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ORIGINAL RESEARCH

Knowledge Mapping of Opioids and Immunomodulation: A Bibliometric Analysis (2000–2022)

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Background: Increasing evidence indicates that opioids markedly affect the immune system. However, there are few studies on opioids and immunomodulation using bibliometric analysis.

Purpose: We aimed to provide a comprehensive overview of the research status and trends of the influence of opioids on immunomodulation using a bibliometric approach.

Methods: Articles related to opioids and immunomodulation published from 2000 to 2022 were obtained from the Science Citation Index Expanded of the Web of Science Core Collection by searching keywords related to opioids and immunomodulation. Bibliometric analyses and visualizations were conducted using the CiteSpace and VOSviewer software programs.

Results: From 2000 to 2022, a total of 3242 research articles on opioids and immunomodulation were published in 1126 academic journals by 16,555 authors in 3368 institutions from 102 countries/regions. A majority of publications were from the US and China, and the University of Minnesota System and Chinese Academy of Sciences were the most active institutions. Tsong-long Hwang had published the most papers, while Sabita Roy had the most cocitations. The *Journal of Ethnopharmacology* published the most papers on opioids and immunomodulation, the *Journal of Immunology* was the top cocited journal, and the major area of these publications were molecular, biological, and genetic. The top three keywords were "expression", "activation", and "inflammation."

Conclusion: The number of studies on opioids and immunomodulation has increased sharply all over the world in the last two decades. This is the first bibliometric study to comprehensively summarize the collaboration network in this field. It will help scholars to understand not only the basic knowledge structure but also potential collaborations, research trend topics, and hot directions.

Keywords: opioids, immunomodulation, bibliometric analysis, VOSviewer, CiteSpace

Introduction

The term "opioids" is used broadly to describe all compounds that work at the opioid receptors, which have a long history of medicinal use. Three classical opioid receptors, which are all homologous G protein–coupled receptors — known as mu (μ), delta (δ), and kappa (κ) — were renamed MOP, DOP, KOP, respectively, in 2000.[1] Endogenous opioids include enkephalin (binds to DOP), dynorphin (binds to KOP), endorphin, and endomorphine (binds to MOP).[2] The nociceptin peptide receptor is classified as a nonopioid branch of the opioid receptor family, which cannot be reversed by naloxone.[3] Opioid receptors are widely distributed in the human body and are vitally involved in many physiological processes.[4] They are most prevalent in the central and peripheral nervous system and play a major role in pain processing, human mood, reward, and well-being, but are also widely expressed in many other tissue types regulating such functions as reproduction, growth, respiration, and immunological response.[5–7]

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Opioid receptors and their ligands produce powerful analgesia.[8,9] Opioids can also manipulate the immune system, not only participating in the functioning of immune cells but also modulating innate and adaptive immunoresponses.[10] In 1979, Wybran reported that opioids can affect the rosette formation of normal human T lymphocytes, thus confirming for the first time that opioids have immunomodulatory effects on T lymphocytes.[11] Research had uncovered that multiple opioid receptors are distributed on various types of immune cells.[12–14] Du et al[15] discovered that morphine can reduce both T-lymphocyte proliferation and the content of T-cell subtypes ($CD3^+$, $CD4^+$, and $CD8^+$), while β-endorphin exerts an opposite effect on those cell populations, as well as NK cells. Met-enkephalin gives rise to promoting DC maturation and can enhance their functions.[16] Beilin et al demonstrated that administration of low doses of fentanyl during the perioperative period led to faster recovery of the function of NK cells. In contrast, higher doses of fentanyl showed NK-cell suppression.[17]

Due to their great potential, opioids and immunomodulation are the subject of an increasing number of publications. With the rapid development of opioids and immunomodulation, many reviews have summarized relevant studies from various angles;[18–20] however, we need to systematically understand the development process and research trends in the field and there is a lack of bibliometric and visualization analyses. This bibliometric study focused on both immunomodulation and opioids and the direct connections between them.

Bibliometrics is a tool that can observe the status of science and technology through overall production of science literature at a specialized level and measure science by exploring research activity among countries, scientific research institutions, and individual scientists. It is based on the act of counting and statistical methods of scientific payoff in the form of articles, publications, citations, patents, and other particular indicators. By providing new information, bibliometrics can be an aid to decision-making in science and research management. Bibliometrics cannot justify a decision or replace experts, but it can be a practical tool when used in combination with other indicators. It constitutes a way to quantify and identify the status quo and trending issues in a particular area. Nowadays, it is a fact that there is a growing demand for bibliometric data from the scientific community.[21–23] This bibliometric analysis used CiteSpace and VOSviewer software to visually analyze the literature on opioids and immunomodulation from 2000 to 2022, explore this area for the first time, and describe the current situation of this field to help researchers quickly grasp information on the contributions and cooperation of authors, institutions, countries, and journals, as well as evaluate the knowledge base and trending research topics at the same time.

Methods

Data Collection

The Web of Science Core Collection contains the highest number of journal articles of international social science research. Literature related to opioids and immunomodulation was searched for on June 30, 2022 using the Science Citation Index Expanded (SCI-expanded) of the Web of Science Core Collection database. The search formulae are given in Supplementary Material 1. Original articles published in English from 2000 to 2022 were retrieved. The detailed search procedure is presented in Figure 1. Search results were downloaded as "Full record and cited references" and "Plain text."

Data Analysis

VOSviewer (version 1.6.18) is a freely available computer program for constructing and viewing bibliometric maps. It can extract key information from numerous publications, and is often used to build collaboration, cocitation, and co-occurrence networks.[24] In this study, the software mainly used for country/region and institution analysis, journal and cocited journal analysis, author and cocited author analysis, and keyword co-occurrence analysis. The nodes in the figures represent different items, while the size of circles was determined by the weight of the item, reflecting productivity. Lines between items represent links. Thicker lines mean stronger links. For building a visualization network, the number of items on each research topic was limited according to their respective condition. CiteSpace software is also an important analytical and visualization tool in the field of scientometrics and was developed by Professor Chaomei Chen.[25,26] In this study, CiteSpace (version 6.1. R3) was used to calculate the centralities between

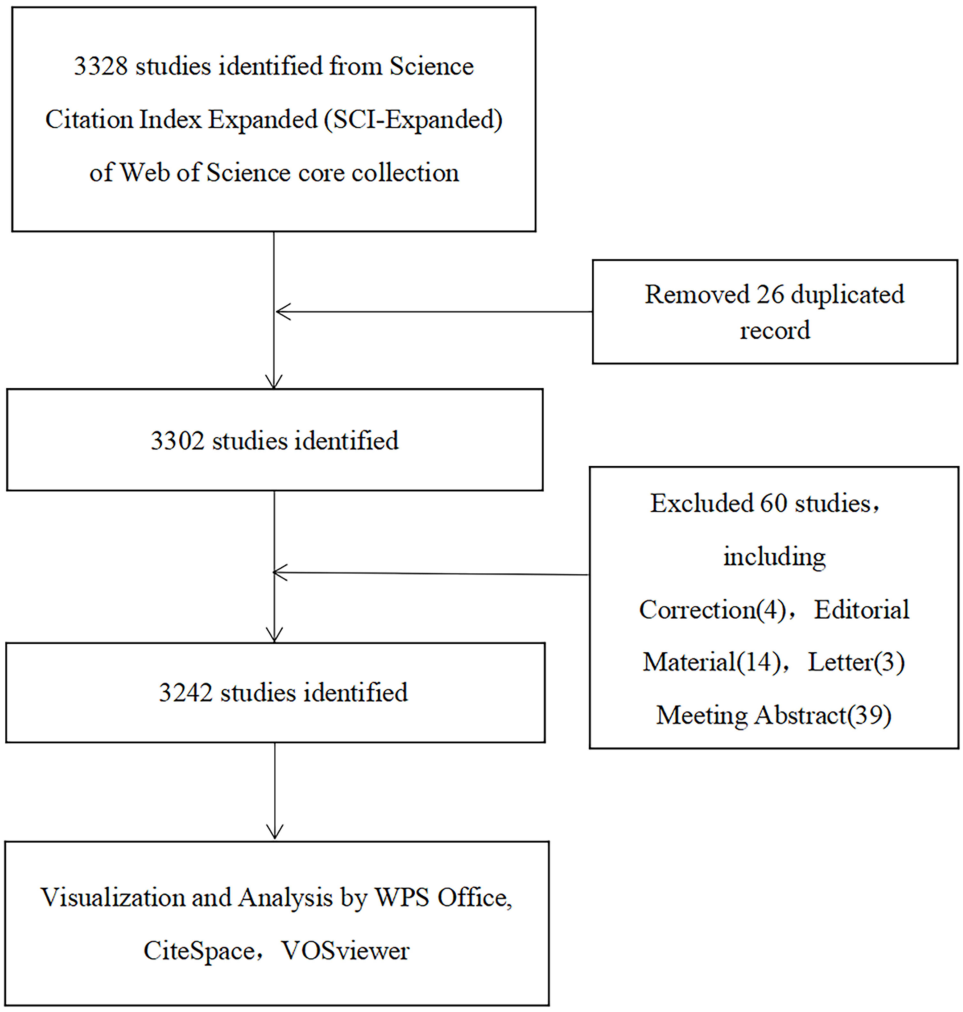


Figure 1 Publication-screening flowchart.

countries and institutions and analyze dual maps of journals, cocited references, reference bursts, reference timelines, and keyword bursts.

Results

Annual Publications

A total of 3242 articles on opioids and immunomodulation published during 2000–2022 were obtained after screening. The annual publication and cumulative publication of the literature on opioids and immunomodulation over the past 22.5 years is presented by counting the volume of literature on opioids and immunomodulation during 2000–2022 (Figure 2). It shows that both annual and cumulative trends of opioid- and immunomodulation-related literature increased year by year: 2000–2009 could be seen as the first phase, with development being relatively slow and fluctuating; 2010–2018 could be seen as the second phase and showed a steady and obvious increase; 2019–2021 could be seen as third phase, the number of publications beginning to increase significantly and reaching a peak in 2021. By fitting the data, a statistically significant relationship was observed between publication year and the number of cumulative publications (R^2=0.9826).

Literature Analysis

In Table 1, we list the 10 most-cited papers. Four of them were cited more than 500 times. The top article was "Exercise and the immune system: regulation, integration, and adaptation" by Pedersen et al, published in *Physiological Reviews*

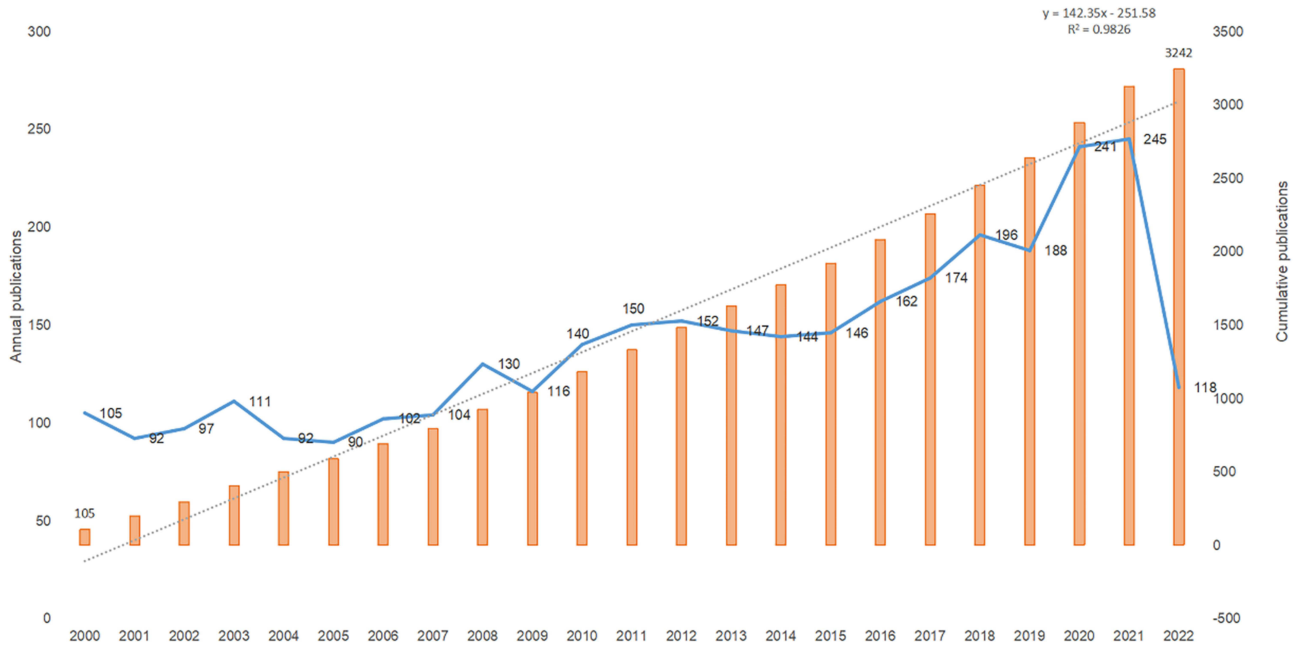


Figure 2 Annual and cumulative output of research on opioids and immunomodulation.

(IF=46.5) in 2000. This paper addressed the interactions between exercise and infectious diseases as well as exercise and neoplasia within the context of both aging and nutrition, and received 1004 citations. Among the top 10 papers, the top journal-level article was "The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US

Table 1 Ten most-cited papers

Rank	Title	Author	Type	Journal	Year	Citations	IF	Q	Main finding
1	Exercise and the immune system: regulation, integration, and adaptation	Bente Klarlund Pedersen	Review	Physiological Reviews	2000	1004	46.50	Q1	Interactions between exercise and infectious diseases as well as exercise and neoplasia within the context of both aging and nutrition
2	Chemistry and biology of roseophilin and the prodigiosin alkaloids: a survey of the last 2500 years	Alois Fuerstner	Review	Angewandte Chemie International Edition	2003	749	16.82	Q1	Prodigiosins act synergistically with cyclosporine A or FK 506
3	The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states	Ali H Mokdad	Article	Journal of the American Medical Association	2018	629	157.33	Q1	Specific diseases and risk factors are increasing and warrant increased attention
4	Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity	David Artis	Article	Nature	2015	584	69.50	Q1	ILC2s can regulate adipose function and metabolic homeostasis, in part via production of enkephalin peptides that elicit beiging.

(*Continued*)

Table 1 (Continued).

Rank	Title	Author	Type	Journal	Year	Citations	IF	Q	Main finding
5	Use of plant extracts in fish aquaculture as an alternative to chemotherapy: current status and future perspectives	M Reverter	Review	Aquaculture	2014	435	5.13	Q1	Studies carried out on the use of plant products on fish aquaculture and their biological effects on fish
6	Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions	Ru-Rong Ji	Article	Nature Medicine	2010	404	87.24	Q1	A role for resolvins in normalizing the spinal synaptic plasticity that has been implicated in generating pain hypersensitivity
7	New insights into the placebo and nocebo responses	Paul Enck	Review	Neuron	2008	382	18.68	Q1	Current neurobiological models like expectation-induced activation of brain reward circuitry
8	Impact of plant products on innate and adaptive immune system of cultured finfish and shellfish	Moon-Soo Heo	Review	Aquaculture	2011	372	5.13	Q1	The role of medicinal herbs and their products in innate and adaptive immunoresponse of finfish and shellfish
9	The neuroscience of placebo effects: connecting context, learning and health	Tor D Wager	Review	Nature Reviews Neuroscience	2015	357	38.75	Q1	Neuropsychological processes that mediate placebo effects may be crucial for a wide array of therapeutic approaches
10	Herbal biomedicines: a new opportunity for aquaculture industry	Thavasimuthu Citarasu	Article	Aquaculture International	2010	352	2.95	Q2	Herbal plants for their biological effects, such as immunostimulation

states" by Ali et al, published in the *Journal of the American Medical Association* in 2018(IF=157.33). This study examined 333 causes and 84 risk factors and demonstrated that health in the US improved from 1990 to 2016, although the drivers of mortality and morbidity had changed in some states, with specific risk factors, such as drug-use disorders, high body-mass index, and alcohol-use disorders, being associated with adverse outcomes. Of the 10 most-cited articles, six were reviews and four were articles (Table 1).

Distribution of Countries/Regions and Institutions

The articles retrieved in this study were from 102 countries. Figure 3A shows the geographic distribution of the 30 countries with the highest number of published papers. For better visualization, Figure 3B displays a collaboration network of the top 30 countries. Notably, there was a lot of active cooperation among these countries: different colors represent different countries, and the length of each color indicates the productivity of the corresponding country. Figure 4A presents an overlay visualization of the top 30 countries. These countries were distributed in Asia, North America, and Europe (Table 2). Among these, the country with the largest number of publications was the US (n=891, 27.5%), followed by China (n=795, 24.5%), Brazil (n=203, 6.2%), and Japan (n=195, 6.0%). The combined number of publications from China and the US accounted for over half the total (52%). In CiteSpace, centrality was used to quantify the importance of a node's position in the network. High centrality is often well recognized as a turning point or pivotal point in a field, and thus can be seen as a "bridge."[27,28] The centrality analysis showed that the US and France had the same centrality at the top (0.25), followed by Germany (0.24) and Italy (0.19) (Table 2). Figure 4B illustrates the

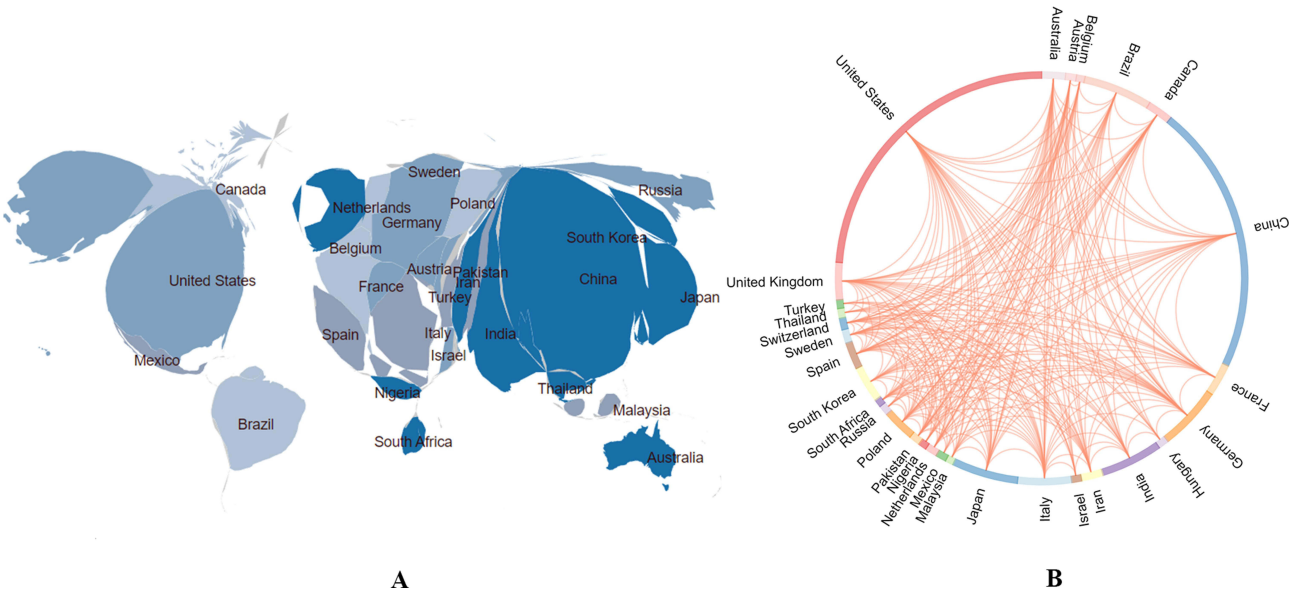


Figure 3 Geographic distribution (**A**) and cooperation among countries/regions (**B**).

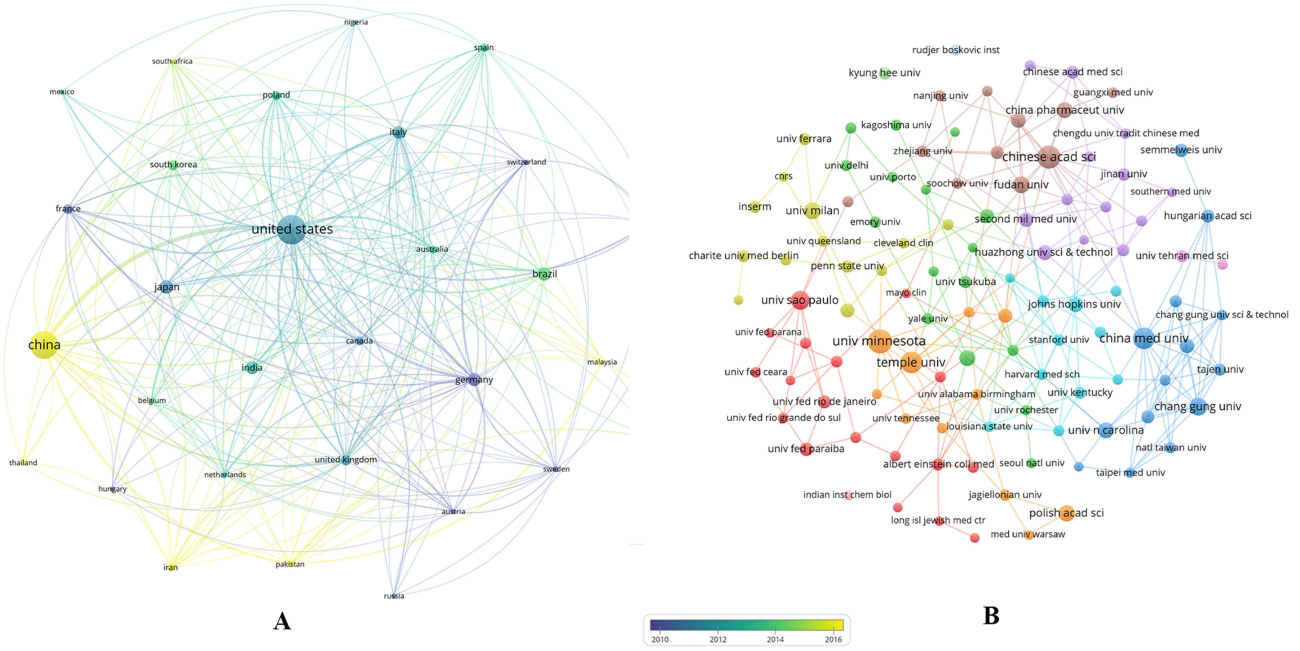


Figure 4 Network of cooperative relationships among countries/regions (**A**) and visualization of institutions (**B**).

cooperation network of institutions. We selected 112 institutions based on a minimum number of publications of 10 for visualization. The top 10 institutions were located in five countries. The three institutions that published the most relevant papers were the University of Minnesota System (n=64, 2.0%), Chinese Academy of Sciences (n=60, 1.9%), and China Medical University (n=51, 1.6%). These institutions were also the top three institutions in terms of centrality (Table 2).

Journals and Cocited Journals

A total of 1126 academic journals published articles on opioids and immunomodulation research. The top 15 journals published 620 papers, accounting for 19.12% of all publications (Table 3). The *Journal of Ethnopharmacology* had the greatest number of publications (n=101), followed by *International Immunopharmacology* (n=82) and the *Journal of*

Table 2 Top 10 countries and institutions

Rank	Country	Continent	Centrality	Count	Institution	Count	Centrality
1	USA	North America	0.25	891 (27.5%)	University of Minnesota	64 (2.0%)	0.03
2	China	Asia	0.14	795 (24.5%)	Chinese Academy of Sciences	60 (1.9%)	0.11
3	Brazil	Europe	0.05	203 (6.2%)	China Medical University	51 (1.6%)	0.08
4	Japan	Asia	0.05	195 (6.0%)	Temple University	51 (1.6%)	0
5	Germany	Europe	0.24	187 (6.0%)	University of São Paulo	39 (1.2%)	0
6	India	Asia	0.02	182 (5.7%)	Chang Guang University	34 (1.0%)	0.01
7	Italy	Europe	0.19	159 (4.9%)	Fudan University	32 (1.0%)	0.03
8	UK	Europe	0.14	110 (3.4%)	University of Milan	32 (1.0%)	0.01
9	South Korea	Asia	0.06	107 (3.3%)	Polish Academy of Sciences	30 (0.9%)	0.01
10	France	Europe	0.25	95 (2.9%)	China Pharmaceutical University	28 (0.8%)	0.01

Table 3 Top 15 journals and cocited journals

Rank	Journal	Count	IF	Q	Cocited journal	Cocitations	IF	Q
1	Journal of Ethnopharmacology	101	5.19	Q2	Journal of Immunology	3657	5.42	Q2
2	International Immunopharmacology	82	5.71	Q1	Proceedings of the National Academy of Sciences of the United States of America	2630	12.77	Q1
3	Journal of Neuroimmunology	54	3.22	Q3	Journal of Biological Chemistry	2307	5.48	Q2
4	Brain Behavior and Immunity	44	19.22	Q1	Journal of Neuroimmunology	2284	3.22	Q3
5	PLoS One	44	3.75	Q2	Journal of Pharmacology and Experimental Therapeutics	1920	4.40	Q2
6	Journal of Immunology	39	5.42	Q2	Nature	1813	69.50	Q1
7	Molecules	38	4.92	Q2	Journal of Ethnopharmacology	1773	5.19	Q2
8	Phytomedicine	31	6.65	Q1	Pain	1734	7.92	Q1
9	Journal of Neuroimmune Pharmacology	28	7.28	Q1	Science	1554	63.71	Q1
10	Frontiers in Immunology	28	8.78	Q1	Phytochemistry	1472	4.00	Q3
11	Planta Medica	28	3.00	Q3	PLoS One	1414	3.75	Q2
12	Natural Product Research	27	2.48	Q3	European Journal of Pharmacology	1393	5.19	Q2
13	Scientific Reports	26	4.99	Q2	Journal of Neuroscience	1331	6.70	Q1
14	Pain	25	7.92	Q1	Journal of Natural Products	1323	4.80	Q2
15	European Journal of Immunology	25	6.68	Q2	Anesthesiology	1197	8.98	Q1

Neuroimmunology (n=54). Among the top 15, the journal with the highest impact factor was *Brain Behavior and Immunity* (IF=19.22), followed by *Frontiers in Immunology* (IF=8.78). We selected 59 journals based on a minimum number of publications of 10 for visualization (Figure 5A). Figure 5A shows that *International Immunopharmacology* had the most activecitation relationships with the *Journal of Ethnopharmacology*, *Journal of Neuroimmunology*, and *Brain Behavior and Immunity.*

Among 15,196 cocited journals, 45 had more than 500 citations, among which the *Journal of Immunology* (3657), *Proceedings of the National Academy of Sciences of the United States of America* (2630), and *Journal of Biological Chemistry* (2307) were the top three. The impact factor of *Nature* was the highest (IF=69.50), followed by *Science* (IF=63.71) (Table 3). Journals with a minimum of 200 cocitations were filtered to map the cocitation network (Figure 5B). As shown in Figure 5B, the *Journal of Immunology* had positive cocitation relationships with *Proceedings of the National Academy of Sciences of the United States of America*, *Journal of Biological Chemistry*, and *Journal of Neuroimmunology.*

A dual-map analysis was used to reveal the connections between multiple disciplines and topic distribution of academic journals (Figure 6).[29] Citing journals are on the left, cited journals are on the right, and curved paths indicate

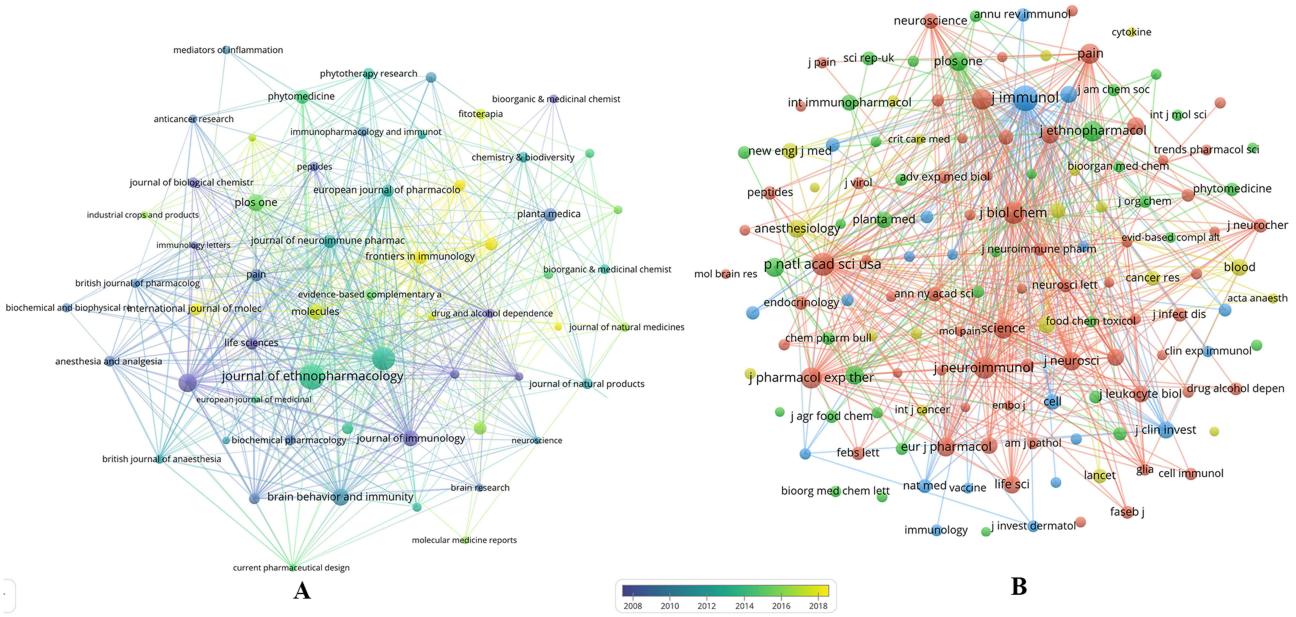


Figure 5 Visualization of journals (**A**) and cocited journals (**B**).

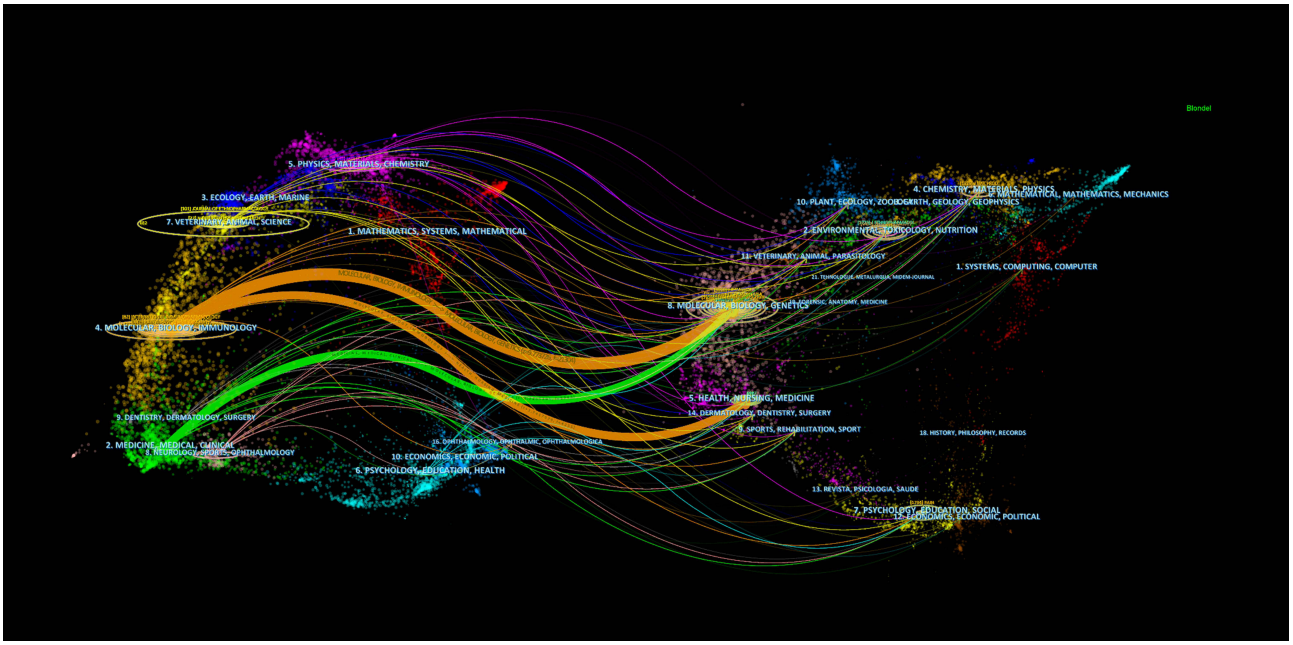


Figure 6 Dual-map overlay of journals.

citation relationships. Figure 6 shows there were three main citation paths. The one with the strongest relationship is the path from molecular/biology/immunology journals to molecular/biology/genetics journals.

Authors and Cocited Authors

A total of 16,555 authors participated in opioid and immunomodulation research. Among the top 10, three published more than 20 papers (Table 4). We built a collaborative network of 162 authors with five or more published papers (Figure 7A). Tsong-long Hwang published the most opioid- and immunomodulation-related articles (n=23), followed by

Table 4 Top 10 authors and cocited authors

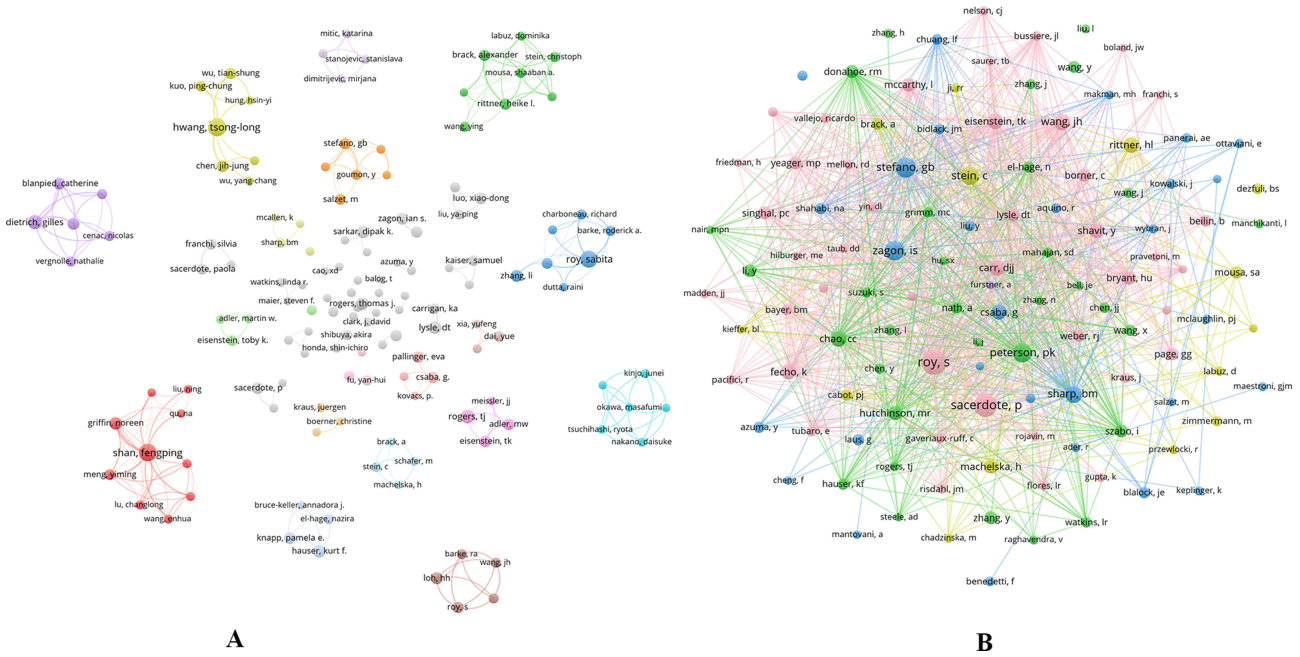
Rank	Authors	Count	Total link strength	Cocited authors	Citations	Total link strength
1	Tsong-long Hwang (China)	23	37	Sabita Roy (USA)	469	13,637
2	Fengping Shan (China)	22	57	Paola Sacerdote (Italy)	390	8077
3	Sabita Roy (USA)	21	31	George Bogdan Stefano (Czech Republic)	305	4955
4	Gilles Dietrich (France)	14	39	Ian S. Zagon (USA)	284	4831
5	TJ Rogert (UK)	13	10	Phillip Peterson (USA)	268	8644
6	Donald T Lysle (USA)	12	8	Christoph Stein (Germany)	248	4679
7	Noreen Griffin (USA)	11	32	M Sharp (USA)	216	5508
8	Kurt F Hauser (USA)	11	21	JH Wang (USA)	201	5896
9	Dipak K Sarkar (USA)	11	9	Heike Rittner (Germany)	183	3711
10	Catherine Blanpied (France)	10	32	Toby K Eisenstein (USA)	180	5161

Fengping Shan (n=22) and Sabita Roy (n=21). The relationships between authors can also be observed in this map. Fengping Shan had the highest total link strength, followed by Gilles Dietrich and Tsong-long Hwang.

Cocited authors are two or more authors who are cited by one or more papers at the same time, and these authors constitute a cocited relationship.[30] Among the 86,859 cocited authors, 119 were cocited more than 50 times. The most cocited was Sabita Roy (469), followed by Paola Sacerdote (390) and George Bogdan Stefano (305). In sum, 119 authors with a minimum cocitations of 50 were filtered to map cocitation-network graphs (Figure 7B). As shown in Figure 7B, there were also active collaborations among different cocited authors. There are five colors in this map, representing five clusters among authors. Active collaborations usually exist in the same cluster, such as Sabita Roy and Paola Sacerdote. There were also collaborations among linked two nodes in different clusters, such as Sabita Roy and Phillip Peterson.

Cocited References and Reference Bursts

Table 5 shows the 10 most-cocited references. Among these, "Mccarthy L et al (2001), *Drug and Alcohol Dependence*" (113), "Eisenstein TK et al (1998), *Journal of Immunology*" (76), and "Weber RJ et al (1989), *Science*" (58) were the top



A B

Figure 7 Visualization of authors (**A**) and cocited authors (**B**).

Table 5 Top 10 cocited references

Rank	Cocited reference	Citations	Type	Centrality
1	Mccarthy L, 2001, Drug Alcohol Depen, V62, P111, DOI10.1016/S0376-8716(00)00181–2	113	Review	0.15
2	Eisenstein TK, 1998, J Neuroimmunol, V83, P36, DOI 10.1016/S0165-5728(97)00219–1	76	Review	0.03
3	Weber RJ, 1989, Science, V245, P188, DOI 10.1126/science.2749256	58	Article	0.01
4	Mosmann T, 1983, J Immunol Methods, V65, P55, DOI 10.1016/0022-1759(83)90303–4	57	Article	0.00
5	Zimmermann M, 1983, Pain, V16, P109, DOI 10.1016/0304-3959(83)90201–4	52	Editorial	0.03
6	Vallejo RICARDO, 2004, Am J Ther, V11, P354, DOI 10.1097/01.mjt.0000132250.95650.85	51	Review	0.03
7	Lysle DT, 1993, J Pharmacol Exp Ther, V265, P1071	47	Article	0.02
8	Szabo I, 1993, J Pharmacol Exp Ther, V267, P703	45	Article	0.04
9	Sharp BM, 1998, J Neuroimmunol, V83, P45, DOI 10.1016/S0165-5728(97)00220–8	44	Article	0.02
10	Bayer BM, 1990, Neuropharmacology, V29, P369, DOI 10.1016/0028-3908(90)90096-A	40	Review	0.02

three. These studies had impact factors of 4.85, 5.42, and 63.71, respectively. Of the 10 references, five were articles, four reviews, and one editorial material. Cocited references were analyzed by CiteSpace for visual correlation analysis, from which the visualizations, reference burst, and timeline view of cocited references were obtained. In the connection map (Figure 8), each node represents a cited paper, the size of the nodes is closely related to the frequency of citations, and the thickness of the lines between the nodes indicates the link strength. The outermost circle in purple represents the centrality of each paper, which means it is a "bridge" paper in this mapping and has an important position in the knowledge network. The timeline perspective of the clustering diagram, combined with an analysis of clustering and time, displays the distribution of topics, trends, and interrelationships of research topics over time (Figure 9). The cluster theme is located in the rightmost diagram.

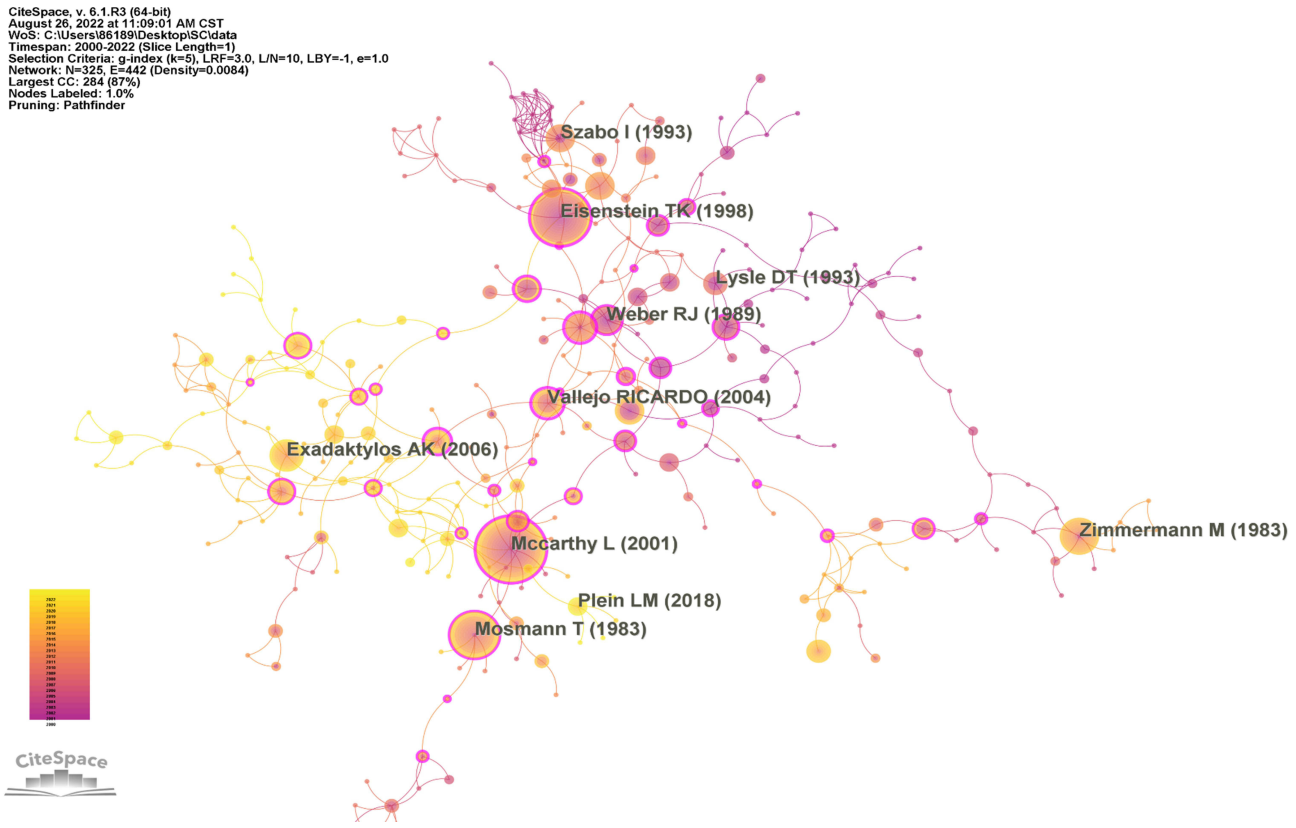


Figure 8 Visualization of cocited references.

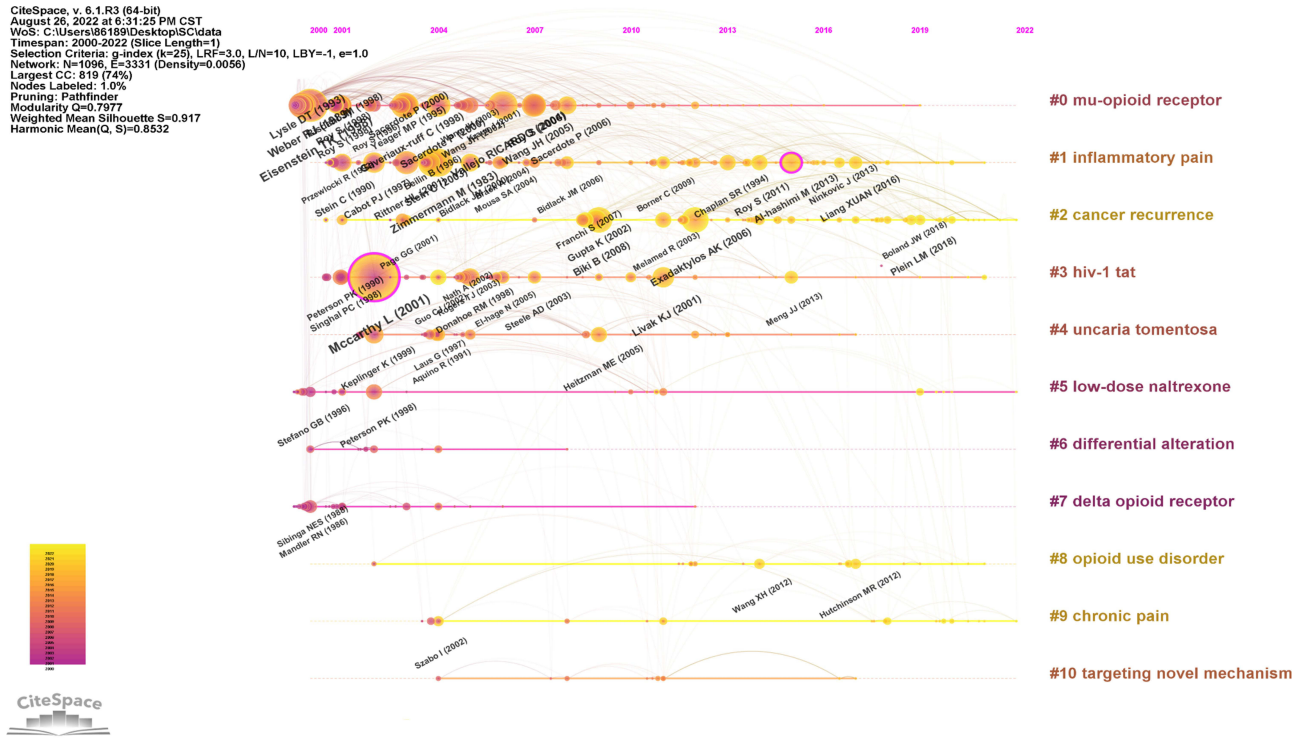


Figure 9 Timeline of cocited references.

The cluster analysis revealed 11 clusters: μ-opioid receptor, inflammatory pain, cancer-recurrence, HIV1 Tat, *Uncaria tomentosa*, low-dose naltrexone, differential alteration, α-opioid receptor, opioid use disorder, chronic pain, and targeting novel mechanism. The closest clusters on the timeline were inflammatory pain (1), cancer recurrence (2), low-dose naltrexone (5), opioid-use disorder (8), and chronic pain (9). References with citation bursts are those that have been cited significantly and more frequently over a period.[27] A total of 253 references were detected as citation bursts, and we chose the top 20 for Figure 10. The strongest "burstness" (strength 17.34) occurred for "Opioids and the immune system-friend or foe" by Plein et al,[18] published by the *British Journal of Pharmacology* in 2018, with citation burstness from 2019 till today. Notably, another seven references were still in burstness. Roy et al[20] reviewed opioid drug abuse and modulation of immunofunction, Exadaktylos et al retrospectively reviewed whether anesthetic technique for primary breast cancer surgery affects recurrence or metastasis,[31] Al-Hashimi et al reviewed opioids and immunomodulation,[32] Liang et al reviewed how the opioid system modulates immunofunction,[33] Ninkovic et al reviewed the role of the μ-opioid receptor in opioid modulation of immunofunction,[34] Hutchinson et al reviewed how the opioid activation of TLR4 contributes to drug reinforcement,[35] and Boland et al reviewed the influence of opioids on immunofunction in patients with cancer pain.[36]

Keyword Analysis of Trending Research Topics

A total of 14,699 keywords were obtained, among which 588 appeared at least 10 times. Table 6 shows the top 20 keywords in research on opioids and immunomodulation. Among these, "expression", "inflammation", and "activation" appeared more than 300 times, which represented the main research direction of opioids and immunomodulation. We filtered keywords with more than or equal to 20 occurrences and performed cluster analysis through VOSviewer (Figure 11A). The thicker the lines between the nodes, the stronger the connection between the keywords. As shown in Figure 11A, we obtained four clusters in total, representing four research directions. Figure 11B shows the high-frequency keywords as an overlay map, where the color indicates the average published year. As we can see, oxidative stress, antioxidant, regulatory T cells, angiogenesis, and recurrence were emerging fields (in yellow). VOSviewer was

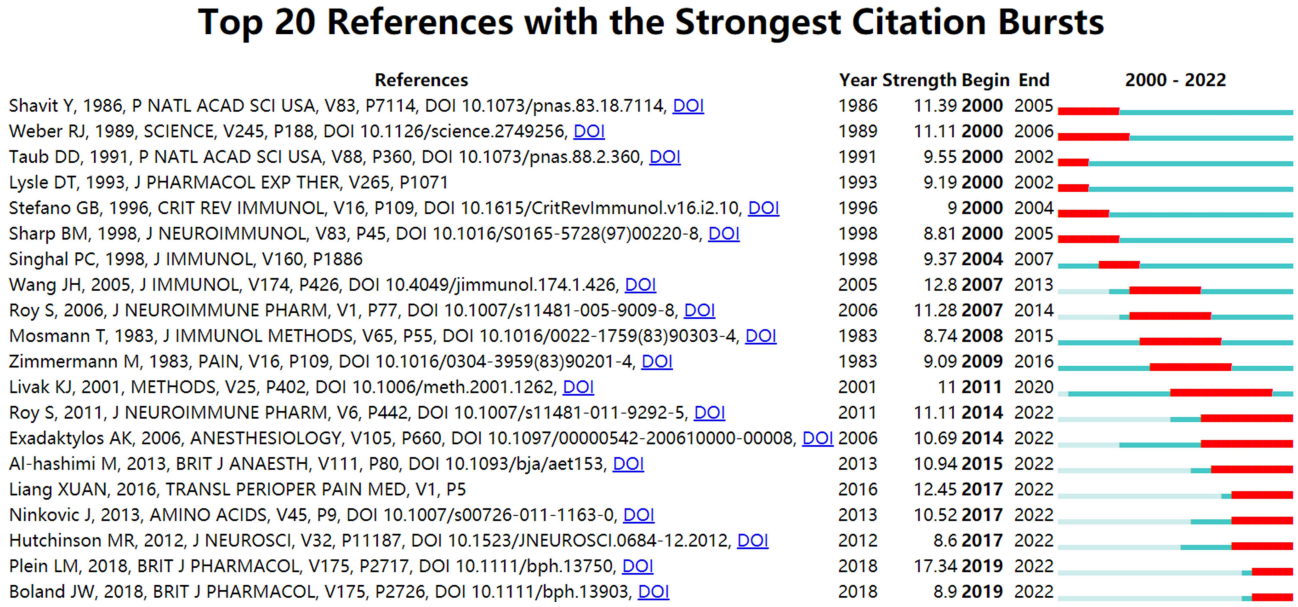


Figure 10 Top 20 citation bursts.

also used to determine the density based on the frequency of the keywords (Figure 12A). In the density visualization, regions with higher optical density suggested a research hotspot in this area. Burst keywords between 2000 and 2022 were identified by CiteSpace. In Figure 12B, the green line represents the time period from 2000 to 2022, and the interval of the burst keyword is shown by the red line. The keyword with the greatest burst strength was "beta endorphin" (16.02). Other burst keywords presented in recent years included "pathway" (2016–2022), "regulatory T cell" (2016–2022), "antioxidant" (2017–2022), "oxidative stress" (2018–2022), "prevalence" (2018–2022), and "root" (2018–2022). In this study, we tried to objectively evaluate the hotspots and frontiers of opioid and immunomodulation research through analysis of dual-map overlay of journals (Figure 6), cocited reference timeline, and burst (Figures 9 and 10) and keyword co-occurrence, overlay, and burst (Figures 11 and 12 and Table 6).

Discussion

Studies have shown that persons with opioid-use disorders are more likely to develop infections, including HIV.[37] These findings suggest that misusing opioids is harmful to immunofunction. It has been proven that opioids have broad immunomodulatory activity.[38] Most opioids were previously thought to be suppressive to the immune system, but recent

Table 6 Top 20 keywords

Rank	Keyword	Count	Rank	Keyword	Count
1	Expression	425	11	Beta-endorphin	194
2	Inflammation	325	12	NF-kappa B	181
3	Activation	301	13	Mice	176
4	Alkaloid	270	14	Macrophage	170
5	Morphine	260	15	Rat	169
6	In vitro	259	16	Mechanism	162
7	Cell	243	17	Opioid receptor	151
8	Apoptosis	243	18	Immune response	149
9	Inhibition	211	19	Pain	138
10	Receptor	199	20	Cytokine	124

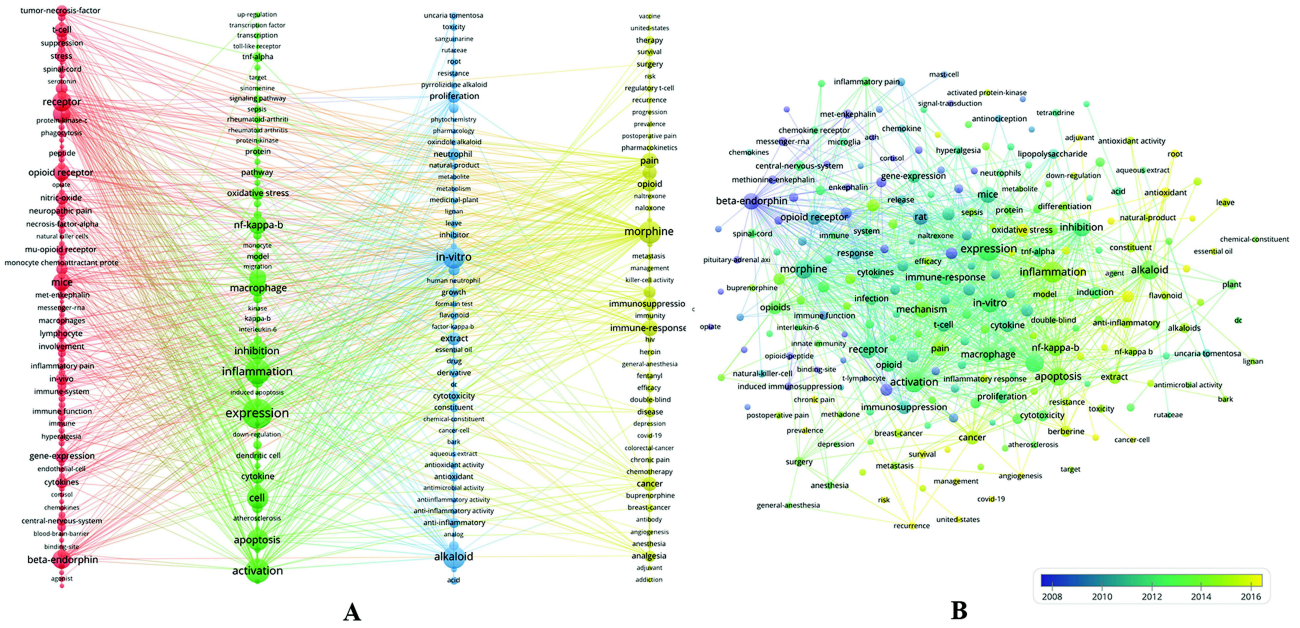


Figure 11 Keyword-cluster analysis (**A**) and overlay visualization (**B**).

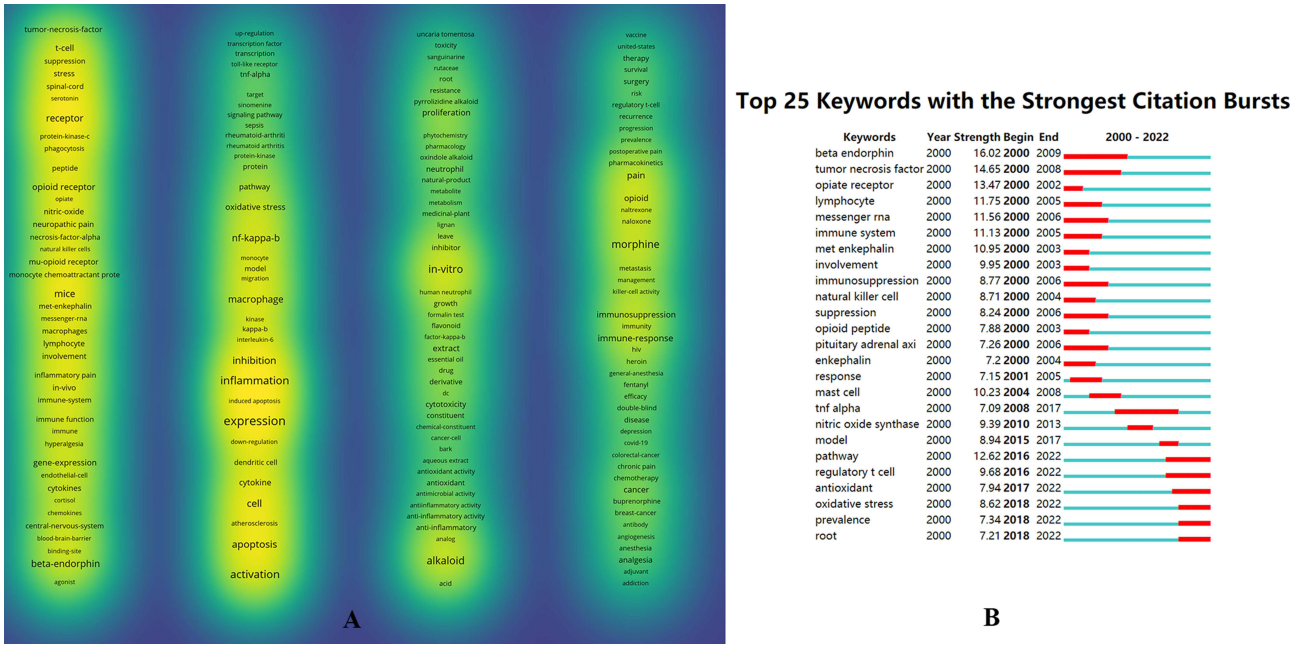


Figure 12 Density visualization of keywords (**A**) and top 20 keywords (**B**).

research suggests that opioids may exert a dual effect, closely related to source, duration, and dose.[31] In vitro and in vivo experiments have shown the different mechanisms of immunomodulation by opioids. In vitro experiments have revealed that many exogenous opioids, such as morphine impair, the phagocytic and chemotactic function of neutrophils and monocytes, reduce the effector response of B and T lymphocytes, and promote lymphocyte and phagocytic cell apoptosis. In vivo studies have also shown a detouring effect of opioids, especially morphine, involving reduction of NK-cell function and lymphocyte proliferation.[10] Another experiment showed that the proliferation of spleen T lymphocytes was significantly inhibited and the contents of $CD3^+$, $CD4^+$, and $CD8^+$ T lymphocytes significantly lower in a rat model of bone cancer pain than the normal control group. Such exogenous opioids as morphine can only improve pain, but have

no improvement on T lymphocytes. The endogenous peptide β-endorphin can promote the proliferation of T lymphocytes, although the analgesic effect is not as good as morphine. $CD3^+$, $CD4^+$, and $CD8^+$ T lymphocytes indicate that β-endorphin is beneficial to immunofunction.[15]

General Information

Based on the data from the SCI-expanded from 2000 to 2022, a total of 3242 opioid- and immunomodulation-related articles were published in 786 academic journals by 19,687 authors in 885 institutions from 82 countries/regions. The relevant research onficially started in 1979, when Wybran et al[11] discovered that opioids had effects on immunofunction. Since then, opioid- and immunomodulation-related documents have been increasing persistently. The number of published articles in 2021 was double that of 2000. Based on to the current trend, research on opioids and immunomodulation will continue to maintain overall growth in the future.

In country/region analysis, China and the US are the principal countries involved in research on opioids and immunomodulation, and the US ranks first. About 50% of the top 10 research institutions were located in China, followed by the US (n=2, 20%), with the other three in Brazil, Italy, and Poland. Interestingly, the centrality of the US and France was the highest, while China ranked fifth. This showed that the US and France had "bridge" roles in this research field. Germany and Italy also had high centrality, which means that they also played significant roles in global cooperation on opioid and immunomodulation research. The Chinese Academy of Sciences had the highest centrality and was the second–most productive institution. When it comes to the cooperative relationships between research institutions, there were close relationships among some, such as the Chinese Academy of Sciences, China Pharmaceutical University, and Fudan University, but some had little collaboration with others, especially in geographically distant institutions. This can be harmful to the long-term development of academic research. Overlay visualization of countries indicated that although some Western countries still have strong scientific research strength, the focus of research in this field has been gradually shifting to the East, especially to Asia, in recent years.

Most of the research on opioids and immunomodulation was published in the *Journal of Ethnopharmacology* (IF=5.19, Q2), indicating it is currently the most popular journal in this research field. More than half of the top 15 academic journals and cocited journals could be classified as immunology and pharmacology journals, although the rest were classified as comprehensive journals covering opioids and immunomodulation. This is coordinated with the dual-map analysis, which showed the main citation paths in this research area were related to molecular, biology, immunology, genetics, and medicine. These results also suggest that researchers may select interdisciplinary journals to increase the attention of other disciplines and further enhance the research breadth and depth on opioids and immunomodulation.

Among the top 10 authors and cocited authors, as a representative scholar in this field, Sabita Roy not only ranks third in the number of papers published on opioids and immunoregulation but also first among cocited authors, with 469 citations, indicating her outstanding contribution to this field of research. Sabita Roy is a scholar at the Surgery Department of the University of Miami Miller School of Medicine, focusing on opioids and immunomodulation. In 2006, her team published a review that described the effects of morphine on innate and adaptive immunity, identified the role of the μ-opioid receptor, and discussed how morphine increased the risk of opportunistic infection.[39] This paper maintained a citation burst from 2007 to 2014. Another article published in the *Journal of Neuroimmune Pharmacology* in 2011 has also had a reference bust from 2014 till today.[20]

Knowledge Base and Research Hotspots

The collection of cocited references cited by the corresponding research documents could partly represent the knowledge base.[29] In this bibliometric study, we selected the 10 most-cocited references to determine the research basis on opioids and immunomodulation. Four of them were reviews, and all were focused on the immunomodulating effects of opioids.[19,40–42] The other half of the top 10 were articles related to opioids and the immune system.[43–47] The other one was editorial material that provide ethical guidelines for investigations of experimental pain in conscious animals.[48] Of the top 10 cocited references, Mccarthy et al reviewed the relationship among opioids, opioid receptors, and immunoresponse in 2001 and received the most citations.[40] Eisenstein et al reviewed opioid modulation of

immunoresponse and its effects on phagocyte and lymphoid cell populations in 1998, which received the second-most.[19] Richard et al suggested that periaqueductal gray matter mediates opiate-induced immunosuppression in 1989 and ranked third.[43]

Via keyword co-occurrence, we were able to quickly identify research hotspots in an academic area. Overlay and timeline view can elucidate the evolution of hotspots, while reference clusters and bursts are important indicators of emerging trends and research frontiers.[27,49,50] In this study, the three newest burst keywords with the highest strength were "pathway", "regulatory T cell", and "oxidative stress." This suggests that in recent years, research hotspots in this area focused on the pathways[51–53] and roles of regulatory T cells involved in the mechanism of the immunomodulating effects of opioids,[54–56] and also on oxidative stress and inflammation caused by misuse of opioids.[57–59]

Advantages and Limitations

The present research makes some novel contributions to this field. Firstly, this is the first bibliometric study to systematically analyze opioid- and immunomodulation-related research. It can provide an oversight of the collaboration network and research trends for scholars who pay attention to this area. Secondly, we used VOSviewer and CiteSpace to provide richer results in multiple dimensions, as well as present the results more comprehensively and objectively. However, there are some limitations in our study. On one hand, the data were only from the SCI-expanded, and other databases were ignored, and on the other hand, we chose only publications in English. Those written in languages other than English, such as Chinese, were excluded, so some relevant studies may thus have been missed.

Conclusions

Opioids are one of the most powerful analgesics available to treat pain. Nevertheless, numerous studies have shown the immunomodulating effects of opioids and suggested they modulate both innate and adaptive immunoresponses. Endogenous and exogenous opioids may play diverse roles in this process, depending on source, duration, and dose. This bibliometric study elucidates the current status and global trends of research on opioids and immunomodulation. The US and China remain in the dominant position in terms of the total number of published articles. However, the connection between countries needs to be strengthened. Based on this study, there is a strong possibility that the number of papers will increase in the coming year. It can be predicted that research on pathways, regulatory T cells, and oxidative stress will be the next hot topics and will receive increased attention.

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Disclosure

The authors report no conflicts of interest in this work.

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