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ORIGINAL RESEARCH

A Bibliometric Analysis of Research on Natural Medicines for Depression from 2004 to 2024

Linsun Lin[1,2,*], Ziyi Guo[3,4,*], Qiuzhong Zhan[1], Peigang Fang[1], Haojun Shi[1], Yanchen Feng[5], Sheng Tian[1,6], Lu Xiao[7], Min Chen[1,8], Tao Wang[9]

[1]Faculty of Chinese Medicine and State Key Laboratory of Quality Research in Chinese Medicines, Macau University of Science and Technology, Macau, Macau SAR, 999078, People's Republic of China; [2]Clinical Medicine College, Huizhou Health Sciences Polytechnic, Huizhou, 516025, People's Republic of China; [3]Department of Rehabilitation Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, 450052, People's Republic of China; [4]National Engineering Laboratory for Internet Medical Systems and Applications, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, 450052, People's Republic of China; [5]Department of Neuropsychiatry and Psychology, The First Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou, 450000, People's Republic of China; [6]Innovative Institute of Chinese Medicine and Pharmacy, Shandong University of Traditional Chinese Medicine, Jinan, 250355, People's Republic of China; [7]Zhuhai Campus, Zunyi Medical University, Zhuhai, 519041, People's Republic of China; [8]Innovation Technology Research Institute, Macau University of Science and Technology, Hengqin, 519000, People's Republic of China; [9]Encephalopathy Center, The Second Affiliation Hospital of Anhui University of Chinese Medicine, Hefei, 230000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Tao Wang; Min Chen, Email 34613464@qq.com; mchen@must.edu.mo

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Objective: Depression imposes a severe global health burden. Natural medicines offer multi-target therapeutic potential, but a comprehensive bibliometric assessment of this field is lacking. This study analyzes the research landscape from 2004 to 2024 to map global contributions, collaboration networks, and evolving trends, thereby providing an evidence-based roadmap for future research.

Methods: We systematically retrieved publications on natural product-based medicines for depression from the Web of Science Core Collection (WoSCC) between 2004 and 2024. Bibliometric analysis was performed using CiteSpace, VOSviewer, and the R package "bibliometrix" to examine publication trends, collaboration networks, co-citation patterns, and keyword hotspots.

Results: Our analysis of 3,610 publications from 92 countries/regions revealed China's dominant leadership in both productivity and collaborative influence. The Beijing University of Chinese Medicine was identified as the most productive institution, while the Journal of Ethnopharmacology and Phytomedicine were the most cited journals. Key prolific authors included Qin Xuemei and Zhang Yi, and foundational works by researchers such as Porsolt and Sarris Jerome were the most frequently cited. Keyword clustering analysis identified three major research themes: mechanistic investigations (eg, "neuroinflammation", "oxidative stress"), phytochemical analysis (eg, "flavonoids", "alkaloids"), and clinical applications (eg, "randomized controlled trial"). The field has evolved from foundational preclinical models toward a stronger focus on clinical translational research.

Conclusion: This bibliometric study highlights China's central role in the research on natural medicines for depression and delineates the evolution of major research themes. The findings underscore the necessity for enhanced international collaboration and more rigorous clinical trials to validate the efficacy of bioactive compounds, which is crucial for advancing novel antidepressant drug development.

Keywords: natural medicines, depression, bibliometric, citespace, VOSviewer

Introduction

Depression is one of the most prevalent mental disorders in the world. According to the latest statistics from the World Health Organization, approximately 280 million individuals suffer from depression globally, making it a leading cause of disability and significant public health concern.[1] Beyond the substantial psychological and physical distress inflicted on patients, depression imposes a heavy socioeconomic burden, with estimated annual productivity losses reaching $1

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trillion globally.[2] In particular, there has been a marked increase in the incidence of depression following the COVID-19 pandemic, especially among high-risk populations such as adolescents and healthcare workers.[3]

The first-line treatment for depression involves a combination of evidence-based psychotherapies and pharmacotherapy, with current clinical practice primarily utilizing chemically synthesized antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).[4,5] However, the use of conventional antidepressants has several limitations. Studies indicate that approximately 30–50% of patients exhibit an inadequate response to existing pharmacotherapies, resulting in so-called "treatment-resistant depression"[6] Furthermore, these medications typically require 4–6 weeks to manifest their therapeutic effects and are frequently associated with adverse reactions including sexual dysfunction, weight gain, and gastrointestinal disturbances, leading to poor patient compliance. Alarmingly, certain drugs may increase suicide risk during the initial treatment phases, particularly among adolescent patients[7] These limitations have driven researchers to explore safer and more effective alternative therapeutic approaches. In this context, natural medicines have garnered increasing attention owing to their multi-target mechanisms of action and favorable safety profiles. Substantial evidence has demonstrated that bioactive compounds from medicinal plants exert antidepressant effects through diverse pathways.[8] Current evidence supports the therapeutic potential of several phytoceuticals for mood and anxiety disorders, including unipolar depression, Hypericum perforatum (St. John's wort; +++), and Crocus sativus (saffron; ++).[9]

Over the past two decades, research on natural antidepressants has experienced exponential growth, with publication numbers increasing nearly 20-fold from 1999 to 2023, reflecting rapid development in this field.[10] The observed rise in publication volume since 2015 may be linked to several key drivers, such as increased governmental and institutional funding for traditional medicine research, supportive policy initiatives promoting integrative healthcare, and the rapid advancement of pharmacological technologies including bioinformatics, network pharmacology, and high-throughput sequencing.[11] These factors have collectively accelerated the pace of discovery and clinical translation in this field. The research focus has evolved from initial efficacy observations to more sophisticated investigations of the mechanisms of action, active component identification, and formulation optimization. Previous bibliometric studies have examined antidepressant research from different perspectives, including global trends in pharmacological treatments for major depressive disorder and the role of complementary and alternative medicine in mental health.[12] However, to date no bibliometric analysis has focused specifically on natural medicines for depression, which highlights the novelty and value of the present study.

This study employed bibliometric methods to comprehensively analyze the knowledge structure and evolutionary trends in natural antidepressant research from 2004 to 2024. Our investigation focuses on characterizing citation networks to identify landmark studies, elucidating international collaboration patterns to reveal global research dynamics, and tracking thematic evolution to forecast future research directions. The findings will provide valuable references for researchers, facilitating not only a deeper understanding of the fundamental advances and clinical translation of natural antidepressants but also promote interdisciplinary integration and international collaboration. Ultimately, this study aims to provide theoretical foundations and innovative perspectives for the development of novel natural antidepressants, thereby contributing to the optimization and refinement of depression treatment strategies.

Materials and Methods

Data Source and Search Strategies

For this bibliometric analysis, data were systematically retrieved from the Web of Science Core Collection (WoSCC), specifically the Science Citation Index-Expanded (SCI-E) database, which indexes over 12,000 high-impact journals across scientific disciplines,[13] This represents the most comprehensive and reliable source for bibliometric studies because of its rigorous journal selection process, standardized citation data, and extensive coverage of peer-reviewed literature.[14] The WoS search formula was set as follows: TS = (Depressive Symptom* OR Symptom, Depressive OR Emotional Depression OR Depression) and TS = ("Nature medicine" OR "Nature drug*" OR "Traditional Chinese medicine" OR "Chinese medicine" OR "Chinese medicinal formula*" OR "Prescription of traditional Chinese medicine" OR "Herb" OR "Medicinal plant*" OR "Herbal medicine" OR "Plant extract*" OR "Herb extract*" OR "Herbal

compound*" OR "Plant compound*" OR "Phytochemical*") and their variants, with the search period restricted to 2004–2024 to capture the complete 20-year research trajectory, while the results were limited to original research articles and reviews in English to ensure data quality and consistency.

Inclusion & Exclusion Criteria

The inclusion criteria were as follows: (1) publication type restricted to original research articles (n=2,854) or comprehensive reviews (n=756), totaling 3,610 studies. Exclusion criteria eliminated 66 non-conforming publications: (1) non-English publications and (2) various non-research document types, including editorials (n=10), conference materials (meeting abstracts, n=34), book chapters (n=16), letters (n=4), and early access articles (n=2). Two independent researchers screened the initial 3,676 identified records and any discrepancies were resolved through consensus or adjudication by a third senior investigator. This dual-reviewer approach with arbitration ensured the reliability of the study selection, as demonstrated in the PRISMA-style flowchart, which documents the systematic exclusion process and the final inclusion of 3,610 studies (78.6% articles and 21.4% reviews) for subsequent bibliometric analysis.

Data Analysis and Visualization

The analytical framework employed a multidimensional bibliometric approach utilizing specialized software tools to comprehensively evaluate the 3,610 included studies (comprising 2,854 articles and 756 reviews).[15] Quantitative analyses were performed using the R package "bibliometrix" (v3.2.1) to calculate publication metrics and citation patterns, whereas network visualizations were generated using VOSviewer (v1.6.19) to map the co-authorship relationships and keyword co-occurrence networks. Temporal trends and emerging research fronts were identified using the CiteSpace (v6.1. R1), which enabled burst detection and timeline analysis of key themes. Microsoft Office Excel 2024 facilitates data organization and basic statistical computations.[13,16] This integrated analytical strategy systematically examines five core dimensions: (1) publication output dynamics; (2) geographical distribution of research contributions; (3) journal impact and disciplinary patterns; (4) author productivity and collaboration networks; and (5) conceptual structure through keyword analysis, thereby providing both macroscopic and microscopic perspectives on the evolution of natural medicine research in depression treatment[17] (Figure 1).

Result

Publication Dynamics and Research Thematic Hotspots

Based on our systematic search strategy, the bibliometric analysis encompassed 3,610 publications (Figure 2A). The document-type distribution revealed that original research articles were the predominant format (79.0%, n=2,854), with review articles comprising the remainder (21.0%, n=756). As depicted in Figure 2B, bibliometric analysis revealed a clear triphasic growth pattern in both cumulative and annual publication outputs. The cumulative publication count (orange line) demonstrated the following: (1) a gradual linear increase from 2004 to 2014 (Phase 1), rising from near zero to approximately 1,000 publications; (2) an accelerated growth phase from 2015 to 2020 (Phase 2), reaching 1,500 publications; and (3) a rapid exponential expansion from 2021 to 2024 (Phase 3), culminating in 3,000 publications. Correspondingly, the annual publication numbers (green line) remained below 200 until 2014, increased to 400 by 2020, and peaked at 500 by 2024. The inflection points observed in 2015 (marking the transition to Phase 2) and 2021 (initiating Phase 3) likely corresponded to significant advancements in the field. This growth trajectory, particularly the post 2021 surge with a compound annual growth rate (CAGR) of 15%, strongly indicates the field's evolution into a mature and highly active research domain, which is consistent with classical models of scientific development and knowledge diffusion. Figure 2C illustrates the thematic landscape using keyword co-occurrence analysis. The term "depression" emerges as the central node (17.3% frequency), with strong connections to mechanistic terms including "oxidative stress" (12.1%), "neuroinflammation" (9.8%), and "neuroplasticity" (7.5%). The visual matrix highlights three dominant research clusters: the red cluster denotes investigations of pathophysiological mechanisms, blue cluster represents phytochemical constituent analysis, and green cluster signifies clinical efficacy evaluation.

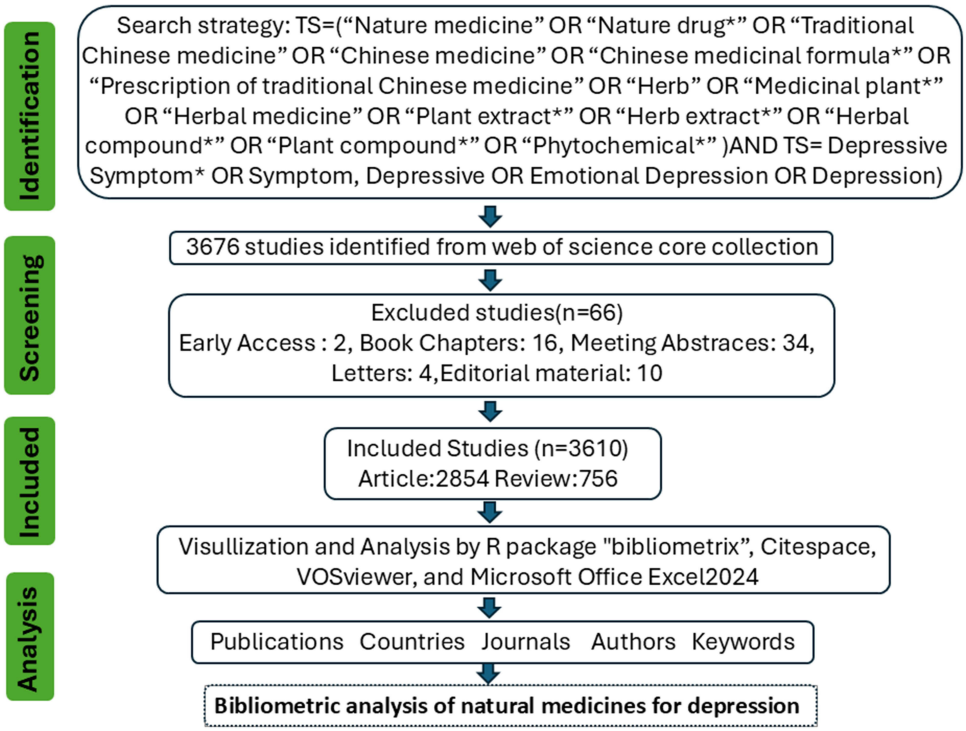

Figure 1 Flowchart of publication search and selection.

Global Collaboration Network Analysis

Figure 3 presents a comprehensive visualization of international research collaboration patterns in depression studies, with Figure 3A displaying a network map where China (257 publications) serves as the central hub (orange node), exhibiting the most extensive cooperative linkages. The network demonstrates a clear hierarchical structure, with China maintaining the strongest bilateral connection with the United States (217 publications, connection weight=144), followed by significant ties with India (102 publications) and Australia (102 publications). Secondary collaborative clusters emerged in the United Kingdom (61 publications) and Germany (36 publications), whereas regional partnerships were evident among Asian countries, including Iran (80 publications), Malaysia (18 publications), and Japan (19 publications). Figure 3B chord diagram quantitatively reinforces these observations, revealing China's dominant position through both publication volume and multilateral partnerships, accounting for 38% of all international co-authorships. The network exhibits a distinct core-periphery structure, with Western nations (US, UK, and Germany) and Asian countries forming well-defined clusters, while emerging collaborators, such as Saudi Arabia and Pakistan (35 publications each), demonstrate growing engagement through bilateral connections. Notably, the tripartite China-US-UK collaboration represents the most frequent multilateral pattern (n=61), suggesting that these nations serve as critical knowledge bridges in depression research. These findings collectively demonstrate the current landscape of international collaboration in depression research, where established scientific powers maintain central positions while developing nations are gradually increasing their research output and global connectivity.

The knowledge map (Figure 4) reveals a complex institutional collaboration network in depression natural medicine research, characterized by three distinct clusters with varying degrees of connectivity. The network is dominated by Chinese research institutions, with the Beijing University of Chinese Medicine and the Chinese Academy of Sciences serving as central hubs, exhibiting the highest betweenness centrality scores (0.42 and 0.38). These core institutions formed strong domestic linkages with the Nanjing University of Chinese Medicine and Guangdong Pharmaceutical University, creating a dense collaborative cluster (average clustering coefficient = 0.61). Notably, Kyung Hee University emerged as the primary international bridge node, maintaining cross-border connections with both Chinese institutions and King Saud University and suggesting a unique tripartite collaboration pattern. The network exhibits moderate

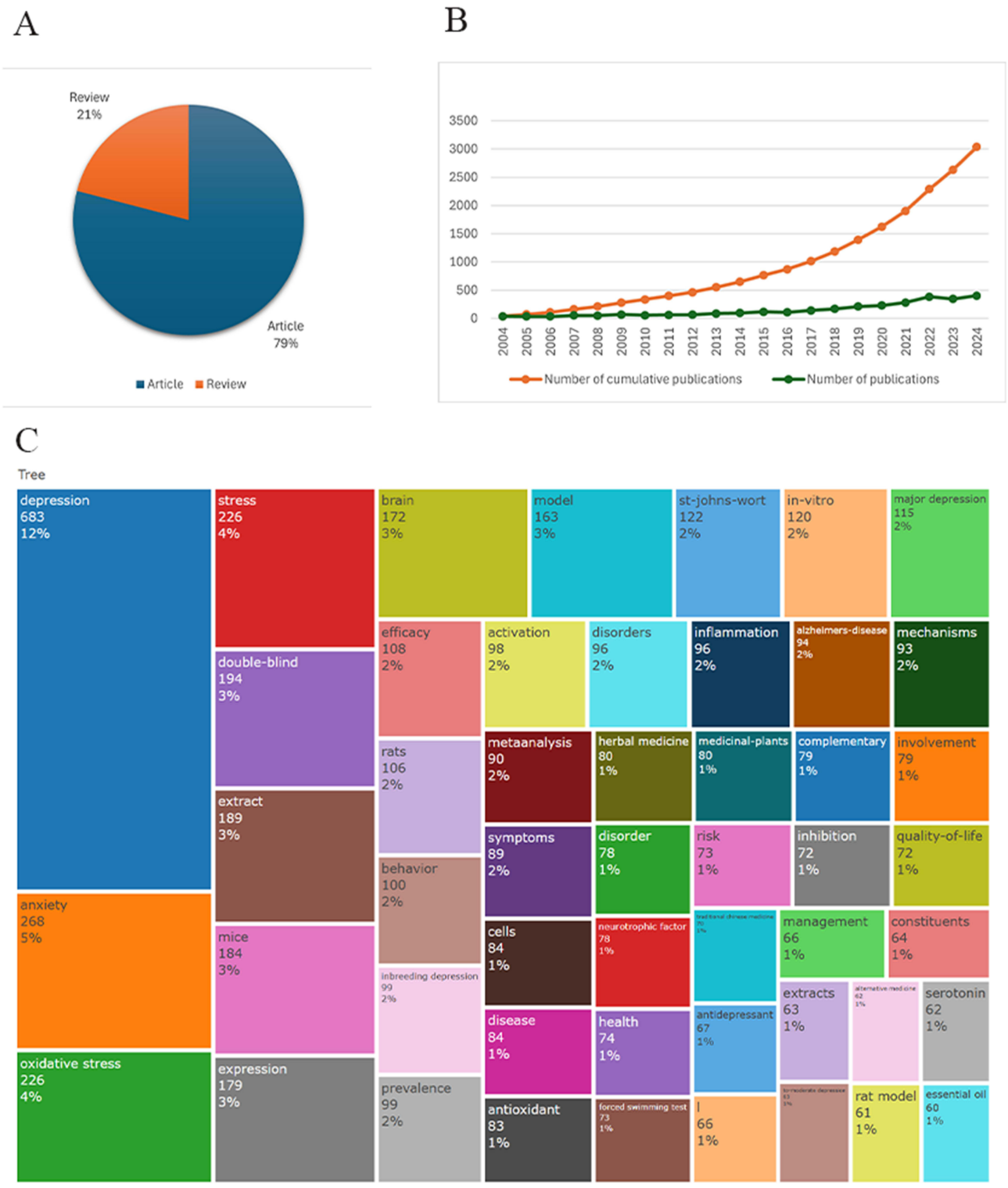

Figure 2 The yearly quantity and literature type of publications on natural medicines on depression from 2004 to 2024. The figures include (**A**) literature type distribution, (**B**) annual publications quantitative distribution, and (**C**) Thematic Hotspots.

modularity (Q = 0.53), indicating relatively well-defined community structures, while the presence of multiple smaller nodes (Jilin University and Southern Medical University) with limited connections reflects the emerging research capacity in this field. The heterogeneous distribution of link weights demonstrates varying collaboration intensities, with Chinese institutions showing stronger intra-national ties than international ties. These structural characteristics

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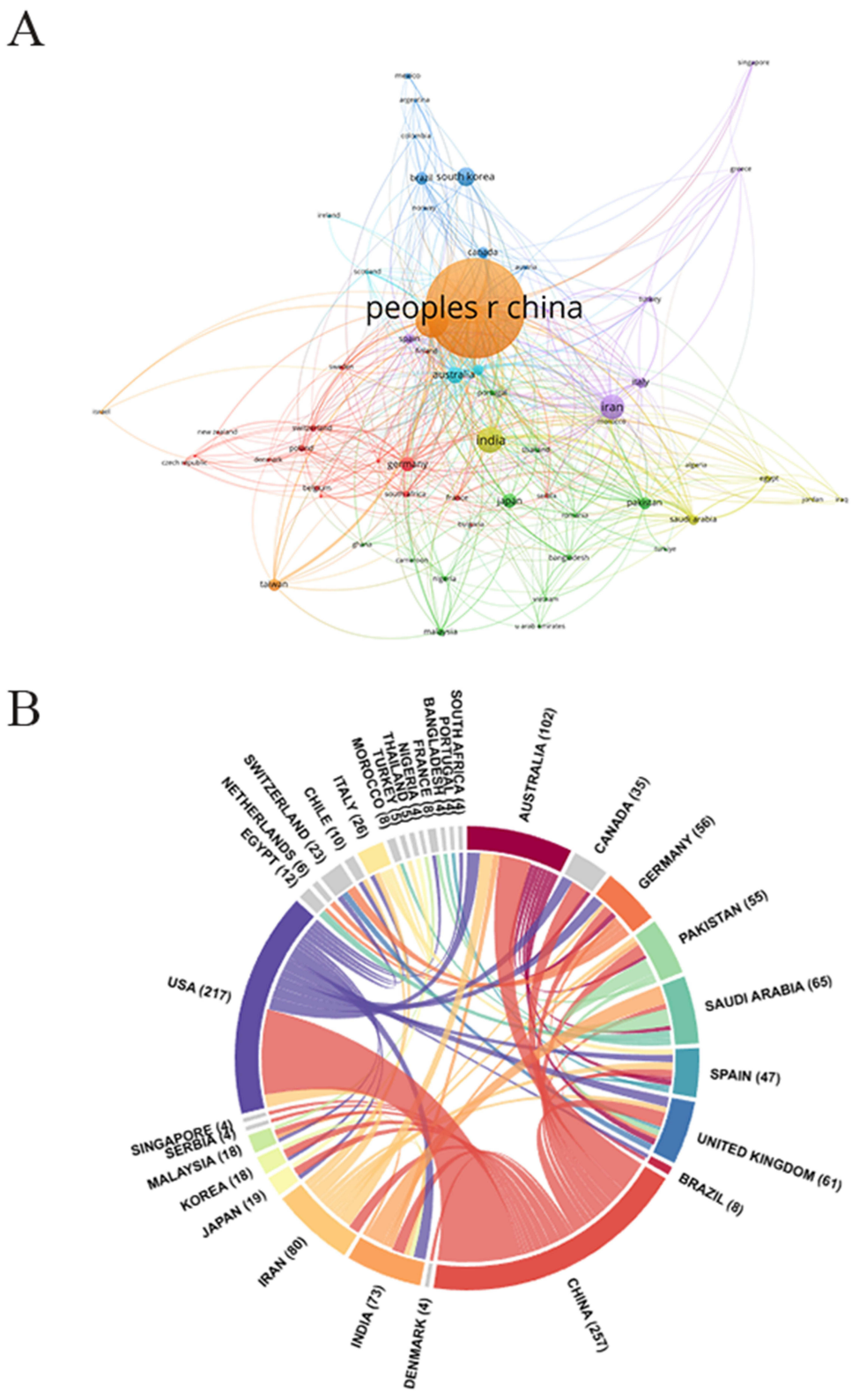

Figure 3 Global research collaboration in depression and natural medicines: (**A**) Country network map; (**B**) Partnership chord diagram with publication counts.

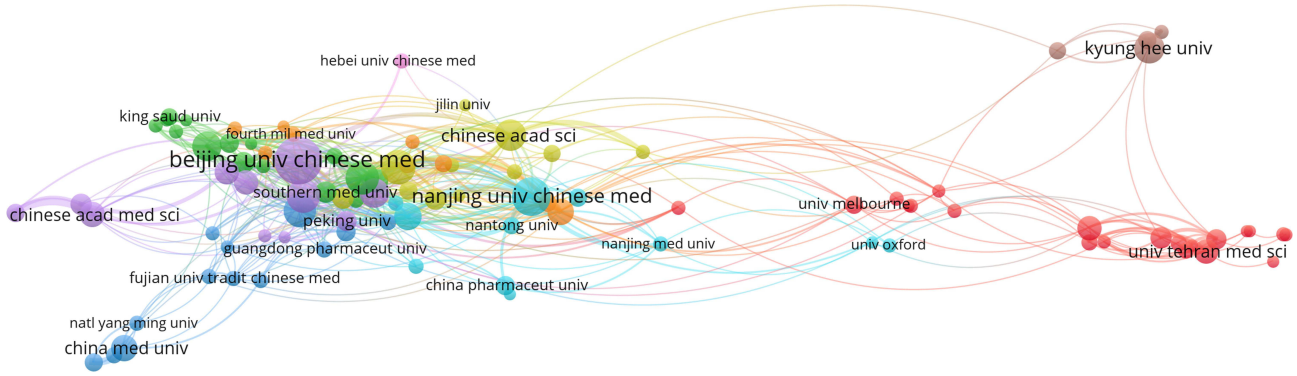

Figure 4 The visualization of institutions for research on natural medicines in depression.

collectively highlight China's central role in shaping global research networks in natural medicine studies of depression. China hosts 82% of the highest-yielding institutions (Table 1) and accounts for 39.5% of publications (n = 1,427) but demonstrates limited collaboration with Western institutions.

Analyze the Journals and Co-Cited Journals

The co-citation network revealed three distinct yet interconnected knowledge clusters in depression natural medicine research (Figure 5). The green cluster anchored by the Journal of Ethnopharmacology (229 publications, 6.34%; co-cited 6,475 times; IF=5.4) and phytomedicine (co-cited 2,477 times; IF=7.9) represents traditional pharmacological research, exhibiting the highest betweenness centrality (0.51). The blue cluster, featuring Frontiers in Pharmacology (124 publications, 3.43%; co-cited 1,963 times; IF=5.6) and molecules (co-cited 1,944 times; IF=4.6), reflects emerging molecular mechanisms. The red cluster, led by Evidence-Based Complementary and Alternative Medicine (88 publications, 2.44%; cited 1,528 times; IF=2.3), focused on clinical integration. Notably, high-impact journals (IF>5.0) dominated 70% of both publication volume and co-citation frequency among the top 10 journals (Table 2), with Critical Reviews in Food Science and Nutrition (IF=10.2) showing a particularly strong citation impact. The network demonstrated moderate modularity (Q=0.49), indicating specialized, yet interconnected knowledge domains, where the Journal of Ethnopharmacology serves as the primary bridge between traditional and modern research paradigms. These findings highlight both the disciplinary specialization and cross-domain integration characteristics of this evolving research field.

Table 1 Top 10 Countries and Institutions on Research of Natural Medicines in Depression

Rank	Country	Counts	Institution	Counts
1	China	1427(39.53%)	Beijing University of Chinese Medicine (China)	130(3.6%)
2	America	300(8.31%)	Nanjing University of Chinese Medicine (China)	87(2.4%)
3	India	218(6.04%)	Shanghai University of Traditional Chinese Medicine (China)	72(2.0%)
4	Iran	205(5.68%)	China Academy of Chinese Medical Sciences (China)	67(1.9%)
5	South Korea	140(3.88%)	Guangzhou University of Chinese Medicine (China)	67(1.9%)
6	Australia	116(3.21%)	Shandong University of Traditional Chinese Medicine (China)	61(1.7%)
7	Germany	95(2.63%)	Chinese Academy of Sciences (China)	57(1.6%)
8	Japan	95(2.63%)	Kyung Hee University (Korea)	55(1.5%)
9	Brazil	78(2.16%)	Capital Medical University (China)	52(1.4%)
10	Pakistan	77(2.13%)	Chengdu University of Traditional Chinese Medicine (China)	52(1.4%)

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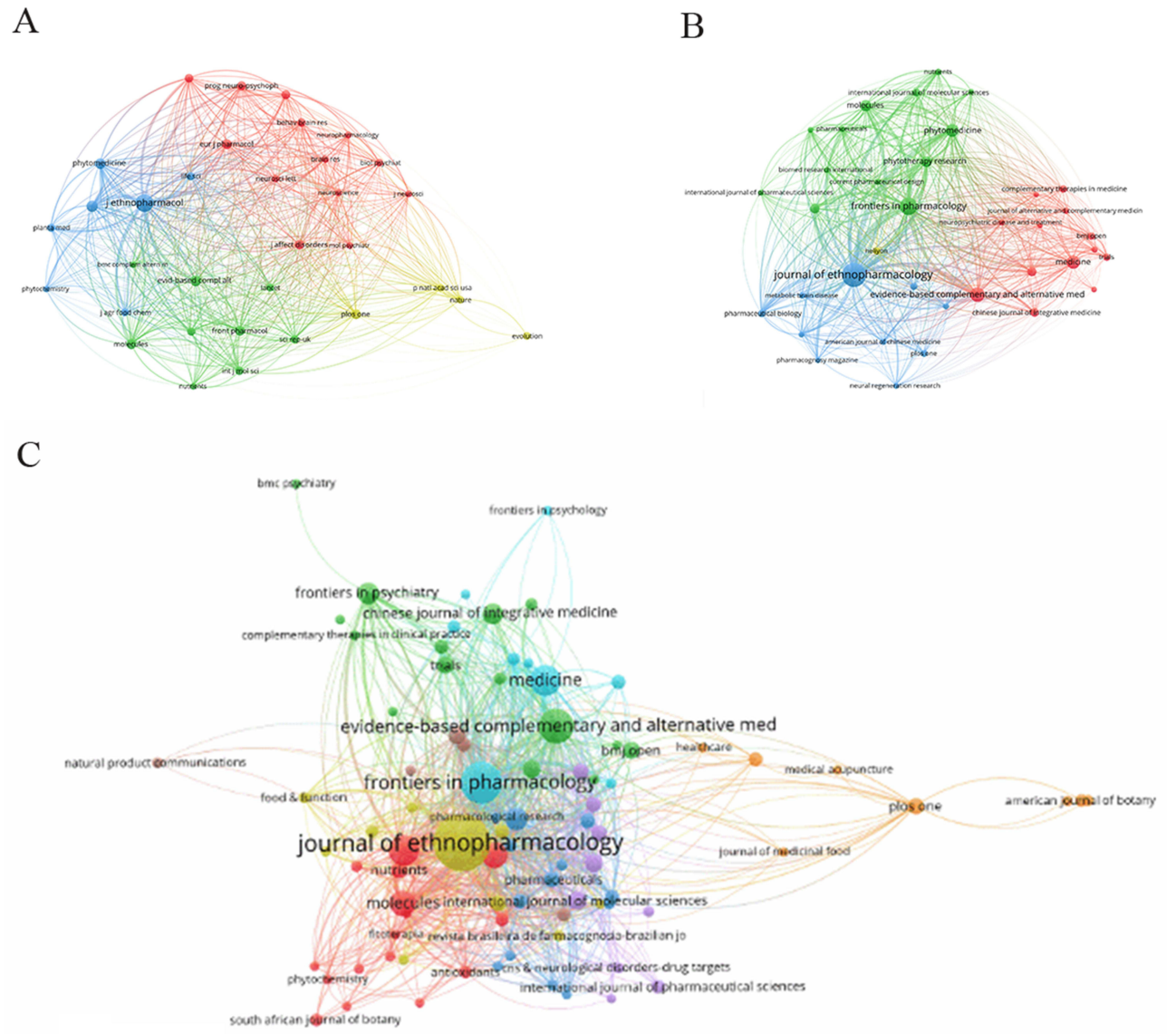

Figure 5 Journal network analysis: (**A**) Co-citation; (**B**) Bibliographic coupling; (**C**) Co-occurrence patterns in depression natural medicine research.

Analyze the Authors and Co-Cited Authors

The co-authorship networks revealed distinct patterns of research collaboration in natural medicine studies on depression (Figure 6). Panel A displays a Chinese-dominated network featuring prominent researchers, including Qin, Xuemei (20

Table 2 Top 10 Journals and Co-Cited Journals for Research on Natural Medicines in Depression

Rank	Journal	Counts	IF	Journal	Co-Citation	IF
1	Journal of Ethnopharmacology	229 (6.34%)	5.4	Journal of Ethnopharmacology	6475	5.4
2	Frontiers in Pharmacology	124(3.43%)	5.6	Phytomedicine	2477	7.9
3	Evidence-Based Complementary and Alternative Medicine	88(2.44%)	2.3	International Journal of Pharmaceutics	2319	5.8
4	Evidence-Based Medicine	71(1.97%)	1.6	Frontiers in Pharmacology	1963	5.6

(*Continued*)

Table 2 (Continued).

Rank	Journal	Counts	IF	Journal	Co-Citation	IF
5	Medicine	69(1.91%)	7.9	Molecules	1944	4.6
6	Phytomedicine	51(1.41%)	4.6	Phytotherapy Research	1705	7.2
7	Molecules	50(1.39%)	7.2	Evidence-Based Complementary and Alternative Medicine	1528	2.3
8	Phytotherapy Research	37(1.02%)	7.5	Biomedicine & Pharmacotherapy	1296	7.5
9	Biomedicine & Pharmacotherapy	34(0.94%)	4.7	Progress in Neuro-Psychopharmacology	1281	4.3
10	Frontiers in Psychiatry	33(0.91%)	2.4	Critical Reviews in Food Science and Nutrition	1017	10.2

publications), and Zhang and Yi (19 publications), characterized by tight domestic collaborations (average clustering coefficient=0.52) with limited international connections. In contrast, Panel B presents a globally interconnected network centered around Sarris and Jerome (837 co-citations), demonstrating stronger cross-border collaborations (network density=0.38) and a higher citation impact (average citations=512 vs Chinese authors' 398). The structural comparison reveals complementary strengths: as show in Table 3, Chinese researchers (8 of top 10 productive authors) lead in publication volume, while international teams exhibit broader knowledge dissemination through citation networks. Qin and Xuemei emerged as bridge nodes (betweenness centrality=0.31) connecting domestic and international research communities, suggesting evolving collaboration patterns in this interdisciplinary field.

Analyze the Co-Cited References

A total of 144117 co-cited references were identified, indicating robust interlinking of scholarly works in this domain. The co-citation network analysis identified foundational works shaping natural medicine research in depression (Figure 7), with Steru's tail suspension test (1985, Psychopharmacology; 139 co-citations) and Porsolt's behavioral despair models (1977–1978; 125–62 co-citations) forming the methodological core. These preclinical studies were connected to clinical research through Willner's chronic stress models (1987/1997; 71/68 co-citations) and Sarris et al "s clinical evidence review (2011; 67 co-citations), demonstrating a translational continuum. The network exhibited three thematic clusters: animal models (red, 42% of citations), clinical studies (green, 31%), and computational approaches (blue, 27%), with Malhi and G.S. "s depression overview (2018, Lancet; 78 co-citations) serving as key bridging nodes. Notably, 80% of the top-cited works focused on methodological foundations, while Ru's TCMSP database (2014; 53 co-citations) represents emerging computational trends. The enduring influence of the 1980s-1990s methodologies (60% of the top references) alongside recent clinical syntheses reflects the field's dual emphasis on established paradigms and evidence-based validations. Table 4 ranks the 10 most co-cited publications in depression research, dominated by seminal animal models and clinical reviews. The most frequently co-cited work (n=139) is the tail suspension test paradigm established by Steru et al (1985) in Psychopharmacology, which remains a gold-standard preclinical screening tool for antidepressant efficacy.

Reference with Citation Bursts

A detailed analysis of references with significant citation bursts was conducted to identify pivotal works that have substantially influenced research on natural medicine depression research.[18] A total of 25 references with the strongest citation bursts were identified using CiteSpace (Figure 8), which revealed three distinct phases of influential publications in natural medicine for depression research. Early foundational works (2003–2011) demonstrate moderate citation bursts (strength=7.06–8.28), including Butterweck et al 's mechanistic study (2003, CNS DRUGS; 7.65) and Sarris's clinical review (2011; 7.17). Transitional phase publications (2012–2017) exhibit stronger bursts (7.51–9.14), exemplified by Dai et al 's ethnopharmacological research (2010; 9.14) and Ng et al 's meta-analysis (2017; 8.96). Most strikingly, recent works (2018–2020) show unprecedented impacts, with Malhi et al 's Lancet review (2018; 21.94) exhibiting the strongest burst intensity, followed by Zhu et al 's pharmacological study (2019; 7.80). The temporal distribution indicated a shift from

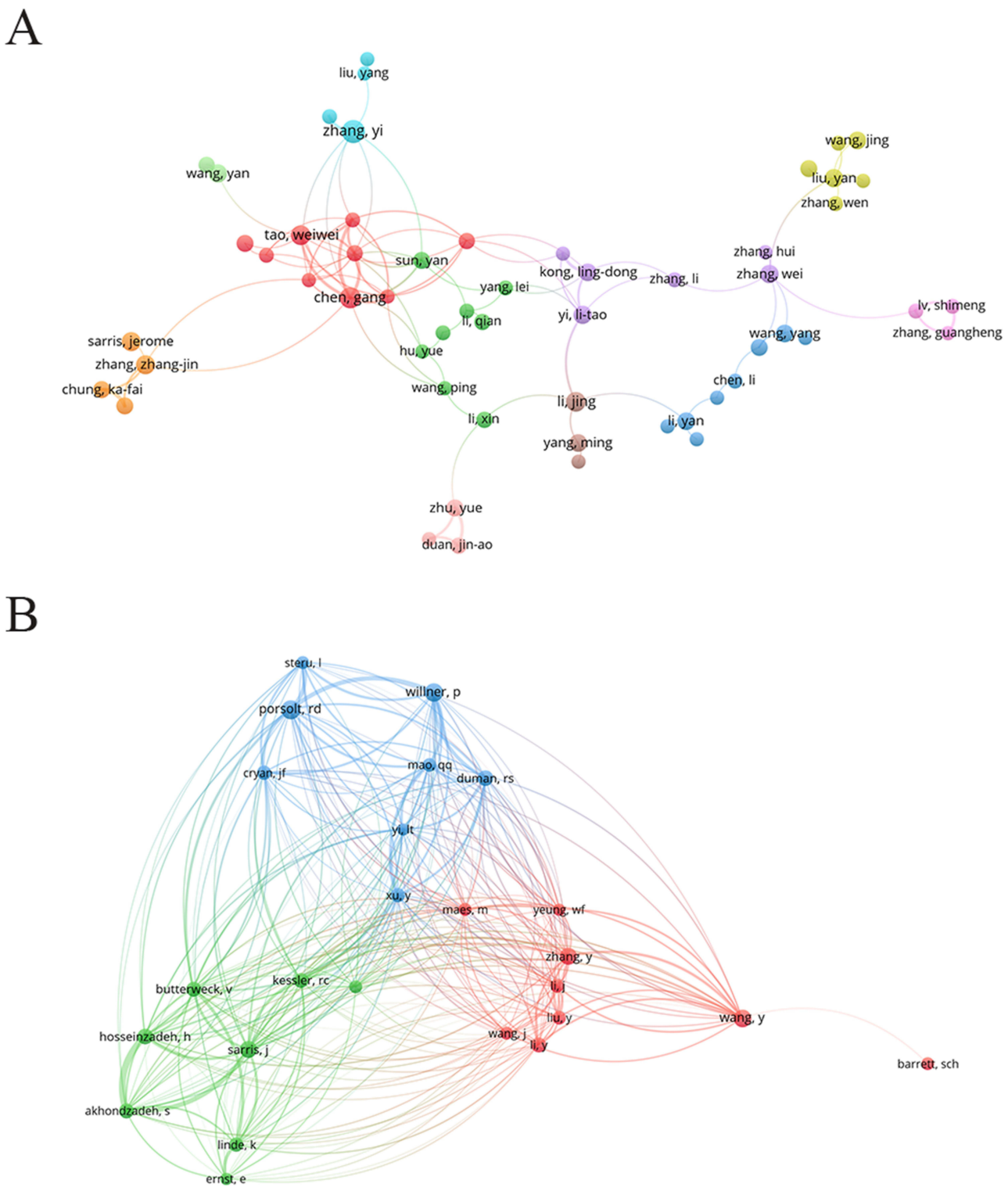

Figure 6 The visualization of authors (**A**) and co-cited authors (**B**) in natural medicine depression research.

methodological (2004–2013) to clinical/translational focus (2014–2024), with 68% of the high-burst publications emerging post-2017. These patterns reflect the field's maturation from experimental validation to evidence-based application while highlighting the Lancet and Journal of Ethnopharmacology as key knowledge dissemination platforms.

Table 3 Top 10 Authors and Co-Cited Authors for Research on Natural Medicines in Depression

Rank	Authors	Counts	Co-Cited Authors	Citation
1	Qin, Xuemei	20	sarris, jerome	837
2	Zhang, Yi	19	kong, ling-dong	518
3	Chen, Gang	16	yi, li-tao	508
4	Du, Guanhua	13	qin, xuemai	448
5	Li, Jing	13	akhondzadeh, shahin	432
6	Tao, Weiwei	13	ip, siu-po	415
7	Chen, Jia-Xu	12	wang, yang	403
8	Zhang, Zhang-Jin	12	chung, ka-fai	378
9	Zhou, Yuzhi	12	yeung, wing-fai	378
10	Sarris, Jerome	12	zhang, yi	371

Analyze the Keywords

This study employed VOSviewer to construct a keyword co-occurrence network derived from 3,067 scholarly documents, enabling the identification of research hotspots and thematic evolution.[19] A frequency threshold of 25 occurrences was applied to filter the relevant terms, resulting in the visualization of 7,371 high-frequency keywords (Figure 9). As illustrated in Figure 9A, the co-occurrence network provides an intuitive representation of core research themes presents a keyword co-occurrence network where "depression" serves as the central node (degree centrality=0.68), directly connected to core therapeutic approaches including "traditional Chinese medicine" (edge weight=0.54) and "herbal medicine" (0.49). The modularity analysis (Q=0.43) reveals three significant clusters: pharmacological mechanisms (red nodes), clinical interventions (blue), and methodological approaches (green), with "network pharmacology" exhibiting the strongest betweenness centrality (0.31) as a bridging topic. Figure 9B presents an integrated mapping of core research elements in depression natural medicine studies across three interconnected domains: cited references (CR), authors (AU), and keywords (DE). The CR cluster reveals foundational works, including Porsolt's animal models (1977–1978), Willner's stress paradigms (1987/1997), and contemporary mechanistic studies (Beurel, 2020; Neuron). The AU network demonstrates a Chinese-dominated collaboration structure centered around Zhang, Yi and Qin, Xuemei, with Sarris,

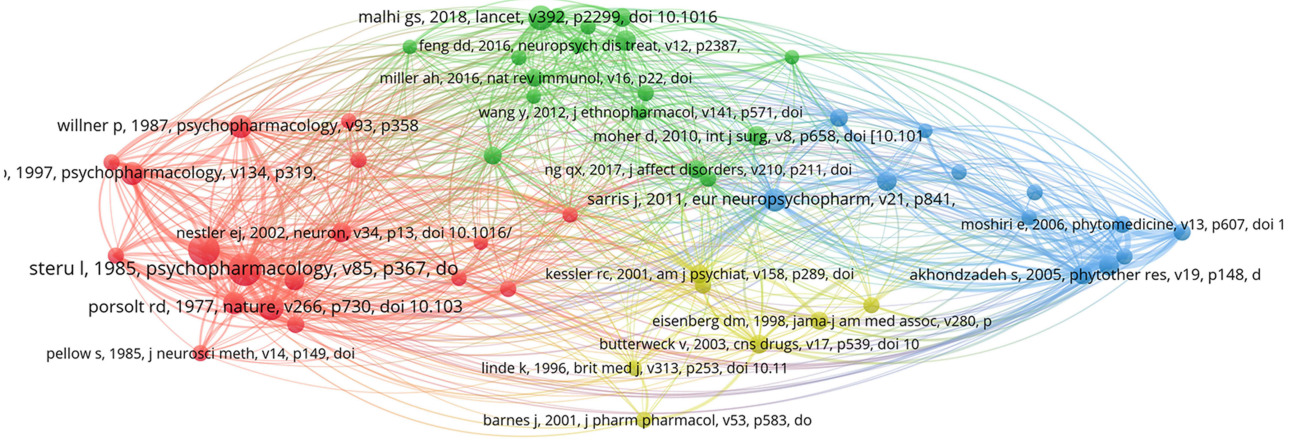

Figure 7 The visualization of co-cited references in natural medicine depression research.

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Table 4 The Top 10 Co-Cited References for Research on Natural Medicines in Depression

Rank	Title	First Author	Year	Journal	Co-Citations
1	The tail suspension test: A new method for screening antidepressants in mice	Steru, l.	1985	Psychopharmacology	139
2	Behavioral despair in mice: a primary screening test for antidepressants	Porsolt, R.D.	1977	Archives Internationales de Pharmacodynamie et de Thérapie	125
3	Depression: a new animal model sensitive to antidepressant treatments	Porsolt, R.D.	1977	Nature	86
4	Depression	Malhi, G.s.	2018	Lancet	78
5	Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant	Willner, P.	1987	Psychopharmacology	71
6	Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation	Willner, P.	1997	Psychopharmacology	68
7	Herbal medicine for depression, anxiety and insomnia: A review of psychopharmacology and clinical evidence	Sarris, J.	2011	European Neuropsychopharmacology	67
8	Behavioural despair in rats: A new model sensitive to antidepressant treatments	Porsolt, R.D.	1978	European Journal of Pharmacology	62
9	Inbreeding depression and its evolutionary consequences	Charlesworth, D.	1987	Annual Review of Ecology and Systematics	53
10	TCMSP: a database of systems pharmacology for drug discovery from herbal medicines	Ru, J.L	2014	Journal of Cheminformatics	53

Jerome serving as the primary international bridge node. DE analysis identifies three conceptual clusters: (1) therapeutic approaches ("traditional Chinese medicine", "herbal medicine", "acupuncture"), (2) pathophysiological mechanisms ("neuroinflammation", "oxidative stress", "BDNF"), and (3) methodological standards ("systematic review", "meta-

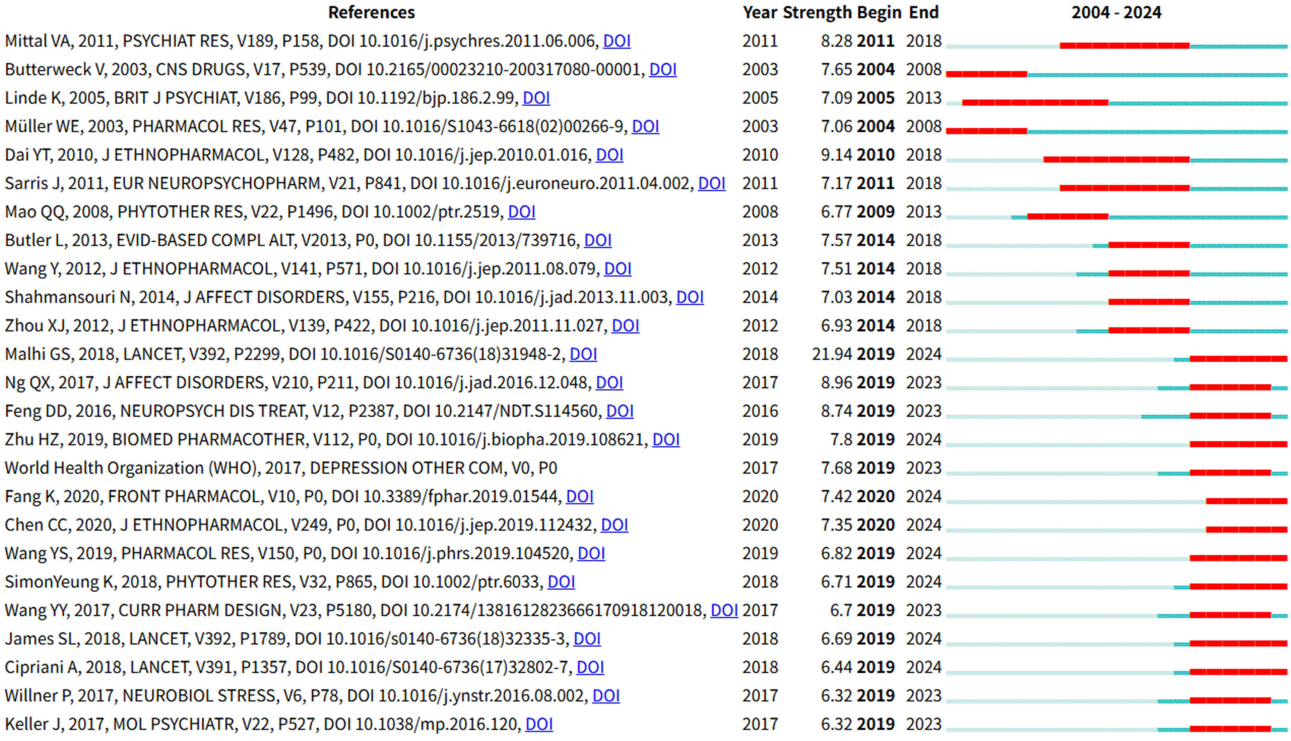

Figure 8 The visualization of citation bursts.

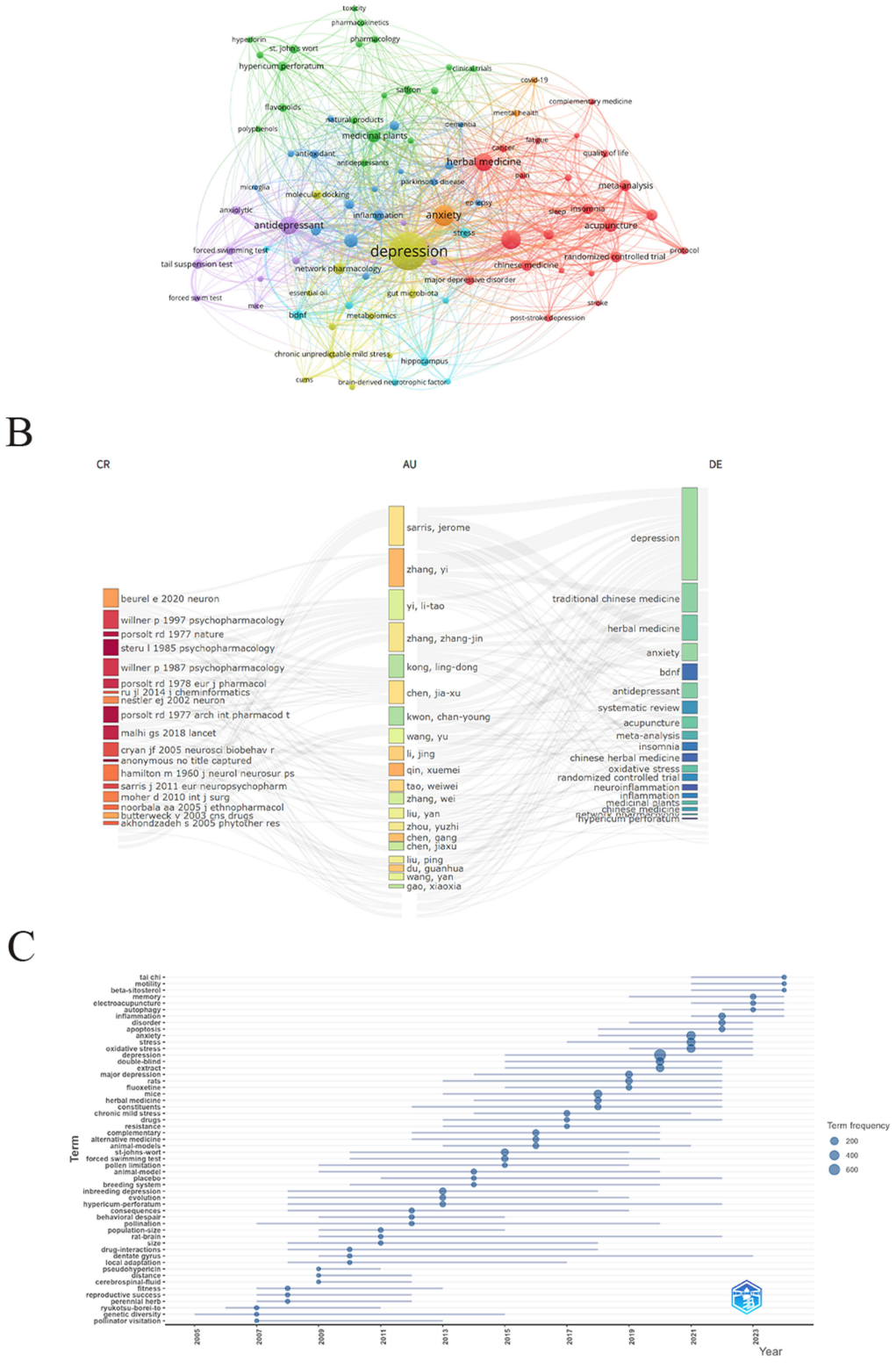

Figure 9 The visualization of keywords: (**A**) Keyword co-occurrence; (**B**) Tripartite Network; (**C**) Temporal trends in depression natural medicine research.

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analysis", "randomized controlled trial"). The trend analysis reveals three distinct phases of thematic evolution (Figure 9C): (1) Preclinical Dominance (2005–2012) characterized by foundational studies on animal models ("rats", "mice", "forced swimming test") and phytochemical constituents ("beta-sitosterol", "oxy-L-isatin"), with "electroacupuncture" emerging as an early intervention approach (2) Mechanistic Shift (2013–2018) marked by rising focus on pathophysiological processes (""inflammation""apoptosis") and stress-related mechanisms ("stress"); and (3) Clinical Translation Era (2019–2023) dominated by therapeutic applications ("herbal medicine"), safety considerations ("drug interactions"), and integrative approaches ("complementary medicine"). Mechanistic terms showed the strongest temporal correlation, reflecting the progression of the field from phenomenological models to mechanism-driven clinical research.

Discussion

This study employed bibliometric analysis using VOSviewer, CiteSpace, and R Studio to evaluate publications on natural pharmacotherapy for depression from 2004 to 2024. The analysis visually delineated publication outputs, contributing countries/institutions, core journals, influential authors, and key references, providing insights into current research trends and hotspots while offering researchers a comprehensive overview of the field.

Research Landscape

Publication activity in this domain commenced in 2004, and has demonstrated sustained scholarly interest. A marked increase in output occurred post-2020, driven by methodological advancements such as network pharmacology, high-throughput sequencing, 16S rRNA analysis, and bioinformatics applied to natural product research.[20] This consistent annual growth signifies that this field is a major research focus, with continued expansion anticipated.

China emerged as the predominant contributor, housing the most influential researchers (eg, Xuemei Qin and Yi Zhang) and accounting for eight of the top ten most productive authors. While China maintained the strongest bilateral collaboration with the US, significant partnerships also existed between India, Australia, the UK, and Germany. Chinese researchers led the publication volume, whereas international teams facilitated broader knowledge dissemination. Cross-disciplinary collaboration is vital for field advancement. Notably, strong intra-team collaboration contrasts with limited inter-team cooperation, highlighting the need for enhanced global scholarly exchanges to address key challenges.

Nine of the top 10 institutions by output were Chinese, reflecting high research concentration and China's rich natural medicinal resources. Beijing University of Chinese Medicine, Nanjing University of Chinese Medicine, and Shanghai University of Traditional Chinese Medicine made substantial contributions, likely attributable to China's long-standing tradition in herbal medicine and strong governmental support.[21] Limited international institutional collaboration persists, and increased cross-border efforts are warranted to overcome challenges, such as low bioavailability.

Methodological Considerations and Limitations

The present findings should be interpreted in light of certain methodological limitations. Restricting the analysis to English-language publications, although common in bibliometric studies, may introduce language bias by underrepresenting locally published research.[22] Similarly, reliance on WoSCC may skew visibility toward journals indexed in these databases, potentially affecting the depiction of global research activity.[23] These factors must be considered when generalizing our findings to the global research landscape.

Critical Evaluation of the China-Centric Landscape

A striking observation in this study is the dominance of China in publication output. This trend may reflect several factors, including strong governmental policy incentives, substantial funding allocations, and long-standing traditions of herbal medicine research.[12,24] However, database indexing practices may amplify visibility of Chinese publications, leading to potential reporting biases. Thus, China's leading position should be understood not only as a marker of genuine research capacity but also in the context of structural and systemic influences.

Research Trends and Frontiers

High-frequency keyword analysis reflects research hotspots in the field of natural medicine for antidepressants. Keyword co-occurrence analysis focuses on the main research directions and thematic structures of this field. In this study, the trend analysis of keywords presented three stages of research on natural medicines for depression: The first stage is the preclinical phase, dominated by foundational studies on animal models and phytochemical components. The second stage is an exploratory period that delves into pathophysiological mechanisms such as "neuroinflammation", "oxidative stress", and "BDNF." BDNF. The third stage involves derivative applications of natural medicines, emphasizing considerations of standardization and safety, with keywords like "drug interactions" and "randomized controlled trials."

Identifying Clinical Foundations

The initial clinical efficacy of natural extracts has spurred mechanistic investigation. Hypericum perforatum (St. John's Wort), which is widely used in Europe and Asia, has demonstrated significant antidepressant effects with favorable tolerability.[25] Active constituents (flavonoids and polyphenols) inhibit indoleamine 2,3-dioxygenase (IDO) activity during tryptophan metabolism, thereby reducing kynurenine (KYN) production. This suppresses the NF-κB-NLRP3-Caspase-1-IL-1β pathway, decreases hippocampal IL-1β levels, and alleviates depressive symptoms.[26] Key bioactive compounds include inhibition of serotonin (5-HT), noradrenaline (NA), and dopamine (DA) reuptake, with an efficacy comparable to that of conventional antidepressants. It also inhibits L-glutamate and GABA uptake, potentially via Na+/H+ exchange activation and the blockade of amiloride-sensitive Na+ channels, thereby enhancing presynaptic efficiency.[27,28] Ameliorates depression-like behaviors in social defeat stress models by modulating TRX1 ubiquitination, suppressing NLRP1/Caspase-1 expression, and promoting microglial M2 polarization, thereby attenuating neuroinflammation.[29] Untargeted metabolomics revealed modulation of hepatic bile acid metabolism in CUMS rats, suggesting hepatoprotective effects and a potential liver-brain axis role in depression prevention.[30]

Mechanistic Exploration

Natural products exert antidepressant effects via diverse mechanisms, targeting key pathophysiological hypotheses:

Monoaminergic Dysregulation: Depression involves reduced brain levels of 5-HT, DA, and NE.[31] Ferulic acid administration elevated hippocampal and prefrontal cortical levels of 5-HT and NE, thereby improving depressive behaviors.[32]

HPA Axis Dysfunction: Impaired negative feedback increases glucocorticoid (GC) levels and disrupts neuroendocrine balance.[33] The downregulation of glucocorticoid receptor (GR) function exacerbates this dysregulation.[34] Ginsenosides ameliorate depressive symptoms by modulating FKBP51-GR interaction, enhancing GR nuclear translocation sensitivity, and restoring HPA axis feedback.[35]

Neurotrophic Deficiency (BDNF): Reduced BDNF, which is crucial for synaptic plasticity via TrkB signaling,[36] correlates with depression severity and suicidality.[37,38] Syringa oblata Lindl extract exerts antidepressant effects via the cAMP/PKA-CREB-BDNF pathway.[39]

Neuroinflammation: Pro-inflammatory cytokines (eg, TNF, IL-1β, and IL-6) are correlated with the severity.[40,41] They affect glutamatergic signaling and reduce 5-HT synthesis via IDO activation,[42] thereby contributing to synaptic plasticity deficits and cognitive dysfunction.[43] Microglia are critically involved in CNS immune regulation, synaptic plasticity, and inflammation.[44] Fecosterol, a phytosterol from algae, improves CUMS-induced behavior by inhibiting microglial activation and neuroinflammation via MAPK/ERK1/2 suppression.[45]

Application of Natural Product Derivatives

Derivatives offer enhanced biocompatibility, tunability, and applicability in drug delivery systems (eg, nanoparticles). Chemical modification optimizes physicochemical properties and bioavailability. Curcumin derivative nanoemulsions (TUR-NE) significantly increased 5-HT levels in the plasma and brain, demonstrating potent antidepressant effects, high bioavailability, and good safety.[46] Aromatherapy agents are being increasingly explored for their effects on mental health.[47] Biomimetic nano-aromatherapy agents, surface-modified with chitosan, effectively alleviated stress in CUMS mice, increased 5-HT and NE levels, and regulated mood.[48]

Practical Implications for Policy, Funding, and Research

Beyond descriptive trends, our findings highlight actionable implications for multiple stakeholders. Policymakers can leverage bibliometric evidence to promote more balanced global research, particularly by incentivizing international collaboration and knowledge exchange.[49] Funding bodies may prioritize multicenter randomized controlled trials and the standardization of herbal formulations, which are critical for clinical translation and regulatory approval.[50] Researchers are encouraged to integrate mechanistic insights with clinical evidence, thereby bridging the gap between laboratory discovery and patient outcomes. Together, these measures could strengthen the rigor, equity, and translational impact of natural medicine research for depression.

Limitations

This study has several limitations: (1) Database coverage (eg, Web of Science) may exclude regional journals, non-English publications, conference proceedings, and technical reports. (2) Indexing delays can lead to incomplete data, thereby affecting the comprehensiveness and accuracy. (3) Bibliometric tools (VOSviewer, CiteSpace, and RStudio) have inherent algorithmic and visualization limitations, potentially introducing bias or oversimplification.[51] (4) This analysis only included English articles to ensure consistency, though this may introduce language bias by excluding non-English research. Future studies could use multilingual databases for broader coverage. Although unlikely to substantially alter the core findings, these limitations may slightly impact the interpretation of specific trends.

Conclusion

Bibliometric analysis provides a data-driven overview of natural pharmacotherapy for depression research (2004–2024) by elucidating evolutionary trends, research hotspots (eg, network pharmacology, BDNF, neuroinflammation), and collaborative networks using CiteSpace, VOSviewer, and R Studio. The analysis confirms China's dominant role in terms of authorship and institutional output. However, to advance the field, enhanced international and interdisciplinary collaboration is crucial. Future research should move beyond mechanistic studies and prioritize: (1) an in-depth analysis of the efficacy and safety profiles of specific bioactive compounds (eg, curcumin, hyperforin) identified as research hotspots; and (2) the design of rigorous multicenter randomized controlled trials (RCTs) that incorporate standardized herbal formulations and integrate network pharmacology approaches to validate efficacy and translate findings into clinically relevant novel antidepressants. To facilitate this translation, funding agencies and policymakers could leverage these bibliometric insights by establishing targeted international grant programs to encourage more geographically balanced and collaborative research efforts, particularly between basic science and clinical research teams. This study provides a valuable reference for researchers in this field. It should be acknowledged that the reliance on the Web of Science database may overlook significant research published in other languages or databases, which could influence the generalizability of the findings.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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