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Unveiling core acupoints in acupuncture treatment for primary depressive disorder: integrating data mining and network acupuncture-based analysis

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ABSTRACT

Objective To identify core acupoint patterns and elucidate the molecular mechanisms of acupuncture for primary depressive disorder (PDD) through data mining and network analysis.

Methods A comprehensive literature search was conducted across PubMed, Embase, Ovid Technologies (OVID), Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), China National Knowledge Infrastructure Database (VIP), Wanfang Data, and SinoMed Database from database foundation to January 31, 2025, for clinical studies on acupuncture treatment of PDD. Descriptive statistics, high-frequency acupoint analysis, degree and betweenness centrality evaluation, and core acupoint prescription mining identified predominant therapeutic combinations for PDD. Network acupuncture was used to predict therapeutic target for the core acupoint prescription. Subsequent protein-protein interaction (PPI) network and molecular complex detection (MCODE) analyses were conducted to identify the key targets and functional modules. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses explored the underlying biological mechanisms of the core acupoint prescription in treating PDD.

Results A total of 57 acupoint prescriptions underwent systematic analysis. The core therapeutic combinations comprised Baihui (GV20), Yintang (GV29), Neiguan (PC6), Hegu (LI4), and Shenmen (HT7). Network acupuncture analysis identified 88 potential therapeutic targets (79 overlapping with PDD), while PPI network analysis revealed central regulatory nodes, including interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, toll-like receptor 4 (TLR4), IL-10, brain-derived neurotrophic factor (BDNF), transforming growth factor (TGF)-β1, C-X-C motif chemokine ligand 10 (CXCL10), mitogen-activated protein kinase 3 (MAPK3), and nitric oxide synthase 1 (NOS1). MCODE-based modular analysis further elucidated three functionally coherent clusters: inflammation-homeostasis (score = 6.571), plasticity-neurotransmission (score = 3.143), and oxidative stress (score = 3.000). GO and KEGG analyses demonstrated significant enrichment of the MAPK, phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), and hypoxia-inducible factor (HIF)-1 signaling pathways. These mechanistic insights suggested that the antidepressant effects mediated through mechanisms of neuroinflammatory regulation, neuroplasticity restoration, and immune-oxidative stress homeostasis.

Conclusion This study reveals that acupuncture alleviates depression through a multi-level

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mechanism, primarily involving the neuroinflammation suppression, neuroplasticity enhancement, and oxidative stress regulation. These findings systematically clarify the underlying mechanisms of acupuncture's antidepressant effects and identify novel therapeutic targets for further mechanistic research.

1 Introduction

Primary depressive disorder (PDD), a psychiatric condition with global significance, is a leading contributor to disability across different populations. A major report by the Lancet-World Psychiatric Association Commission highlights the growing scale of this public health crisis, estimating that 5% of the global adult population experiences depression annually [1]. While conventional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), remain extensively used in clinical practice, their single-target pharmacological approaches frequently lead to postponed symptom relief, treatment resistance, and withdrawal effects [2]. Current data indicate that 50% of patients in the UK and 70% of patients in the USA receive long-term antidepressant treatment regimens exceeding one year [3, 4], a practice correlated with heightened severe withdrawal symptoms, and prolonged recovery timelines [5].

Acupuncture, a promising non-pharmacological intervention, has demonstrated efficacy in alleviating depressive symptoms by modulating neuroplasticity and neuroinflammatory pathways [6]. Recent studies have highlighted its potential as a valuable supplementary therapy to pharmacological treatments for depression, indicating adjunctive benefits in improving efficacy and reducing medication-related side effects [7-11]. Notably, emerging evidence suggests that acupuncture may rival or even surpass antidepressant monotherapy in terms of efficacy [12]. Guided by the holistic principles of traditional Chinese medicine (TCM), acupuncture prescriptions characterized by multi-acupoint synergy exhibit complex mechanistic networks that align with systemic biological interactions. This study employs "network acupuncture", a method combining co-occurrence analysis with biological network topology, to identify core acupoint prescriptions for PDD and their molecular targets. By building a multi-level interaction network that links core acupoints, targets, and PDD, we aim to uncover the systemic biological mechanisms underlying acupuncture's antidepressant effects. Our results are expected to offer a theoretical basis for mechanistic studies and assist in optimizing evidence-based clinical acupuncture strategies for PDD.

2 Data and methods

2.1 Data mining and statistical analysis

2.1.1 Literature search strategy A systematic search for randomized controlled trials (RCTs) on acupuncture for PDD was conducted across PubMed, Embase, Ovid Technologies (OVID), Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), China National Knowledge Infrastructure Database (VIP), Wanfang Data, and SinoMed Database. PubMed medical subject headings (MeSH) terms, including "acupuncture" "electroacupuncture" "moxibustion" "depressive disorder" "endogenous depression" "neurotic depression" "unipolar depression" "depressive syndrome" "melancholia" and related synonyms, were adapted to meet syntax requirements of each database. The search was restricted to studies from database inception to January 31, 2025.

2.1.2 Inclusion and exclusion criteria Inclusion criteria are as follows. (i) Study type: RCTs on acupuncture for PDD. (ii) Participants: the diagnostic criteria for PDD must meet those specified in either the Diagnostic and Statistical Manual of Mental Disorders (DSM-5/DSM-IV) [13, 14] or Chinese Classification of Mental Disorders-3 (CCMD-3) [15]. (iii) Intervention and control measures: the experimental group received acupuncture therapy alone or acupuncture combined with other TCM or Western medical treatments, with a focus on acupoints located on the 14 major meridians. The control group received non-acupuncture interventions, including TCM, Western medicine, sham acupuncture, or placebo treatments. The research design must be sufficiently rigorous to evaluate the therapeutic efficacy of acupuncture. (iv) Reporting: compliance with standardized acupuncture protocols, validated diagnostic/outcome criteria, and documented efficacy.

Exclusion criteria are as follows. (i) Participants: studies involving participants diagnosed with secondary depression or failing to meet PDD diagnostic criteria. (ii) Duplicate publications: redundant studies or overlapping datasets/prescriptions (only the earliest publication was retained). (iii) Study type: abstracts, expert opinions, basic experimental research (e.g., animal studies), theoretical discussions, narrative reviews, meta-analyses, systematic reviews, case reports, and non-research literature. (iv) Interventions: acupuncture prescriptions with undefined components or non-meridian techniques (e.g., auricular acupuncture, wrist-ankle acupuncture, or scalp acupuncture).

2.1.3 Literature quality control All screening phases followed a standardized quality assurance framework. Two evaluators independently conducted preliminary

title and abstract assessments, excluding publications failing predefined eligibility criteria. Subsequently, two separate analysts performed full-text evaluations to confirm parameter compliance. The methodological quality of included RCTs was evaluated using the Cochrane Risk of Bias Tool (RoB 2) [16]. Any discrepancies in quality assessment or inclusion decisions were resolved through panel deliberation, or when necessary, by arbitration from an independent adjudicator.

2.1.4 Database construction and standardization EndNote X9 was employed for deduplication, categorization, and preliminary screening of retrieved articles, culminating in a curated "Acupuncture for PDD" database. Metadata, including article titles, authors, journals, acupoint prescriptions, needle manipulation techniques, treatment durations, and effect estimates were systematically compiled and cataloged using Microsoft Excel 2019. Acupoint names were standardized to the World Health Organizition (WHO) nomenclature. To ensure data integrity, all procedures were independently executed by two researchers and verified by a third investigator, with discrepancies resolved through consensus adjudication.

2.1.5 Statistical methods for data mining All statistical analyses were performed using R software (v4.4.2). Heterogeneity among studies reporting effective rates was assessed using the I^2 statistic within random-effects models to evaluate betweenness centrality. Substantial heterogeneity was defined as $I^2 > 50\%$, following established thresholds for meta-analytic interpretation. Stratified subgroup analyses of documented acupuncture parameters (needle manipulation techniques and treatment duration) were conducted to explore heterogeneity sources using the meta package. When substantial heterogeneity persisted ($I^2 > 50\%$), iterative leave-one-study-out analyses were performed to identify influential studies causing heterogeneity.

Frequency distributions of individual acupoints were quantified via the itemFrequency function within the arules package. Acupoints demonstrating a utilization frequency $\geqslant 10$ were classified as high-frequency acupoints. The topological centrality indices were calculated using Cytoscape (v3.10.0), and the degree and betweenness centrality metrics were used to evaluate the network hub property of the acupoints. Those ranking within the top 10 for both degree and betweenness centrality metrics were designated as hub acupoints.

2.1.6 Core acupoint prescription identification via association rules To identify frequent acupoint patterns and candidate prescription combinations, association rule mining was implemented through the Apriori algorithm (the arules and arulesViz packages). Initial thresholds were set at Support $\geqslant 15\%$, Confidence $\geqslant 85\%$, and Lift $\geqslant 1$, with reference to empirical practices in the medical data mining [17].

Building on this initial setup, association rule analysis was specifically applied to identify clinically relevant acupoint usage patterns. The Apriori algorithm was executed with the defined thresholds to generate association rules quantifying interdependencies among acupoint variables. Through iterative optimization of support and confidence thresholds, topological pruning was performed to progressively eliminate peripheral acupoints [18], identifying a refined core acupoint prescription for PDD. The resultant association rules, including Support, Confidence, and Lift metrics, were visualized using interactive plotting functions within the arulesViz package, enabling concurrent evaluation of statistical reliability and clinical relevance.

2.2 Network acupuncture analysis

2.2.1 Core acupoint prescription target identification The targets corresponding to the core acupoints were systematically queried across PubMed, Embase, OVID, Web of Science, Cochrane Library, CNKI, VIP, Wanfang Data, and SinoMed Databases with search terms including "experimental" "molecular" "mechanism" and "signaling pathways", with a temporal scope spanning from database inception to January 31, 2025. Individualized target databases were constructed for each core acupoint, adhering to the following criteria. (i) Intervention criteria: the study included only research involving stimulation of core acupoints (excluding studies using combination acupoints or pharmacological interventions). (ii) Study type: preclinical investigations utilizing validated depression models in animal subjects. (iii) Experimental confirmation: statistically significant alterations ($P < 0.05$) measured by standardized methods [Western blot, quantitative polymerase chain reaction (qPCR), or enzyme-linked immunosorbent assay (ELISA)].

Identified targets were annotated and standardized to validated human gene nomenclature using the UniProt (https://www.uniprot.org/), ensuring cross-species translatability.

2.2.2 Target-disease network construction Potential therapeutic targets associated with PDD were retrieved from the GeneCards (https://www.genecards.org/). To prioritize high-confidence targets, those with relevance scores below the median were excluded. Additional candidate targets were supplemented from the Therapeutic Target Database (TTD, https://db.idrblab.net/ttd/), Online Mendelian Inheritance in Man (OMIM, https://www.omim.org/), and DrugBank (https://go.drugbank.com/). Acupoint and disease related targets were analyzed in R software, where the VennDiagram package identified overlapping targets, representing putative mechanisms of the core acupoint prescription. A tripartite "core acupoint prescription-target-PDD" interaction network was

constructed and visualized using Cytoscape, with node-edge relationships weighted by biofunctional relevance.

2.2.3 Protein-protein interaction (PPI) network PPI datasets were acquired from the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) platform (https://string-db.org/) under the following configured parameters. (i) Species restriction: *Homo sapiens*. (ii) Interaction confidence: minimum required score ⩾ 0.900 to retain only high-confidence PPIs. (iii) Active interaction sources: experiments, databases, co-expression, neighborhood, gene fusion, text mining, and co-occurrence.

Nodes lacking functional connections (degree = 0) were pruned to refine network topology. The PPI network analysis was imported into Cytoscape, where the integrated NetworkAnalyzer plugin facilitated the mapping and identification of central hub proteins through topological evaluation. Degree centrality is an indicator used to measure the status of a network's core hub. The top 10 targets ranked by degree centrality were identified as core therapeutic targets.

Following the construction of the PPI network, key functional modules were identified using molecular complex detection (MCODE) plugin (v2.0.3) within Cytoscape. The MCODE analysis was conducted using default topological parameters as established in the original algorithm publication and implemented in Cytoscape: degree cutoff = 2, node score cutoff = 0.2, k-core = 2, and max depth = 100. These widely adopted parameters enable robust detection of densely connected functional modules in biological networks [19]. The resulting modules were ranked based on their MCODE composite scores, and the highest-scoring clusters were selected as key functional modules for subsequent biological interpretation.

2.2.4 Functional enrichment analysis Functional enrichment analysis of targets associated with the core acupoint prescription and PDD was conducted via Database for Annotation, Visualization and Integrated Discovery (DAVID) (https://david.ncifcrf.gov/) to clarify pathway involvement and ontology-based relationships. Input the intersection genes of core acupoint prescription and PDD, and set the parameters as follows. (i) Select identifier: OFFICIAL_GENE_SYMBOL. (ii) Select species: *Homo sapiens*. (iii) List type: Gene List.

Functional enrichment analysis included Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway profiling and Gene Ontology (GO) assessments spanning three domains of molecular function (MF), biological process (BP), and cellular component (CC). Terms demonstrating statistical significance [false discovery rate (FDR)-adjusted $P < 0.01$] were ranked by relevance [20], with the top 20 KEGG enriched pathways and the top 10 enriched GO terms from each category visualized using computational tools (http://www.bioinformatics.com.cn/) for analytical interpretation.

3 Results

3.1 Literature screening and study selection

Initial literature searches across the nine databases identified 2 076 articles screened for relevance to acupuncture in PDD. Following rigorous screening against predefined inclusion and exclusion criteria, 71 studies were retained in the "Acupuncture for PDD" database for analysis (Figure 1). These studies yielded 71 unique acupoint prescriptions. To assess data heterogeneity, stratified subgroup analyses were conducted on the subset of 32 studies (of the total 71 included) reporting effectiveness rates, focusing on documented acupuncture intervention parameters, such as acupuncture manipulation techniques and treatment duration (Table 1). Subgroup analysis showed low heterogeneity (I^2 = 35.8%), suggesting minimal variability in therapeutic efficacy evaluations across different acupuncture manipulation techniques and duration. As the observed heterogeneity was below the conventional threshold of 50%, leave-one-study-out analyses were not performed. After a process of deduplication and data extraction protocols, 57 unique acupoint prescriptions were identified, spanning 75 distinct acupoints.

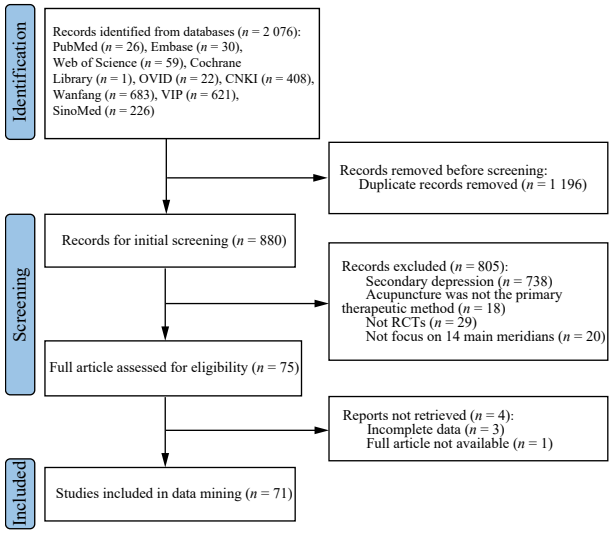

Figure 1 Flow chart of literature screening

3.2 Frequency and centrality of acupoints

The 57 acupoint prescriptions comprised 391 acupoint applications, with a mean of 6 – 7 acupoints per prescription. High-frequency acupoints (frequency ⩾ 10) accounted for 62.15% of total applications, including Baihui (GV20), Taichong (LR3), Neiguan (PC6), Yintang (GV29), Hegu (LI4), Sanyinjiao (SP6), Shenmen (HT7), Shenting (GV24), Ganshu (BL18), Fengchi (GB20), and Zusanli (ST36). Hub acupoints (ranked in the top 10 for both degree and betweenness centrality) included Baihui

Table 1 Subgroup analysis of the efficacy of acupuncture treatment for PDD

Analysis type	Subgroup	Number of studies	RR	CI	tau²	*P* value	I^2 value
By method	Acupuncture	28	1.15	1.10 – 1.20	0.004 4	0.018 3	39.40%
	Acupuncture & moxibustion	2	1.21	1.02 – 1.43	0	0.332 1	0.00%
	Electroacupuncture	2	1.19	1.06 – 1.34	0	0.342 5	0.00%
By duration	⩽ 4 weeks	5	1.15	1.01 – 1.31	0.012 6	0.018 9	66.10%
	5 – 8 weeks	25	1.16	1.11 – 1.21	0.002 7	0.188 4	19.70%
	> 8 weeks	2	1.17	1.05 – 1.31	0	0.852 2	0.00%
Overall	All studies	32	1.15	1.11 – 1.20	0.004 1	< 0.000 1	35.80%

RR, risk ratio. CI, confidence interval.

(GV20), Taichong (LR3), Neiguan (PC6), Hegu (LI4), Sanyinjiao (SP6), Yintang (GV29), Ganshu (BL18), and Shenmen (HT7). Table 2 quantitatively shows comparison of the topological properties for these high-frequency acupoints.

Table 2 Frequency, degree, and betweenness centrality of the high-frequency acupoints for PDD

No.	Acupoint	Frequency [*n* (%)]	Degree	Betweenness centrality
1	Baihui (GV20)	44 (11.25)	54	0.114
2	Taichong (LR3)	31 (7.93)	54	0.112
3	Neiguan (PC6)	29 (7.42)	49	0.076
4	Yintang (GV29)	28 (7.16)	40	0.044
5	Hegu (LI4)	23 (5.88)	48	0.067
6	Sanyinjiao (SP6)	22 (5.63)	44	0.064
7	Shenmen (HT7)	20 (5.12)	32	0.046
8	Shenting (GV24)	15 (3.84)	34	0.029
9	Ganshu (BL18)	11 (2.81)	35	0.079
10	Fengchi (GB20)	10 (2.56)	27	0.041
11	Zusanli (ST36)	10 (2.56)	35	0.039

Degree represents the number of direct connections that an acupoint has within the treatment network. Higher values indicate greater local influence. Betweenness centrality measures how often an acupoint acts as a "bridge" along the shortest paths between other points. Values are normalized (0 – 1), where 0 = no bridging role and 1 = maximum bridging potential. Higher values denote critical pathway control.

3.3 Core acupoint prescription identification by association rule mining

3.3.1 Association rules of high-frequency acupoints

Within the big-data framework, association rules quantified interdependencies among variables. By evaluating Confidence, Support, and Lift metrics, we identified relevant acupoint prescription patterns. Using the arules package in R software, the Apriori algorithm (Support ⩾ 15%, Confidence ⩾ 85%, Lift ⩾ 1) generated 25 association rules (Table 3).

3.3.2 Optimization and final identification of the core acupoint prescription

The Apriori algorithm was applied with an iterative threshold optimization strategy to differentiate robust clinical associations from coincidental patterns, guided by established data mining practices where increasing stringency filters out lower-probability rules to identify a core set of highly stable associations. Initial analysis with relaxed thresholds (Support ⩾ 15%, Confidence ⩾ 85%, Lift ⩾ 1) captured a broad set of potential acupoint prescriptions (Figure 2A). Subsequently, to identify the most clinically prevalent and statistically robust prescription, we incrementally increased the thresholds. A final threshold of Support ⩾ 25% and Confidence ⩾ 95% was selected, as it represented a statistical equilibrium where further stringency increases did not materially alter the core acupoint prescription pattern (Figure 2B). This methodological approach ensures that the results reflect intrinsic data structures rather than arbitrary parameter selection, thereby validating the reliability of the identified association rules.

Topological pruning at these elevated thresholds progressively excluded peripheral acupoints, yielding a refined core acupoint prescription: Baihui (GV20), Yintang (GV29), Neiguan (PC6), Hegu (LI4), and Shenmen (HT7). The validity of this core acupoint prescription is supported not only by its statistical robustness under stringent criteria but also by its convergence with independent analytical methods and established clinical practice. Specifically, its exact correspondence with the high-frequency and hub acupoints identified through network centrality analysis (Section 3.2) provides corroborating evidence from a separate quantitative perspective. Furthermore, this combination is well-documented in clinical guidelines for depression [21], offering external validity to the data-driven results.

3.4 Mechanistic exploration through targets and pathways

3.4.1 Target database compilation for core acupoints

Following systematic data mining, literature meeting stringent inclusion criteria was quantified as follows: Baihui (GV20; 98 articles), Yintang (GV29; 84 articles), Neiguan (PC6; 12 articles), and Shenmen (HT7; 15 articles). Although a high-frequency hub acupoint, Hegu

Table 3 Association rules analysis of high-frequency acupoints for PDD

No.	Antecedent	Consequent	Count	Support (%)	Confidence (%)	Lift
1	Yintang (GV29), Shenmen (HT7)	Baihui (GV20)	12	21.05	100.00	1.30
2	Hegu (LI4), Sanyinjiao (SP6)	Baihui (GV20)	10	17.54	100.00	1.30
3	Yintang (GV29), SanyinjiaoSP6	Baihui (GV20)	12	21.05	100.00	1.30
4	Hegu (LI4), Neiguan (PC6)	Baihui (GV20)	12	21.05	100.00	1.30
5	Yintang (GV29), Neiguan (PC6)	Baihui (GV20)	16	28.07	100.00	1.30
6	Yintang (GV29), Shenmen (HT7), Neiguan (PC6)	Baihui (GV20)	9	15.79	100.00	1.30
7	Yintang (GV29), Neiguan (PC6), SanyinjiaoSP6	Baihui (GV20)	9	15.79	100.00	1.30
8	Hegu (LI4), Taichong (LR3), Neiguan (PC6)	Baihui (GV20)	10	17.54	100.00	1.30
9	Yintang (GV29), Taichong (LR3), Neiguan (PC6)	Baihui (GV20)	9	15.79	100.00	1.30
10	Yintang (GV29)	Baihui (GV20)	27	47.37	96.43	1.25
11	Hegu (LI4)	Baihui (GV20)	22	38.60	95.65	1.24
12	Shenmen (HT7)	Baihui (GV20)	19	33.33	95.00	1.23
13	Hegu (LI4), Taichong (LR3)	Baihui (GV20)	18	31.58	94.74	1.23
14	Yintang (GV29), Taichong (LR3)	Baihui (GV20)	16	28.07	94.12	1.22
15	Shenting (GV24)	Baihui (GV20)	14	24.56	93.33	1.21
16	Shenmen (HT7), Neiguan (PC6)	Baihui (GV20)	14	24.56	93.33	1.21
17	Shenmen (HT7), Taichong (LR3)	Baihui (GV20)	13	22.81	92.86	1.20
18	Yintang (GV29), Hegu (LI4)	Baihui (GV20)	13	22.81	92.86	1.20
19	Shenmen (HT7), Sanyinjiao (SP6)	Baihui (GV20)	12	21.05	92.31	1.20
20	Yintang (GV29), Hegu (LI4), Taichong (LR3)	Baihui (GV20)	11	19.30	91.67	1.19
21	Shenmen (HT7), Taichong (LR3), Neiguan (PC6)	Baihui (GV20)	9	15.79	90.00	1.17
22	Neiguan (PC6)	Baihui (GV20)	26	45.61	89.66	1.16
23	Taichong (LR3), Neiguan (PC6)	Baihui (GV20)	16	28.07	88.89	1.15
24	Taichong (LR3)	Baihui (GV20)	27	47.37	87.10	1.13
25	Yintang (GV29), Hegu (LI4)	Taichong (LR3)	12	21.05	85.71	1.58

(LI4) was excluded from the mechanistic analysis because no qualifying studies investigated its effects in isolation. All available research involved combinations with non-core acupoints, preventing attribution of specific mechanistic targets. Following data collation, validation, and duplicate removal, each acupoint demonstrated distinct target associations: Baihui (GV20; 79), Yintang (GV29; 68), Neiguan (PC6; 11), and Shenmen (HT7; 16). Integration of these datasets identified 88 non-redundant potential therapeutic targets, forming the mechanistic foundation of the core acupoint prescription. The complete list of core acupoint targets is presented in Supplementary Table S1.

3.4.2 Overlap analysis between acupoint targets and PDD-associated targets A total of 17 036 targets were initially identified from the GeneCards database. Targets with relevance scores below the median threshold (score $\leqslant$ 2.87) were excluded, yielding 8 518 high-confidence candidates. Subsequent integration of supplemental targets from the TTD (55 targets), OMIM (474 targets), and DrugBank (152 targets) resulted in 8 552 non-redundant disease-associated targets following deduplication (Supplementary Table S2). Of the 88 core acupoint prescription-associated targets, 79 (89.8%) overlapped with PDD-related disease targets (Figure 2C). These overlapping targets represent putative mediators of acupuncture's antidepressant effects and demonstrate strong alignment between the core acupoint prescription and PDD pathological mechanisms. A tripartite core acupoint prescription-target-PDD network was constructed (Figure 2D).

3.4.3 PPI network construction and hub target identification PPI network analysis of 79 key targets was identified using STRING (Supplementary Table S3). Only the highest-confidence interactions (combined score > 0.900) were retained. A disconnected node (Heparanase) was identified and subsequently removed during network pruning, yielding a refined PPI network comprising 78 nodes and 89 edges (Figure 2E). The 10 highest-degree centrality targets—interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, toll-like receptor 4 (TLR4), IL-10, brain-derived neurotrophic factor (BDNF), transforming growth factor (TGF)-β1, C-X-C motif chemokine ligand 10 (CXCL10), mitogen-activated protein kinase 3 (MAPK3), and nitric oxide synthase 1 (NOS1)—were identified as core therapeutic targets. These targets functioned as pivotal network hubs, exhibiting significant topological influence through extensive connectivity within the PPI

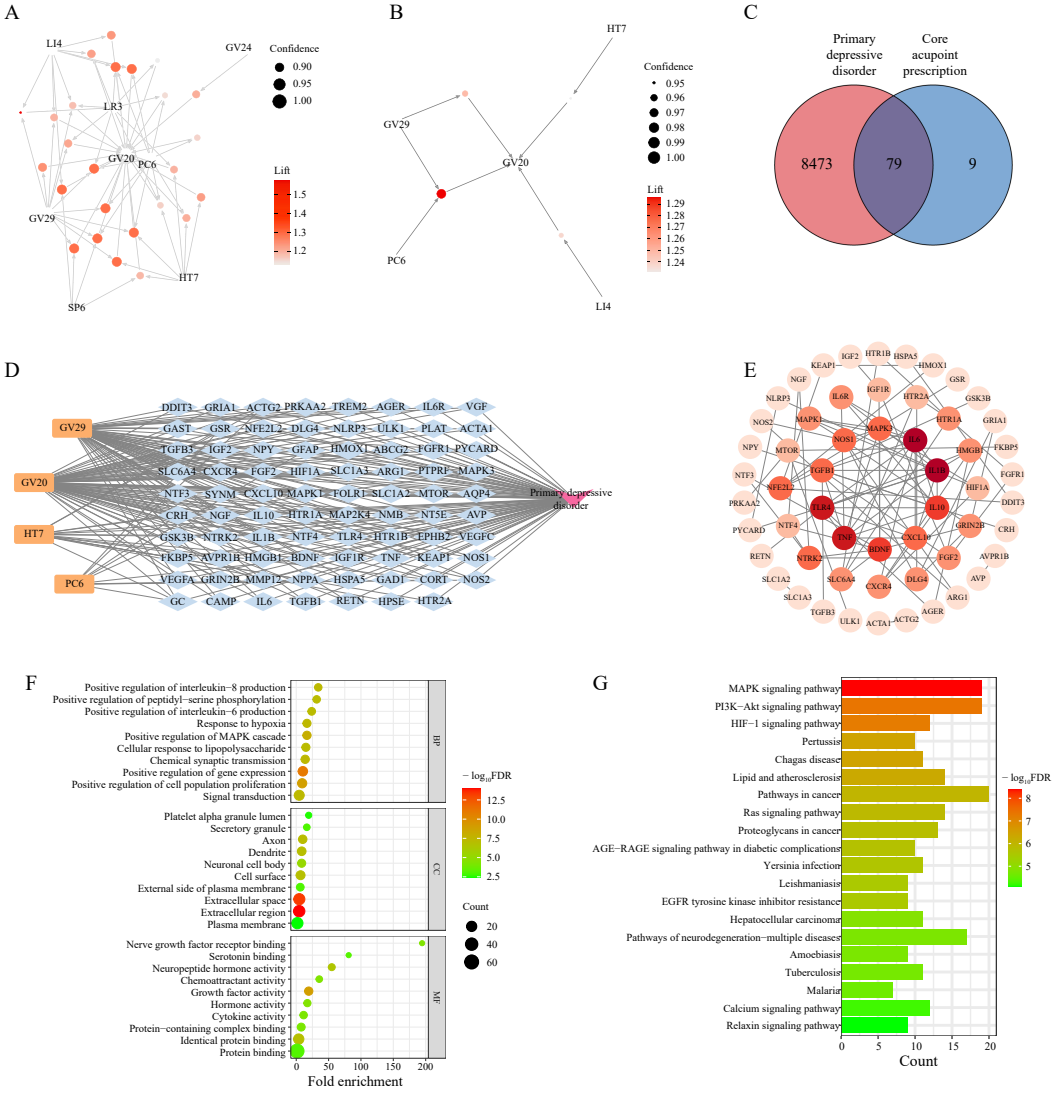

Figure 2 Network acupuncture analysis of core acupoint prescription for PDD

A, association rules of core acupoint prescription (Support ⩾ 15%, Confidence ⩾ 85%). B, association rules of core acupoint prescription (Support ⩾ 25%, Confidence ⩾ 95%). C, the potential target of acupuncture treatment. D, core acupoint prescription-target-PDD network. Orange stands for the core acupuncts, blue for the targets, and pink for the disease PDD. The lines represent how the three interact with each other. E, PPI network of core acupoint prescription. Each node represents a target, and each line represents the correlation between two targets. The network was visualized using a radial layout sorted by descending degree centrality. Node coloring follows a gradient spectrum from dark red (highest centrality) to pale yellow (lowest), with spatial positioning radiating from the network core to periphery. F, the top 10 enriched GO terms from each category. G, the top 20 enriched KEGG pathways.

network. MCODE analysis revealed three functional modules corresponding to therapeutic mechanisms: Clusters 1 (inflammation-homeostasis), 2 (plasticity-neurotransmission), and 3 (oxidative stress) (Table 4). MCODE analysis showed Cluster 1 achieved the highest MCODE score (6.571), suggesting that inflammatory pathways represent a central mechanism of acupuncture's anti-depression effects.

Table 4 Topological parameters and key targets of functional modules identified by MCODE analysis

Cluster	Score	Node	Edge	Node ID
1	6.571	8	23	TLR4, CXCL10, IL-1B, IL-6, IL-6R, IL-10, TNF, TGF-B1
2	3.143	8	11	SLC6A4, HTR1B, HTR1A, DLG4, GRIA1, HTR2A, GRIN2B, BDNF
3	3.000	3	3	KEAP1, NFE2L2, HMOX1

SLC6A4, solute carrier family 6 member 4. HTR1B, 5-hydroxytryptamine receptor 1B. HTR1A, 5-hydroxytryptamine receptor 1A. DLG4, discs large membrane-associated guanylate kinase (MAGUK) scaffold protein 4. GRIA1, glutamate ionotropic receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type subunit 1. HTR2A, 5-hydroxytryptamine receptor 2A. GRIN2B, glutamate ionotropic receptor N-methyl-D-aspartate (NMDA) type subunit 2B. KEAP1, kelch-like enoyl-CoA hydratase (ECH)-associated protein 1. NFE2L2, nuclear factor erythroid 2-related factor 2. HMOX1, heme oxygenase 1.

3.4.4 Functional characteristics and pathway enrichment of key targets GO functional enrichment and KEGG pathway analyses were conducted on the 79 key targets using the DAVID database. This analysis identified 417 BP, 57 CC, and 105 MF terms (Supplementary Table S4). The top 10 most statistically significant GO terms for each category were visualized in Figure 2F. KEGG pathway analysis revealed 122 signaling pathways (Supplementary Table S5), with the top 20 most enriched pathways depicted in Figure 2G. Among these, the most significant functions and pathways identified were as follows.

(i) BP: positive regulation of gene expression (FDR = 1.09×10^{-11}), positive regulation of cell population proliferation (FDR = 1.09×10^{-9}), positive regulation of MAPK cascade (FDR = 8.70×10^{-9}), response to hypoxia (FDR = 4.24×10^{-8}), and chemical synaptic transmission (FDR = 4.24×10^{-8}).

(ii) CC: extracellular region (FDR = 1.02×10^{-14}), extracellular space (FDR = 5.70×10^{-14}), axon (FDR = 6.89×10^{-8}), dendrite (FDR = 9.36×10^{-8}), and cell surface (FDR = 1.15×10^{-7}).

(iii) MF: growth factor activity (FDR = 9.71×10^{-10}), identical protein binding (FDR = 1.15×10^{-7}), neuropeptide hormone activity (FDR = 3.04×10^{-7}), hormone activity (FDR = 3.44×10^{-5}), and nerve growth factor receptor binding (FDR = 3.93×10^{-5}).

(iv) KEGG: MAPK signaling pathway (FDR = 4.06×10^{-9}), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway (FDR = 4.42×10^{-8}), hypoxia-inducible factor (HIF)-1 signaling pathway (FDR = 5.86×10^{-8}), Chagas disease (FDR = 3.69×10^{-7}), and pertussis (FDR = 3.69×10^{-7}).

4 Discussion

4.1 Core acupoint prescription and clinical relevance

Baihui (GV20) emerged as the most critical component in the identified association rules, consistently forming high-frequency combinations with Yintang (GV29), Neiguan (PC6), and Hegu (LI4). This finding aligns with TCM theoretical framework, wherein Baihui (GV20; confluence point) governs systemic Yang Qi circulation. Its synergistic action with Yintang (GV29; calming the spirit), Neiguan (PC6; harmonizing blood), Hegu (LI4; regulating Qi), and Shenmen (HT7; stabilizing consciousness) addresses spirit-Qi-blood disequilibrium, potentially modulating prefrontal-limbic circuitry [22]. The high confidence (100%) of key combinations [e.g., Yintang (GV29) + Neiguan (PC6) + Baihui (GV20)] further supports their clinical robustness.

The identified core acupoints—Baihui (GV20), Yintang (GV29), Neiguan (PC6), Hegu (LI4), and Shenmen (HT7)—are largely consistent recommendations from clinical practice guidelines [21] and empirical studies [23], where Baihui (GV20) and Yintang (GV29) are consistently prioritized as primary acupoints due to their well-documented neuromodulatory effects [24, 25], which include reducing anxiety, improving sleep quality, and enhancing cognitive function. Neiguan (PC6), Hegu (LI4), and Shenmen (HT7) are classified as secondary acupoints, widely employed to alleviate symptoms such as depression, anxiety, and insomnia [21]. Their inclusion in the association rules reflects their clinical application in managing comorbid conditions and enhancing treatment efficacy. Notably, Taichong (LR3)—despite its empirical use for "liver Qi stagnation", a common TCM pattern in emotional disorders, was excluded from the high-confidence combinations. The exclusion stems from statistical thresholds (Support < 25% and Confidence < 95%), which prioritize combinations with higher frequency and consistency in the dataset. Such discrepancies highlight a potential divergence between traditional pattern-specific acupoint selection and data-driven approaches that emphasize empirical efficacy. This gap underscores the need for further research to reconcile TCM theories with modern, evidence-based methodologies, particularly in elucidating the mechanisms underlying acupoint synergy and optimizing treatment protocols for complex disorders.

4.2 Mechanistic insights from PPI network analysis

Integrated network and MCODE analyses identified core targets across three pathophysiological domains. These computational predictions reveal potential mechanistic associations.

4.2.1 Inflammation-homeostasis Cluster 1 comprised both pro-inflammatory mediators (TLR4, IL-6, IL-1β, TNF-α, and CXCL10) and anti-inflammatory cytokines (IL-10 and TGF-β1), suggesting a potential regulatory role in inflammatory balance. Substantial evidence indicates that psychological and somatic stressors can elevate pro-inflammatory cytokines [26-28], including IL-6 and TNF-α, causing neuronal damage [29, 30], and TLR4 activation drives inflammatory cascades via nuclear factor (NF)-κB signaling pathway induction [31-33]. Furthermore, IL-6 and TNF-α can traverse the blood-brain barrier (BBB) to stimulate central cytokine production [34-36], while CXCL10 can compromise BBB integrity and activate microglia [37]. Conversely, IL-10 and TGF-β1 exert suppressive effects on neuroinflammation and confer neuroprotection [38, 39], highlighting a bidirectional immunomodulatory dynamic within the cluster. While systemic inflammation is widely implicated in depression, our network analysis specifically highlights the functional integration of these immune targets, implying that acupuncture may exert its effects through coordinated modulation of this particular network.

The central role of TLR4, with its high degree of connectivity to both pro- and anti-inflammatory components, suggests its potential as a key regulatory node in

this network. TLR4 activation drives inflammatory cascades via the NF-κB signaling pathway induction, a critical pathway linking innate immune activation to cytokine production. We propose that acupuncture might facilitate a shift toward anti-inflammatory signaling, possibly through modulation of the TLR4/NF-κB signaling pathway, thereby reducing the release of key pro-inflammatory cytokines and attenuating microglial activation. Furthermore, the strong interaction between TLR4 and CXCL10 points to a potential mechanism for preserving BBB integrity, as CXCL10-mediated BBB disruption is a key initiating event in neuroinflammation. While systemic inflammation is widely implicated in depression, our network analysis specifically highlights the functional integration of these immune targets. This implies that acupuncture may exert its effects through coordinated modulation of this particular network, rather than through isolated targeting of individual cytokines.

Notably, the co-occurrence of IL-10 and TGF-β1 with pro-inflammatory factors supports the notion of bidirectional immunomodulation, wherein acupuncture may promote rebalancing of immune homeostasis rather than simply suppressing inflammation. Such rebalancing could create conditions more favorable to neural repair, offering a potential explanation for its therapeutic effects in depression. These network associations suggest testable hypotheses regarding acupuncture-specific mechanisms. However, further functional studies are needed to confirm whether these interactions indeed contribute to its antidepressant effects and to distinguish them from general anti-inflammatory pathways.

4.2.2 Plasticity-neurotransmission Cluster 2 comprised a functionally coherent set of targets central to neural repair and communication, including BDNF, GRIN2B, GRIA1, HTR1A, HTR1B, HTR2A, and SLC6A4. BDNF, as a critical regulator of neuroregeneration and synaptic plasticity, is well established [40], promoting neuronal survival, synaptogenesis, and dendritic remodeling through pathways, such as MAPK3 activation, which in turn reinforces BDNF signaling [41].

The robust co-clustering of BDNF with both serotonin and glutamate receptors suggests that acupuncture may concurrently enhance neurotrophic support and modulate excitatory and monoaminergic neurotransmission. This integrated modulation is particularly notable in light of the delayed therapeutic effects of conventional SSRIs, arising from the interaction between serotonin signaling and BDNF-mediated plasticity [42]. Acupuncture's concurrent modulation of these interconnected systems may thereby underlie its potential to facilitate more rapid neuroadaptive changes.

Furthermore, the network associations between BDNF and inflammatory cytokines supported existing evidence that acupuncture mitigates cytokine-mediated suppression of BDNF [43]. This suggests a dual-mode action whereby acupuncture not only alleviates neuroinflammation-induced BDNF downregulation but also directly facilitates BDNF-MAPK3 signaling. Such synergistic "anti-inflammatory plus pro-plasticity" effects may collectively promote neural circuit restoration. The presence of key synaptic elements within this cluster underscores its role in supporting structural and functional repair of neuronal networks.

4.2.3 Oxidative stress Cluster 3 encompassed core components of the endogenous antioxidant response system, including KEAP1, NFE2L2, and HMOX1. The KEAP1-NFE2L2 axis is a well-established regulator of cellular defense against oxidative damage [44]. The robust functional coupling among these targets suggests that acupuncture may alleviate oxidative stress by activating this key cytoprotective pathway. Moreover, this antioxidant mechanism may operate synergistically with the anti-inflammatory effects mediated by IL-10 and TGF-β1 (as identified in Cluster 1), collectively mitigating neurotoxic stressors in depression. Nevertheless, the specific involvement of acupuncture in modulating the KEAP1-NFE2L2-HMOX1 axis remains to be empirically validated.

4.3 Key findings from GO functional enrichment

GO enrichment analysis corroborated established mechanisms (MAPK signaling and IL-6 modulation) and proposed novel potential therapeutic targets.

(i) BP. Within BP, two notably enriched terms—beyond the anticipated involvement of MAPK signaling and IL regulation—suggest novel mechanistic insights into acupuncture's therapeutic action. (a) Positive regulation of peptidyl-serine phosphorylation emerged as one of the most significantly enriched terms, implying that acupuncture may influence key signaling cascades through targeted modification of serine phosphorylation events on transcription factors such as cAMP response element-binding protein (CREB). This observation offers a plausible mechanistic basis whereby acupuncture could coordinate activity-dependent neuroplasticity and gene expression. (b) Similarly, the statistically significant enrichment of the hypoxia response term, which demonstrates strong association with HIF-1 signaling, suggests a potential role for acupuncture in improving cerebral oxygenation and mitigating neurovascular dysfunction frequently observed in PDD. The concerted enrichment of these processes, in conjunction with those related to inflammation and MAPK activity, points to a concurrent modulation of neuroinflammation, synaptic remodeling, and bioenergetic adaptation, potentially mediated through an integrated IL-6/MAPK/HIF-1 signaling network. This multifaceted regulatory activity may fundamentally underpin the multi-level restorative effects of acupuncture in depression.

(ii) CC. CC analysis highlighted significant enrichment in extracellular regions and spaces, suggesting that acupuncture may primarily modulate the extracellular microenvironment, via the regulation of cytokine, chemokine, or growth factor signaling pathways. Furthermore, pronounced enrichment was observed for neuronal structural components, specifically axons and dendrites, indicating that acupuncture's effects may be spatially targeted to regions critical for neural communication and structural plasticity. This distinct subcellular localization pattern substantiates the hypothesis that acupuncture promotes synaptic remodeling and functional reorganization of neural networks, consistent with established evidence documenting its effects on neurogenesis, synaptic connectivity, and overall neuronal architecture [45].

(iii) MF. MF revealed that neuropeptide hormone activity emerged as one of the most significantly enriched biological functions suggesting that neuropeptide systems (e.g., BDNF, nerve growth factor) may act as pivotal molecular mediators underlying acupuncture's antidepressant effects. Notably, nerve growth factor receptor binding demonstrated exceptionally robust enrichment, strongly implicating potentiated neurotrophic signaling as a key mechanistic pathway. This enrichment pattern potentially aligns with observations of synergistic interactions between neurotrophin signaling and broader growth factor networks, which collectively promote synaptic remodeling and neuronal repair, promoting neural regeneration. These findings highly indicate that acupuncture may predominantly influence neurotrophic and neuropeptide-mediated signaling pathways, whereby neuropeptides such as nerve growth factor initiate receptor binding and activate downstream neurotrophic cascades that ultimately support synaptic remodeling and neural repair.

4.4 Key pathways identified by KEGG enrichment

KEGG pathway enrichment analysis predicted the involvement of several core signaling pathways in mediating the antidepressant efficacy of acupuncture against PDD, including the MAPK, PI3K-Akt, HIF-1, Chagas disease, and pertussis pathways. Evidence indicates that aberrant MAPK pathway activation in PDD impairs neuroplasticity, whereas acupuncture is proposed to restore synaptic integrity by modulating MAPK cascades, thereby enhancing neuronal growth and synaptic remodeling [46]. The PI3K-Akt pathway, acts as a critical contributor for neuronal survival, metabolism, and plasticity [47], is hypothesized to mediate acupuncture's neuroprotective effects through apoptosis inhibition and functional recovery potentiation [48]. Additionally, the HIF-1 signaling pathway, known for coordinating adaptive responses to hypoxic stress and oxygen homeostasis [49], was identified as a significantly enriched and relatively underexplored mechanism in the context of acupuncture for PDD.

Notably, our analysis suggests functional crosstalk among these pathways, particularly between HIF-1 signaling and the MAPK/PI3K-Akt axes, a relationship supported by shared targets, including IL-6, TNF-α, TLR4, and MAPK3. These findings imply that acupuncture may exert multi-target effects by concurrently modulating neuroinflammation, hypoxia response, and synaptic plasticity through an integrated network, rather than isolated pathways. Such broad-spectrum modulation could disrupt the pathological cycle of PDD, wherein neuroinflammation and cerebral hypoxia mutually reinforce each other.

The observed enrichment of the Chagas disease and pertussis pathways likely reflects their shared involvement in inflammatory signaling rather than pathogen-specific processes. These enrichments originate from conserved TLR4/NF-κB inflammatory modules, supporting the hypothesis that acupuncture alleviates PDD partly through broad suppression of neuroinflammatory cascades.

4.5 Limitations and future prospects

This study has several limitations that should be acknowledged. First, as an *in silico* investigation, our findings rely exclusively on computational analyses and public database mining. The proposed mechanisms, such as HIF-1 modulation or KEAP1-NFE2L2 activation, remain hypothetical and require experimental validation to confirm their biological relevance. Second, although subgroup analyses suggested that certain parameters (e.g., needle manipulation and treatment duration) may influence efficacy, quantitative synthesis was limited by inconsistent outcome reporting across studies. The available data were insufficient to fully explore potential sources of heterogeneity, and unmeasured confounding factors may remain. Third, the multi-level inference approach—integrating acupoint, gene, and disease interactions—introduces translational uncertainties, including interspecies differences between animal models and human pathophysiology, as well as the indirect nature of many bioinformatically inferred connections.

Future studies should prioritize three key directions: experimental validation of the identified therapeutic targets using cellular and animal models, clinical research with standardized protocols to confirm the impact of specific acupuncture parameters, and the integration of multi-omics data and advanced computational methods to enhance the precision and biological relevance of network acupuncture predictions.

5 Conclusion

This study employed data mining to identify a core five-acupoint prescription for PDD. Integrative network acupuncture analyses suggest that acupuncture may

alleviate depressive pathology via a multi-dimensional regulatory framework involving neuroinflammation-hypoxia adaptation, plasticity-neurotransmission integration, and neural microenvironment optimization. The findings offer novel insights into the systems-level mechanisms of acupuncture and identify potential targets for future experimental research, thereby supporting further investigation into multi-target interventions for PDD.

Competing interests

The authors declare no conflict of interest.

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针灸治疗原发性抑郁症的核心穴位研究：结合数据挖掘和网络针灸学分析

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【摘要】目的 通过数据挖掘和网络分析，识别针灸治疗原发性抑郁障碍（PDD）的核心穴位处方并阐明其分子机制。**方法** 系统检索 PubMed、Embase、Ovid Technologies、Web of Science、Cochrane Library、中国知网、维普数据库、万方数据库和中国生物医学文献服务系统自建库至 2025 年 1 月 31 日发表的针灸治疗 PDD 的临床研究文献。采用描述性统计、高频穴位分析、度与介数中心性分析及核心穴位处方挖掘以确定 PDD 治疗的优势配伍。通过网络针灸学预测核心穴位处方的治疗靶点。进行蛋白质-蛋白质相互作用（PPI）网络与分子复合物检测（MCODE）分析以确定关键靶点和功能模块。通过基因本体（GO）和京都基因与基因组百科全书（KEGG）通路分析探究核心穴位处方治疗 PDD 的潜在生物学机制。**结果** 分析共纳入了 57 个穴位处方。核心处方包括百会（GV20）、印堂（GV29）、内关（PC6）、合谷（LI4）和神门（HT7）。网络针灸学鉴定出 88 个潜在治疗靶点（其中 79 个与 PDD 重叠）。PPI 网络分析揭示了关键靶点，包括白细胞介素（IL）-6、IL-1β、肿瘤坏死因子（TNF）-α、Toll 样受体 4（TLR4）、IL-10、脑源性神经营养因子（BDNF）、转化生长因子（TGF）-β1、C-X-C 基序趋化因子配体 10（CXCL10）、丝裂原活化蛋白激酶 3（MAPK3）和一氧化氮合酶 1（NOS1）。MCODE 模块分析识别出三个功能一致的簇：炎症-稳态（评分为 6.571）、可塑性-神经传递（评分为 3.143）和氧化应激（评分为 3.000）。GO 和 KEGG 富集分析表明，主要通路涉及 MAPK、磷酸肌醇 3-激酶/蛋白激酶 B（PI3K/Akt）和缺氧诱导因子（HIF）-1 等，提示其作用机制涉及神经炎症调节、神经可塑性恢复以及免疫-氧化应激稳态的调控。**结论** 本研究揭示了针灸通过多层次作用机制缓解抑郁症状，主要涉及抑制神经炎症、增强神经可塑性及调节氧化应激，系统阐明了针灸的抗抑郁作用，并为进一步的机制研究提供了新靶点。

【关键词】针灸；原发性抑郁障碍；数据挖掘；网络针灸学；关联分析