural pathways. These findings establish that both acupoint selection and stimulation intensity exhibit specificity in modulating acupuncture-mediated anti-inflammatory pathways[61,62].

The findings from our mechanistic investigation of acupuncture-mediated anti-inflammatory effects through vagal modulation revealed several key aspects: First, acupuncture exerts anti-inflammatory effects primarily through vagal regulation via two distinct pathways: the cholinergic anti-inflammatory pathway (mediated through enteric or splenic mechanisms) and the vagus-adrenal axis pathway (hypothalamic-pituitary-adrenal [HPA] axis). Second, our analytical framework incorporated key inflammatory mediators including interleukin IL-10, IL-12, tumor necrosis factor TNF-α, and IL-6, along with critical signaling molecules such as nuclear factor kappa B (NF-κB) and Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) . Third, electroacupuncture at Zusanli (ST36) emerged as the predominant intervention modality, demonstrating stimulation parameter-dependent anti-inflammatory outcomes that vary with acupoint combinations and electrical stimulation intensities. Fourth, the therapeutic scope of acupuncture-mediated vagal anti-inflammatory mechanisms has expanded beyond initial sepsis models to encompass various inflammatory pathologies including inflammatory bowel disease, hepatitis, and chronic obstructive pulmonary disease (COPD). Finally, while current mechanistic investigations remain predominantly concentrated on animal models, significant translational gaps persist between preclinical findings and clinical applications.

Table 9. Summary of Major Research on Acupuncture and the Vagus Nerve in Inflammation Regulation

Anti-inflammatory pathways	Disease	Stimulation Methods	Stimulating area	Research subject	Evaluate metrics	Result	Citation
Cholinergic anti-inflammatory pathway (intestine-	Colitis	EA	Zusanli（ST36）	Rat	TNF-α, IL-1β, IL-6, Autonomic nervous function	Improve colitis caused by TNBS.	[50]
	Postoperative intestinal obstruction	EA	Zusanli（ST36）	Mice	TNF-α, IL-6, CD11b+Macrophage, JAK2/STAT3	Suppress intestinal inflammation and promote gastrointestinal motility.	[51]

mediated)	Intestinal ischemic injury	EA	Zusanli（ST36）	Rat	TNF-α, IL-8, Intestinal permeability（FITC-Glucan）, ZO-1 protein	Protect the intestinal barrier and mitigate systemic inflammatory responses.	[52]
	Hemorrhagic shock	EA	Zusanli（ST36）	Rat	TNF-α, IL-6, DAO, D-LA, Intestinal permeability	It has reduced systemic inflammatory responses, improved organ function, and enhanced survival rates following hemorrhagic shock.	[53]
	Sepsis	EA	Zusanli（ST36）Quchi（L11） Tianshu（ST25）	SD Rat	TNF-α, IL-10, D-LA, DAO, T lymphocyte subpopulations	Reduce serum pro-inflammatory factors and improve intestinal T cell balance.	[54]
		ta VNS	Auricular pavilion				
Cholinergic anti-inflammatory pathway (spleen-mediated)	Endotoxemia	TEAS	Zusanli（ST36）	Mice	TNF-α, IL-1β, IL-6, NF-κB p65	Reduce the generation of TNF in splenic macrophages to achieve an anti-inflammatory effect.	[55]
	chronic obstructive pulmonary disease(COPD)	EA	Zusanli（ST36）Feishu（BL13）	Rat	ACh, AChE, IL-6, TNF-α, α7nAChR, JAK2, STAT3, NF-κB	To alleviate lung inflammation in chronic obstructive pulmonary disease (COPD) and improve lung function.	[56]
	Hepatitis	MA EA	Zusanli（ST36）	Mice	TNF-α, mRNA/Protein, CD11b/CD68, STAT3, PhosphorylationErk1/2	It reduced the expression of inflammatory cell-like tumor necrosis factor TNF-α in	[57]

						plasma and liver cells, alleviating the inflammatory response.	
	Sepsis	EA	Zusanli（ST36）	Mice	DA, TNF, MCP1, IL-6, INF-γ level	Control the systemic inflammation caused by sepsis to improve survival rates.	[58]
Hypothalamic-Pituitary-Adrenal Axis (HPA Axis)	Functional Dyspepsia（FD）	Auricular vagus nerve stimulation（aVNS）	Auricular pavilion	Rat	CRF, ACTH, Corticosterone, CRHR1	Improvement of gastric motility reduces the low-grade inflammation associated with functional dyspepsia (FD).	[59]
	Intestinal Ischemia-Reperfusion Injury（I/R）	EA	Zusanli（ST36）	Rat	DA, TNF-α, MPO, MDA, Intestinal permeability	Alleviate intestinal ischemia-reperfusion injury (I/R)	[60]

3.2.2 Acupuncture and Vagus Nerve Regulation of Gastric Motility

Keyword frequency and clustering analyses have identified the vagus nerve-mediated mechanism of acupuncture in gastric motility regulation as a key research focus. As a cornerstone therapy in traditional Chinese medicine, acupuncture has established efficacy in managing gastric motility disorders including gastroesophageal reflux disease (GERD) and functional dyspepsia (FD). The therapeutic mechanism primarily involves vagal pathway activation through specific acupoint stimulation, which modulates neural signaling to enhance gastric motility and optimize coordinated physiological functions including digestion and nutrient absorption.Systematic review of current evidence (Table 10) demonstrates that acupuncture modulates gastric motility primarily via the hypothalamic paraventricular nucleus (PVN)-dorsal vagal complex (DVC) -vagal pathway. Within this regulatory axis, key nuclei including the dorsal motor nucleus of the vagus (DMV) and nucleus tractus solitarii (NTS) serve pivotal roles as integration centers. These nuclei process afferent signals and initiate efferent vagal impulses to regulate gastric function[63].In feline models of gastric distension-induced transient lower esophageal sphincter relaxations (TLESRs)[64], electroacupuncture at Neiguan (PC6) was shown to upregulate nitric oxide synthase (NOS) and c-Fos protein expression in the medullary reticular formation. This effect inversely correlated with NOS activity suppression in the NTS/DMV complex, facilitating gastric motility through attenuation of distension-related neural signaling, consequently reducing GERD-associated TLESR incidence.Furthermore, numerous studies have shown that acupuncture on the extremities can enhance gastric motility by increasing the activity of the efferent fibers of the gastric vagus nerve[65,66].Electroacupuncture at lower extremity acupoints

along the stomach meridian (e.g., Zusanli (ST36) , Shangjuxu (ST37)) enhanced gastric motility through NTS-DMV pathway activation, accelerating gastrointestinal recovery via modulation of spontaneous electrical activity in the dorsal vagal complex[67]. Notably, auricular acupuncture directly stimulates the auricular branch of the vagus nerve (ABVN) innervation zone to regulate gastric function. Han Li et al.[68] found through animal experiments that auricular acupuncture (AA) directly stimulated the auricular points ST (stomach) and SI (small intestine) in the distribution area of the auricular branch of the vagus nerve (ABVN) , which could directly act on the nucleus tractus solitarius (NTS) in the brainstem responsible for receiving sensory signals from the digestive system. To establish a connection with the dorsal motor nucleus (DMV) of the vagus nerve and transmit signals to achieve the effect of enhancing gastrointestinal motility. In functional dyspepsia models, transcutaneous auricular vagus nerve stimulation (taVNS) significantly augmented gastric vagal efferent activity, resulting in enhanced motility and improved gastric pacing[69]. This neuromodulatory effect is mediated through NTS and PVN interactions with vagal pathways. For burn-induced gastric dysfunction, auricular electroacupuncture elicits NTS neuronal activation and sympathetic inhibition via central connectivity, downregulating COX-2 expression to ameliorate dyskinesia while normalizing delayed gastric emptying[70].

Table 10. Summary of Major Research on Acupuncture and the Vagus Nerve in the Regulation of Gastric Motility

Research subject	Stimulation Methods	acupoint	Result	Mechanism	Citation
Cat	EA	Neiguan（PC6） Zusanli（ST36）	Gastric Motility↑	NTS-DMV pathway	[64]
Rat	EA	Neiguan（PC6） Shangjuxu（ST37）	Gastric Motility↑	NTS-DMV pathway	[67]
Rat	Auricular acupuncture(AA)	Wei（ST） Xiaochang（SI）	Gastric Motility↑	NTS-DMV pathway	[68]
	somatic acupuncture（SA）	Zusanli（ST36）	Gastric Motility↑		
Human	taVNS	Auricular pavilion	Gastric Motility↑	NTS, PVN	[69]
Rat	Auricular electro-acupuncture（AEA）	Specific acupuncture points that govern the auricular-vagus nerve.	Gastric Motility↑	Sympathetic-COX-2 Pathway	[70]

3.2.3 The Application of Acupuncture and Vagus Nerve in Pain Management

According to the keyword frequency and cluster analysis by CiteSpace, the application mechanism of acupuncture and vagus nerve in pain management has attracted much attention in recent years. Current research on the application of acupuncture and vagus nerve in pain management (Table 11) indicates that acupuncture exerts multi-level synergistic effects in pain regulation through the vagus nerve pathway, and its mechanism of action is closely related to the type of pain and intervention targets.The core mechanism of acute inflammatory pain is concentrated in the vagus nerve-mediated peripheral cholinergic anti-inflammatory pathway (CAP). Animal experiments have shown that manual acupuncture (MA) stimulation at Sanyinjiao (SP6) or stimulation of the auricular vagus nerve branch in the auricular concha area can specifically activate the α7 nicotinic acetylcholine

receptor (α7nAChR), inhibit NF-κB signal transduction, and promote the polarization of macrophages to the M2 phenotype, thereby down-regulating pro-inflammatory factors such as IL-1β and TNF-α and up-regulating IL-10 expression, ultimately achieving early inhibition of peripheral nociceptive signal transmission [71,72]. The regulation of chronic pain focuses on the inhibition of central sensitization and the remodeling of autonomic nerve function. Electroacupuncture stimulation at Huantiao (GB30) inhibits spinal dorsal horn glial cell activation through the vagus nerve-nucleus tractus solitarius (NTS) pathway and blocks IL-1β-mediated central sensitization [73]; while transcutaneous auricular vagus nerve stimulation (taVNS) improves the central pain network integration ability of patients with chronic low back pain by enhancing the functional connection between the locus coeruleus (LC) and the secondary somatosensory cortex(S2) [74]. In the treatment of irritable bowel syndrome with constipation (IBS-C), taVNS stimulation can restore intestinal motility and relieve abdominal pain, confirming its bidirectional regulatory effect on the gut-brain axis [75]. Moreover, the CAP pathway of the vagus nerve remains activated in chronic pain, and its function shifts from peripheral anti-inflammation in the acute phase to long-term regulation of the neuroimmune microenvironment homeostasis[76]. The intervention strategies for neuropathic pain focus on the activation of the descending inhibitory pathway and the remodeling of brain networks. taVNS inhibits the pain emotion encoding of the default mode network (DMN) by strengthening the functional connection between the locus coeruleus (LC) and the temporoparietal junction (TPJ), and enhances the conditioned pain modulation (CPM) effect to increase the pain threshold[77,78]; randomized-frequency electroacupuncture (RF-EA) stimulation at Zusanli (ST36) activates the coordinated projection of the dorsal motor nucleus of the vagus nerve (DMV) and the nucleus tractus solitarius, promoting the release of endogenous opioid peptides in the periaqueductal gray (PAG), thereby achieving long-term analgesia in the sciatic nerve compression model[79].

From the perspective of intervention targets, although traditional acupoint electroacupuncture and taVNS share the vagus nerve pathway, there are significant differences in their action nodes: electroacupuncture achieves spinal-cervical level regulation by activating the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus nerve (DMV); while taVNS primarily regulates the brainstem-limbic system loop, driving the reconstruction of the central emotional-cognitive network. Technological innovation has provided multi-dimensional evidence support for mechanism analysis: functional magnetic resonance imaging (fMRI) technology dynamically captured the functional reorganization of the locus coeruleus network and the correlation with pain relief after taVNS stimulation; the anorectal manometry system revealed that taVNS can selectively regulate intestinal sensory signals; neuroregulation technology confirmed that the activation of specific fiber subgroups of the vagus nerve (such as C fibers) is a necessary condition for electroacupuncture analgesia.

Table 11. Summary of Key Research on Acupuncture and Vagus Nerve in Pain Management

Type of Pain	Specific Name	Research subject	Stimulation Methods	Stimulating area	Evaluation criteria	Result	mechanism	Citation
Acute somatic pain	Acetic acid-induced visceral pain	Wistar rats	Auricular branch of the vagus nerve (ABVN) stimulation using ear acupuncture.	Auricular branches vagus nerve.(ABVN-L)	The number of abdominal twists, the response time in the formalin test, vagotomy,	Left-sided ABVN stimulation significantly inhibits	Cholinergic anti-inflammatory pathway	[71]

					and the effect of cholinergic antagonists on the inhibition of nociceptive signal transmission.	pain signals, resulting in reduced bodily pain.		
Acute inflammatory myalgia	Muscle inflammation induced by carrageenan.	mice	Manual acupuncture （MA）	Sanyinjiao（SP6）	Mechanical/thermal pain threshold, macrophage phenotype (M1/M2), and IL-10 levels.	SP6 stimulation increases IL-10, promotes the phenotype transformation of M2 macrophages, and alleviates muscle pain.	Cholinergic anti-inflammatory pathway	[72]
Chronic cancer-related bone pain	Prostate Cancer Bone Metastasis Model	Copenhagen rats	EA	Huantiao（GB30）	Thermal pain threshold, spinal cord IL-1β mRNA expression, and the effects of IL-1 receptor antagonists.	Electroacupuncture significantly alleviates thermal hyperalgesia and inhibits the expression of IL-1β, thereby reducing	Cholinergic anti-inflammatory pathway	[73]

						cancer pain.		
Chronic lower back pain	Chronic nonspecific low back pain	human patients	taVNS	Auricular branches vagus nerve（ABVN region）	Lumbar muscle endurance, balance testing, Oswestry Disability Index	taVNS can significantly improve pain and muscle endurance.	Regulation of the vagus nerve center and local muscle activation.	[74]
Chronic visceral pain	irritable bowel syndrome（IBS-C）	IBS-C patients	taVNS	Auricular region (branches of the vagus nerve)	Total spontaneous bowel movement frequency (CSBMs/week), abdominal pain VAS score, and rectoanal inhibitory reflex (RAIR)	taVNS significantly increases the frequency of bowel movements, alleviates abdominal pain, and improves rectal sensory thresholds.	Autonomic regulation mediated by the vagus nerve; cholinergic anti-inflammatory pathway.	[75]
Chronic musculoskeletal pain	Pain related to systemic lupus erythematosus (SLE)	SLE patients	taVNS	Auricular canal (branch of the vagus nerve)	Pain VAS score, fatigue scale (FACIT-F), joint tenderness/swelling score, levels of IL-8, IL-6, IL-18, IL-10, and IL-1 receptor antagonist (IL-1-RA)	taVNS significantly alleviates symptoms of fatigue and muscle pain.	Autonomic nervous regulation; Cholinergic anti-inflammatory pathway	[76]

Migraine	Migraine without aura	Migraine patients	taVNS	Auricular canal (branch of the vagus nerve)	Activation of brain regions in fMRI (locus coeruleus, solitary nucleus), resting-state functional connectivity.	taVNS reduces locus coeruleus activity and enhances functional connectivity with the somatosensory cortex, resulting in reduced headache.	Regulation of the vagus nerve and locus coeruleus pathway, modulation of the central pain network and descending pain regulation system.（DPMS）	[77]
Trigeminal Neuralgia	Primary Trigeminal Neuralgia	Trigeminal Neuralgia (TN) patients	taVNS	Auricular canal region (branches of the vagus nerve)	Conditioned Pain Modulation (CPM), Pressure Pain Threshold (PPT)	taVNS significantly enhances the CPM effect, improving PPT pain.↓	Activation of the endogenous pain suppression system mediated by the vagus nerve in the descending pain modulation system (DPMS)	[78]
Peripheral neuropathic pain	Chronic compression model of the sciatic nerve	Wistar rats	Random Frequency Acupuncture（RF-EA）	Zusanli（ST36）, Yanglingquan（GB34）/Auricular canal region (branches of	Mechanical/thermal pain threshold, spontaneous pain rating	RF-EA can achieve long-lasting analgesia.	The mechanism of inflammatory regulation and the descending pain modulation	[79]

	the vagus nerve)	system (DPMS)

3.2.4 The Application of Acupuncture and Vagus Nerve in the Treatment of Depression

According to the analysis of co-citation and time zone map by CiteSpace, the regulation of the vagus nerve by acupuncture in the treatment of depression has always been a focus of attention. Depression, characterized by low mood, anhedonia, cognitive impairment, and autonomic symptoms, is expected to become one of the main causes of health burden by 2030[80,81]. In recent years, researchers have found that the pathological mechanism of depression is closely related to the dysfunction of the corticostriatal reward circuit, the neuroendocrine axis, and the neuroinflammatory cascade reaction. The anti-depressive effect of acupuncture is achieved through the coordinated regulation of these links via the vagus nerve pathway (Table 12) . Firstly, studies have confirmed that the occurrence of depression is related to structural abnormalities and functional disorders of the corticostriatal-thalamocortical or limbic-cortico-striato-pallido-thalamic reward circuits[82,83,84,85]. Using functional magnetic resonance imaging (fMRI) to observe the brain cortical network stimulated by two different acupuncture techniques, it was found that the changes in neuronal activity in different brain regions after needling different acupoints were different, but all significantly enhanced the resting-state functional connectivity (rsFC) between the ventral striatum and the medial prefrontal cortex, indicating that acupuncture may achieve an anti-depressive effect by regulating the vagus nerve to activate the corticostriatal reward circuit[86,87]. Secondly, acupuncture can achieve an anti-depressive effect by regulating the vagus nerve to change the indicators of multiple endocrine pathways. The dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis is a key target of endocrine disorders in depression. Clinical data show that auricular electroacupuncture (AEA) stimulation of the auricular concha region (ACR) or press needle (PN) stimulation of acupoints such as Ganyu (PC4) and Shousanli (LI10) can reduce plasma cortisol and adrenocorticotropic hormone (ACTH) to normal levels, correct the hyperactivity of the HPA axis, and improve depressive symptoms[88,89]. In addition, depression is also related to the reduction of circulating melatonin secretion. Transcutaneous auricular vagus nerve stimulation (taVNS) can stimulate the vagus nerve afferent to the ear and project signals to the nucleus tractus solitarius (NTS), and then transmit to the pineal gland, thereby promoting the release of melatonin in the pineal gland to achieve an anti-depressive effect[90]. Acupuncture can also achieve therapeutic effects on depression by inhibiting the inflammatory response of the vagus nerve. There is a mutual influence relationship between depression and inflammation, and they are prone to induce each other. The characteristic is that depression easily triggers the activation of microglia in the brain, increases the permeability of the blood-brain barrier, and leads to the excessive activation of pro-inflammatory cytokines such as IL-1β, IL-1, IL-2, IL-6, IL-10, and TNF-α[91,92]. Studies using a chronic unpredictable mild stress (CUMS) rat model combined with molecular imaging technology found that taVNS inhibits NF-κB signaling by activating the hypothalamic α7nAChR/JAK2/STAT3 pathway, reduces the levels of pro-inflammatory factors such as IL-1β and TNF-α, and reduces microglial activation, providing empirical evidence for the "inflammation-depression" bidirectional regulation theory[93,94]. In addition, in the context of metabolic syndrome and COVID-19-related depression, taVNS demonstrates pleiotropy by suppressing cytokine storms and regulating the brain-gut axis, highlighting its clinical potential of treating multiple diseases with a single acupoint[95,96]. Future research should further explore the combined stimulation of auricular and body acupoints to promote the standardization and internationalization of acupuncture research for depression.

Table 12. Summary of Main Research on Acupuncture and the Vagus Nerve

in the Treatment of Depression

Research subject	Stimulation Methods	Stimulating area	Evaluate metrics	conclusion	mechanism	Citation
Major Depressive Disorder (MDD)patients	taVNS	Auricular Concha Regio （ACR）	Resting-state functional connectivity of the striatum (rsFC) and scores on the Hamilton Depression Rating Scale (HAMD)	Prolonged taVNS may produce beneficial therapeutic effects by modulating the cortical-striatal circuit in patients with MDD.	Regulation of the Cortical-Striatal Reward Circuit	[86]
Major Depressive Disorder (MDD) patients	acupuncture+ Fluoxetine	Zhongwan（ RN12） Xianwan（ RN10） Qihai（RN6） Guanyuan（ RN4） Shangqu（ KL17） Huaroumen（ ST24）	Resting-state functional connectivity (rsFC), Hamilton Depression Rating Scale score (HAMD), Self-Rating Depression Scale score (SDS)	Acupuncture stimulation can enhance the functional connectivity of the cortical-striatal reward circuitry, significantly alleviating symptoms of depression.	Regulation of the Cortical-Striatal Reward Circuit	[87]
Unpredictable chronic mild stress （UCMS） Depressed rats	Auricular electro-acupuncture（ AEA）	Auricular Concha Regio （ACR）	Open Field Test (OFT), Blood Pressure, Heart Rate, Plasma Cortisol and ACTH Levels	Auricular electro-acupuncture（ AEA）It significantly improved OFT behavior, lowered blood pressure, regulated HPA axis activity, and antagonized UCMS-induced depressive state in rats.	Regulate the activity of the hypothalamic-pituitary-adrenal axis (HPA axis).	[88]

Patients with depression vs. healthy controls	Press the needle（PN）	Geshu（PC4） Shousanli（LI10） Yinlingquan（SP9） Sanyinjiao（SP6）	BDI-II (Beck Depression Inventory II) scores, blood pressure, heart rate variability (HRV), plasma cortisol, and adrenocorticotropic hormone (ACTH).	Acupuncture improves BDI-II scores, lowers blood pressure, increases vagal nerve activity, and exerts an antidepressant effect.	Vagus nerve functionality regulation, autonomic nerve balance.	[89]
Zucker diabetic obese rats	taVNS	Auricular Concha Regio	FST, Forced Swim Test,Plasma Melatonin Levels	taVNS exerts an antidepressant effect by reducing the resting time of FST and increasing melatonin secretion.	Activation of the vagus nerve stimulates the pineal gland and peripheral melatonin synthesis.	[90]
Chronic unpredictable mild stress（CUMS）Depressed rats	taVNS	Auricular Concha Regio	The expression of α7nAchR, p-JAK2, p-STAT3, NF-κB p65, p-NF-κB p65, and IL-1β.	Improve depressive behavior and inhibit hypothalamic neuroinflammation.	α7nAchR/JAK2/STAT3/NF-κB signaling pathway	[93]
Chronic unpredictable mild stress（CUMS）Depressed rats	taVNS	Auricular Concha Regio	Expression of hippocampal α7nAChR, NF-κB p65, and IL-1β; morphology of microglia.	Reducing inflammatory factors in the hippocampus reverses the activation of microglial cells and effectively alleviates depressive-like behavior.	The cholinergic anti-inflammatory pathway mediated by α7nAchR suppresses neuroinflammation.	[94]
Zucker diabetic obese rats	taVNS	Auricular Concha Regio	Blood glucose, glycosylated hemoglobin (HbA1c), forced swim test (FST), and insulin receptor (IR) expression.	Reduce blood glucose and HbA1c, upregulate IR expression, and	Regulation of the insulin signaling pathway, vagus	[95]

improve depressive-like behavior.	nerve-metabolic axis.

3.2.5 Zusanli (ST36) is a key acupoint of focus in both acupuncture and vagus nerve research

Through the review of studies on the roles of acupuncture and the vagus nerve in inflammatory responses and gastric motility regulation, it has been found that Zusanli (ST36) , as the He point of the Foot-Yangming Stomach Meridian, is a core acupoint for regulating gastrointestinal function and systemic immune-inflammatory responses. It is first mentioned in *Ling Shu or The Spiritual Pivotas*: "The Stomach Meridian originates from Lidui (ST45) … and enters Xialing (Lower Mound) , which is located three cun below the knee, on the lateral side of the tibia, known as Zusanli (ST36) ." *The Systematic Classic of Acupuncture and Moxibustion* elaborates on its main indications, including "Gastric distension and fullness, borborygmus with abdominal pain, visceral Qi deficiency and exhaustion, insufficiency of genuine Qi." *Tongxuan Zhiyao Fu* emphasizes its role in "Zusanli (ST36) alleviates emaciation and weakness caused by the Five Lao (Five Overstrains) ." The accumulated clinical experience of traditional medical practitioners indicates that ST36 has a bidirectional regulatory effect of tonifying the spleen and stomach and strengthening the body's resistance to pathogenic factors, laying the foundation for the classic application of "retaining the needle at Zusanli for abdominal disorders." Modern research not only validates its traditional functions of "regulating the spleen and stomach and strengthening the body's vital energy," but also reveals its role as a key link between traditional acupuncture theory and modern neuroscience through the cholinergic anti-inflammatory pathway (CAP) and neuroimmune integration mechanisms mediated by the vagus nerve. In clinical studies on the treatment of gastrointestinal diseases with acupuncture, the usage frequency of ST36 is as high as 72.3%, significantly higher than other acupoints, and it is often used as the main acupoint in compound prescriptions, highlighting its irreplaceable clinical value. Research shows that ST25 inhibits gastrointestinal motility through the sympathetic nerve, while ST36 mediates an excitatory effect through the vagus nerve, providing a neurobiological basis for the "near and far acupoint combination"[67]. Clinical studies have confirmed that stimulating ST36 enhances gastric antral contractions through the vagus nerve, thereby shortening the recovery time of gastrointestinal function in patients with postoperative intestinal obstruction [97]. Compared with other acupoints, the specific advantage of ST36 lies in its higher intensity of DMV c-Fos expression. Studies have shown that the intensity of DMV c-Fos expression induced by significant needling stimulation of ST36 is significantly higher than that of Hegu (LI4) , and the activation duration of α7nAChR is prolonged[98,99]. In terms of anti-inflammatory mechanisms, electroacupuncture at ST36 transmits peripheral signals to the nucleus tractus solitarius (NTS) and dorsal motor nucleus of the vagus nerve (DMV) through Aδ/C fibers, activates α7 nicotinic acetylcholine receptors (α7nAChR), and inhibits systemic inflammatory responses. Compared with non-acupoints or other acupoints on the Stomach Meridian (such as Fubu ST32), only ST36 can significantly upregulate the expression of acetylcholine transferase (ChAT) in the spleen and significantly inhibit inflammatory responses[100]. Cross-system disease studies further highlight the integrative advantages of ST36, such as reducing nausea in motion sickness models by activating the IRβ-ERK1/2 pathway in the DMV and synergistically inhibiting colonic inflammation when combined with vagus nerve stimulation (VNS)[101,102]. Current research has systematically analyzed the molecular and circuit mechanisms of vagus nerve activation

through needling ST36. Future research should further quantify the impact of electroacupuncture parameters on vagus nerve activation patterns and explore its synergistic effects with acupoints on the Spleen Meridian and Conception Vessel, promoting the transformation of acupuncture to a precise neuro-regulatory medical paradigm.

4 Conclusion and Outlook

Research on the application of acupuncture and the vagus nerve has become a highly focused academic area, demonstrating significant potential for development. The research scope in this field is extensive, covering multiple dimensions such as disease treatment and mechanism pathways. The current research hotspots in this area mainly revolve around applications in anti-inflammatory responses, gastrointestinal motility regulation, pain management, and depression treatment. The current research also has some limitations: (1) Although extensive studies have confirmed that acupuncture can regulate vagus nerve activity, there is no unified understanding of its specific mechanism in the academic community. To better reveal the neurobiological mechanism, future research needs the support of further clinical trials and more advanced and precise neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to observe and locate the effects of acupuncture stimulation on the vagus nerve in real time; (2) Due to multiple factors such as individual differences, acupoint selection, stimulation intensity and frequency that may affect the therapeutic effect of acupuncture, how to optimize the acupuncture treatment plan to achieve the best vagus nerve regulation effect has become an urgent problem to be solved; (3) In the application of acupuncture and vagus nerve, the current main methods for regulating vagus nerve activity are electroacupuncture (EA), auricular acupuncture (AA) and transcutaneous vagus nerve stimulation (taVNS). To broaden the treatment approaches and improve the overall therapeutic effect, more emerging acupuncture techniques can be introduced into this field. Therefore, future research needs to conduct in-depth exploration in these aspects to reveal the deeper principles and mechanisms of acupuncture and vagus nerve, providing reliable theoretical references for the clinical practice and scientific research of acupuncture and vagus nerve.

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