Hot spots and future directions of research on the neuroprotective effects of nimodipine

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Abstract

Calcium antagonists are widely used in the clinical treatment of ischemic cerebrovascular disease because of their vascular and neuroprotective effects. Nimodipine, a typical calcium antagonist, can cross the blood-brain barrier and act selectively at neurons and blood vessels of target tissues, thus exerting neuroprotective effects. The aim of the present study was to explore the hot spots and future trends of research on the neuroprotective effects of nimodipine. We retrieved 425 articles on the neuroprotective effects of nimodipine that were indexed in the Web of the Science database between 2000 and 2014. The retrieved articles were analyzed using document analysis reporting and the derived information function in the Web of Science, and the information visualization software CiteSpace III. The reference co-citation network was plotted, and the high frequency key words in these publications were used to analyze the research fronts and development trends for nimodipine neuroprotection. According to these co-citation clusters, the research front of nimodipine neuroprotection is the use of randomized controlled trials to study nimodipine intervention of subarachnoid hemorrhage. Using time zone view analysis on hot spots labeled with a key word, the areas of interest in the field of nimodipine neuroprotection are nimodipine pharmacology and therapeutics, blood-brain barrier, trials, and anti-angiospasm.

Key Words: neuroprotection; nerve regeneration; nimodipine; ischemic cerebrovascular disease; Web of Science; CiteSpace; research fronts; development trends; scientific mapping; visualization

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Introduction

Current treatments for acute ischemic cerebrovascular disease include thrombolysis, defibrination and anticoagulation therapy, but these are associated with severe adverse effects such as bleeding, resulting in a poor prognosis. Nimodipine is widely recognized as a neuroprotective agent. It is a fat-soluble drug that can cross the blood-brain barrier and act selectively at target neurons and blood vessels in the brain, exerting protective effects on injured neurons. Therefore, nimodipine is widely used to improve blood circulation during the convalescent period after acute cerebrovascular disease, and to improve cerebral angiospasm caused by subarachnoid hemorrhage (Babu et al., 2011; Wang et al., 2012; Justin et al., 2014).

An area gaining increasing interest is the investigation of study dynamics and development trends in specialist research fields, using knowledge mapping. CiteSpace III is an information visualization tool developed by Professor Chen from Drexel University, Philadelphia, USA in 2005 (Chen, 2005). It can visualize the trends and patterns in a field or domain within a designated period of time. CiteSpace III has been used to analyze the knowledge structure, hot spots, frontiers and pivotal points in regenerative medicine research (Chen, 2014). Here, we present a visualization analysis of articles on the neuroprotective effects of nimodipine indexed in the Web of Science database during 2000–2014, using Citespace III software, to explore the research fronts and trends in studies of nimodipine administration.

Data and Methods

Data source and methodology

Online retrieval (http://apps.webofknowledge.com) from the Web of Science was performed by the first author using the key words "nimodipine" and "nerve" to screen research articles or reviews published in English between 2000 and 2014. The retrieval was carried out on 30th October 2014 and 425 publications were included in the final analysis. The Web of Science Core Collection consists of the Science Citation Index Expanded (SCI-Expanded), Social Sciences Citation Index (SSCI), Arts & Humanities Citation Index (A&HCI), Conference Proceedings Citation Index-Science (CPCI-S), and Conference Proceedings Citation Index-Social Science & Humanities (CPCI-SSH). The following information was downloaded for each publication: authors, title, abstract, institution, descriptors and identifiers. The downloaded data were input into and analyzed by the CiteSpace III visualization tool.

Inclusion criteria

(1) Peer-reviewed articles on the neuroprotective effect of nimodipine, including original basic and clinical studies and reviews. (2) Articles published in 2000–2014 (inclusive). (3) Articles indexed in the Web of Science database. (4) Articles with abstracts and citations.
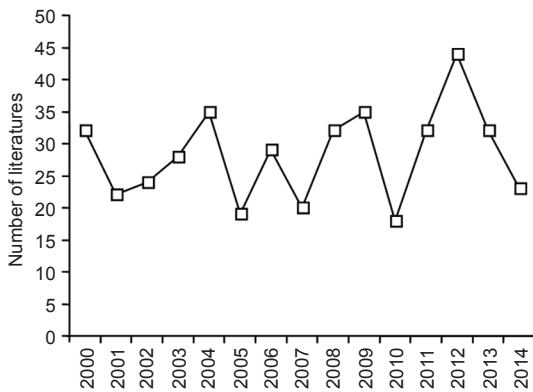
Figure 1 Yearly output of publications on the neuroprotective effect of nimodipine indexed in the Web of Science during 2000–2014.

Figure 3 Authors of the most articles on the neuroprotective effect of nimodipine, indexed in the Web of Science database in 2000–2014.
I: Tang X; II: Xie L; III: Stulzer HK; IV: Ray SB; V: Liu XD; VI: Krishnaiah YSR; VII: Georgarakis E; VIII: Bhaskar P; IX: Wang SL; X: Steiger HJ; XI: Scheller C; XII: Satyanarayana V; XIII: Riekes MK; XIV: He HD; XV: Hanggi D.

Figure 5 Funding sources for published studies on the neuroprotective effects of nimodipine, indexed by the Web of Science database during 2000–2014.
I: National Natural Science Foundation of China; II: National Basic Research Program of China (973 Program); III: Conselho Nacional De Desenvolvimento Científico E Tecnologico Cnpq; IV: National Nature Science Foundation of China; V: Project for Excellent Talents of Liaoning Province; VI: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; VII: Key Project For Drug Innovation of China; VIII: Oak Ridge Institute for Science and Education Orise; IX: NIH; X: Major National Platform for Innovative Pharmaceuticals; XI: Kyung Hee University; XII: German Federal Ministry of Education and Research Bmbf Ptj Bio; XIII: China Medical University; XIV: Bayer Vital Gmbh Leverkusen Germany.
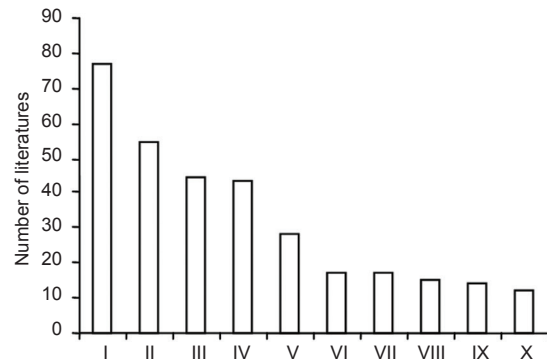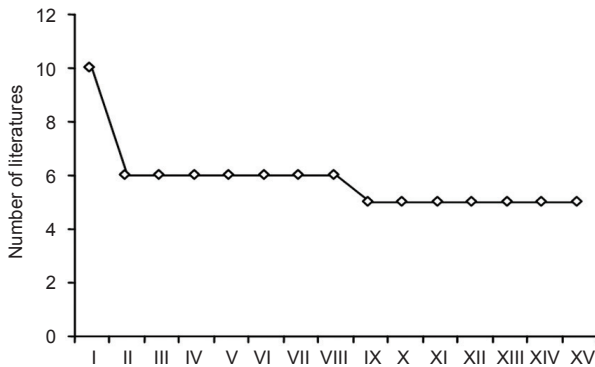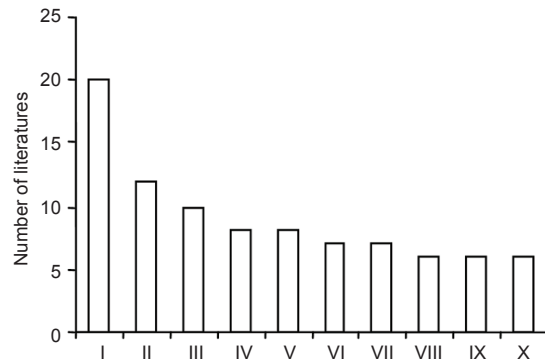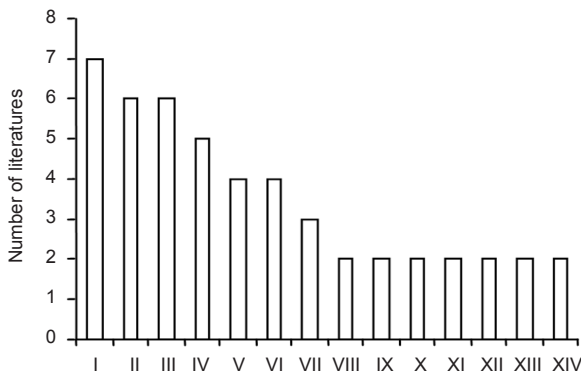

Figure 2 Distribution of publications indexed in the Web of Science between 2000 and 2014 on the neuroprotective effect of nimodipine across different countries.
I: China; II: USA; III: Germany; IV: India; V: Turkey; VI: Italy; VII: Canada; VIII: Brazil; IX: South Korea; X: Greece.

Figure 4 Institutions publishing the most articles on the neuroprotective effect of nimodipine, indexed in the Web of Science database in 2000–2014.
I: Shenyang Pharmaceut Univ; II: China Pharmaceut Univ; III: Univ Dusseldorf; IV: Postgrad Inst Med Educ Res; V: Aristotle Univ Thessaloniki; VI: Univ Toronto; VII: Andhra Univ; VIII: Univ Munich; IX: Univ Fed Santa Catarina; X: All India Inst Med Sci.

Exclusion criteria

(1) Publications that required manual searching or telephone access. (2) Documents that were not published in the public domain. (3) Meeting abstracts, proceedings, corrected articles, and repeated articles.

Quality assessment

English articles or reviews meeting the inclusion criteria were included in this study.

Analysis and discussion

A total of 425 publications were indexed in the Web of Science database between 2000 and 2014 (**Figure 1**). The distribution of these publications across different countries is shown in **Figure 2**.

Number of documents

A total of 425 articles on the neuroprotective effect of nimodipine were published during 2000–2014 and retrieved
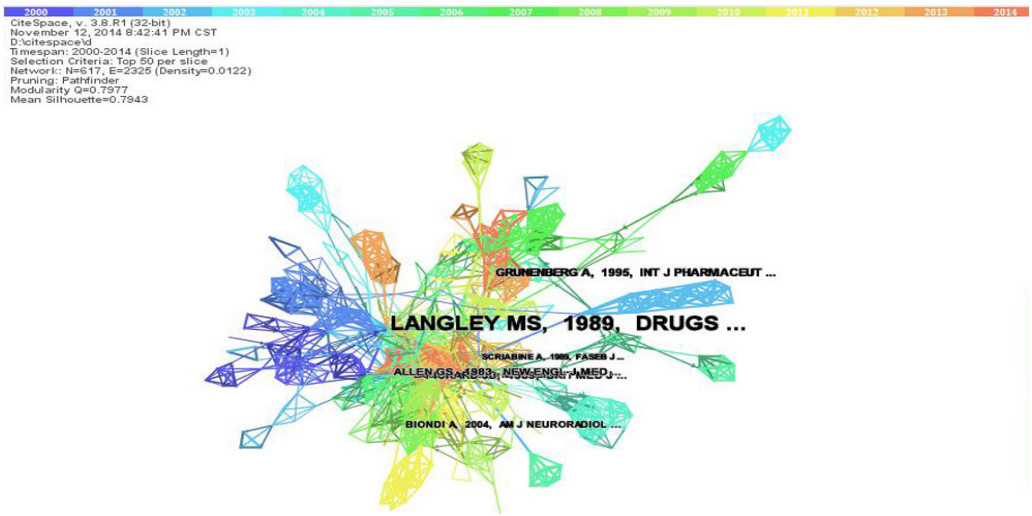
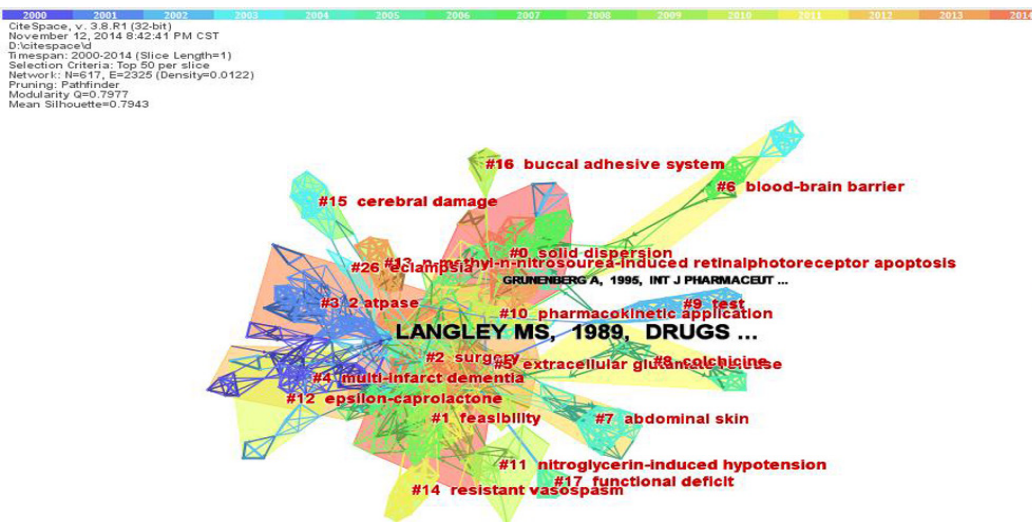**Figure 6 Co-citaion-burst term visualization analysis network knowledge map.**

Figure 7 Literature-co-word network visualization map in the field of nimodipine neuroprotection.
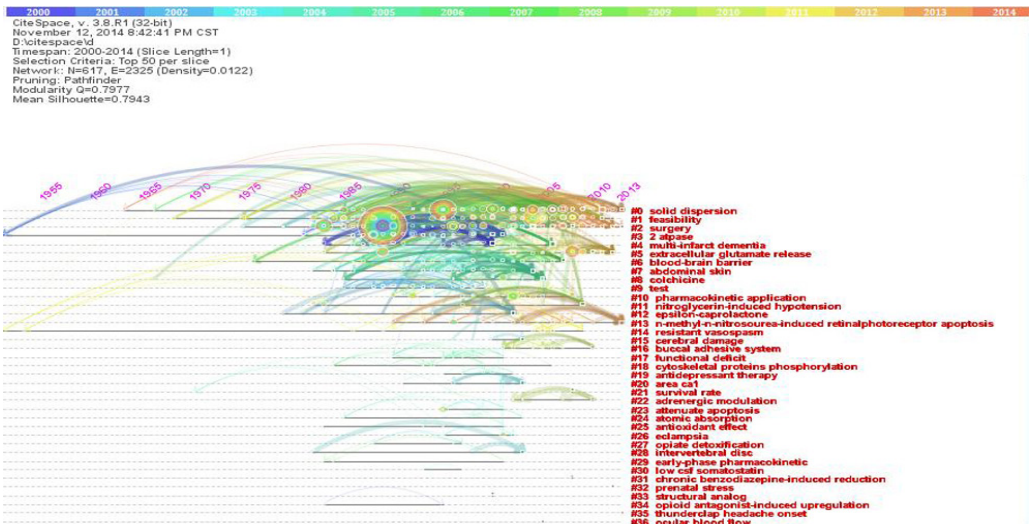

Figure 8 High-frequency key words in publications on nimodipine neuroprotection.

Table 1 Top-cited publications on the neuroprotective effect of nimodipine, indexed in the Web of Science between 2000 and 2014

No	Title	Authors	Journal	Publication year	Total citations
1	Effect of intravenous nimodipine on blood pressure and outcome after acute stroke	Ahmed et al. (2000)	*Stroke*	2000	133
2	Preparation of nimodipine-loaded microemulsion for intranasal delivery and evaluation on the targeting efficiency to the brain	Zhang et al. (2004)	*Int J Pharm*	2004	111
3	A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia	Belfort et al. (2003)	*New Engl J Med*	2003	109
4	Intra-arterial nimodipine for the treatment of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage: Preliminary results	Biondi et al. (2004)	*AJNR Am J Neuroradiol*	2004	103
5	Nimodipine in animal model experiments of focal cerebral ischemia - A systematic review	Horn et al. (2001a)	*Stroke*	2001	99
6	Very Early Nnimodipine Use in Stroke (VENUS) - A randomized, double-blind, placebo-controlled trial	Horn et al. (2001b)	*Stroke*	2001	64
7	Intravenous magnesium *versus* nimodipine in the treatment of patients with aneurysmal subarachnoid hemorrhage: A randomized study	Schmid-Elsaesser et al. (2006)	*Neurosurgery*	2006	63
8	A double blind, randomized clinical trial assessing the efficacy and safety of augmenting standard antidepressant therapy with nimodipine in the treatment of 'vascular depression'	Taragano et al. (2001)	*Int J Geriatr Psych*	2001	57
9	Combined nimodipine and citicoline reduce infarct size, attenuate apoptosis and increase Bcl-2 expression after focal cerebral ischemia	Sobrado et al. (2003)	*Neuroscience*	2003	56
10	Efficacy and safety of nimodipine in subcortical vascular dementia: a subgroup analysis of the Scandinavian Multi-Infarct Dementia Trial	Pantoni et al. (2000)	*J Neurol Sci*	2000	43

Table 2 Highly cited ("classical") publications retrieved by Citespace III visualization software

Centrality	Frequency	Authors	Journal	Publication time
0.58	50	Langley et al. (1989)	*Drugs*	1989
0.25	28	Grunenberg (1995)	*Int J Pharm*	1995
0.2	24	Allen et al. (1983)	*N Engl J Med*	1983
0.18	18	Barker et al. (1996)	*J Neurosurg*	1996
0.14	10	Angelov et al. (1996)	*J Neurosci*	1996
0.13	20	Scriabine et al. (1989)	*FASEB J*	1989
0.12	24	Pickard et al. (1989)	*BMJ*	1989
0.12	13	He et al. (2004)	*Eur J Pharm Sci*	2004
0.09	15	Feigin et al. (1989)	*Neurology*	1998
0.09	14	Tomassoni et al. (2008)	*Clin Exp Hypertens*	2008
0.09	14	Blardi et al. (2002)	*Clin Pharmacol Ther*	2002
0.09	13	Horn et al. (2001a)	*Stroke*	2001

from the Web of Science. The number of relevant publications gradually increased after 2010, and peaked in 2012 (**Figure 2**). The total number of publications in the Web of Science increased over time.

Worldwide distribution
China published the highest number (77) of papers on the neuroprotective effect of nimodipine, followed by the USA (55) and Germany (44) (**Figure 3**).

Authors and institutions
Among the authors indexed by the Web of Science database during 2000–2014 that published on the neuroprotective effect of nimodipine, Tang published the most articles (10) (**Figure 3**). The 10 institutions with the greatest output of articles in this area included Shenyang Pharmaceutical University in China (20), China Pharmaceutical University (12), the Universities of Duesseldorf (10) and Munich (6) in Germany, and in India, the Postgraduate Institute of Medical Education and Research (8), Andhra University (7), and the All India Institute of Medical Science (6) (**Figure 4**).

Funding
The National Natural Science Foundation of China and the National Key Basic Research and Development Program (973

Program) of China sponsored 18 of the articles retrieved in our search. The National Commission on Science and Technology Development in Brazil sponsored 6 publications. The Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (the Brazilian Federal Agency for the Support and Evaluation of Graduate Education) sponsored four publications, and the Oak Ridge Institute for Science and Education, NIH Project, Kyung Hee University, German Federal Ministry of Education and Research and Bayer Vital GmbH Leverkusen each provided funding for two studies (**Figure 5**).

Disciplines and journals

The majority of articles on the neuroprotective effects of nimodipine indexed by the Web of Science database during 2000–2014 were in the field of neuroscience (169), followed by pharmacology (133), surgery (52), chemistry (48), and other fields (30). Neuroscience journals included *Neurosurgery*, *Stroke*, *Brain Research*, and *American Journal of Neuroradiology*; pharmacology journals included *International Journal of Pharmaceutics*, *Drug Development and Industrial Pharmacy*, *Acta Pharmacologica Sinica,* and *Pharmacological Research* (**Table 1**).

Citations

The ten most cited publications on the neuroprotective effect of nimodipine indexed by the Web of Science database during 2000–2014 are shown in **Table 1**.

Visualization analysis of publications on the neuroprotective effect of nimodipine indexed in the Web of Science database between 2000 and 2014

Visualized networks for co-cited burst terms in articles on the neuroprotective effect of nimodipine that were indexed in the Web of Science database during 2000–2014 were created using Citespace III software and based on the following parameters: time slicing = 1; time zone = 5 years (2000–2014, inclusive); threshold value = (2, 2, 20), (4, 3, 20), (4, 3, 20); node type = "burst terms". Data retrieved were processed in 15 different periods, and 50 documents with high citation frequency were selected in each time zone. The networks were streamlined with the Pathfinder network scaling method, and the co-citation-burst term visualization analysis network was mapped (**Figure 6**), revealing 617 nodes and 2,325 lines. The highly cited publications with a centrality of more than 0.09 are shown in **Table 2**.

The research fronts in a field or domain are reflected by positive citations of publications and represent the thinking status of a research field. The most cited publications are located in the center of the diagram and represent the core achievements in this research field. The contribution of the publications in study progression is embodied by burst terms. Based on co-citation networks, top-cited publications were further analyzed and twelve publications were included; each had a new finding and induced a new trend of the study, guiding a new orientation. Horn et al. (2001a) published an article in Stroke in 2001 and ranked fifth in the number of total citations (99 citations), and had high centrality. The article primarily examined the effect of ni-

modipine pharmacokinetics on plasma adenosine levels in 12 cerebral ischemic patients (nine males and three females), with a mean age of 68.88 ± 11.2 years and mean body weight of 67.9 ± 9.3 kg. Intravenous nimodipine (0.03 mg/kg) and oral nimodipine (30, 60, 90 mg) were used. Blood samples were collected at fixed times after nimodipine intervention, at intervals of 480 minutes. Plasma levels were determined with high performance liquid chromatography. The results showed that an injection of nimodipine induces an increase in plasma adenosine levels, which may be associated with drug activity.

A co-citation cluster is a network formed by co-cited publications and is used to investigate research fronts. The visualization analysis results showed that co-citation cluster of publications on neuroprotective effects of nimodipine is an approximately round network map. Each cluster in the periphery is relatively independent. The modularity Q was 0.7977 and the silhouette was 0.7943, suggesting that co-cited publications form an obvious and relatively independent cluster network. The data also indicate that the label of each cluster is relatively accurate and provides reliable evidence for data analysis.

Based on the included co-cited publications in this study, 45 co-citation clusters formed and were numbered 0–44, in ascending order of the number of publications in each cluster. According to the label in the co-citation cluster and analysis of the top-cited publications, the research front in nimodipine neuroprotection is the study of its use after subarachnoid hemorrhage using randomized controlled clinical trials.

Visualized networks for co-cited burst terms were created using the pathfinder method based on the following parameters: key word = node of network; node type = noun phrases; time zone = 1 year; thresholds = (2, 2, 20), (4, 3, 20), (4, 3, 20) (**Figure 7**). To further understand the hotspot in each period of time, a time zone view was used, taking key words as the label and helping us to understand the development of a field or an issue. According to the citation frequency and centricity, a hotspot in each period of time was selected. This revealed that nimodipine pharmacology and therapeutics, as well as blood-brain barrier and antiangiospasm, to be the areas of interest in the field of nimodipine neuroprotection between 2000 and 2014 (**Figure 8**).

Conclusion

A total of 425 articles on nimodipine neuroprotection were indexed in the Web of Science database between 2000 and 2014. The number of Web of Science publications in this field was highest in 2012 and the total number of publications increased with over time. Most publications (10) were authored by Tang. China ranked highest in the countries with most publications, followed by the USA and Germany. Among the institutes, Shenyang Pharmaceutical University and China Pharmaceutical University produced most articles, with the Universities of Duesseldorf and Munich also producing a large number of articles. The National Natural Science Foundation of China and the National Key Basic Re-

search and Development Program (973 Program) of China sponsored 18 relevant articles. The National Commission on Science and Technology Development in Brazil sponsored six publications. Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior sponsored four publications, whereas grants from the Oak Ridge Institute for Science and Education, NIH Project, Kyung Hee University, German Federal Ministry of Education and Research, and Bayer Vital GmbH Leverkusen supported two articles each. Relevant publications were mainly in the field of neuroscience (169), followed by pharmacology (133), surgery (52), and chemistry (48). Neuroscience-related journals included *Neurosurgery, Stroke, Brain Research, American Journal of Neuroradiology*; pharmacology-related journals included *International Journal of Pharmaceutic*s, *Drug Development and Industrial Pharmacy, Acta Pharmacologica Sinica,* and *Pharmacological Research.*

Visualized networks for co-cited burst terms in the field of nimodipine neuroprotection were created using the information visualization tool CiteSpace III and publications with significant influence were acquired. The co-citation cluster of publications on the neuroprotective effects of nimodipine is an approximately round network map, with 45 co-citation clusters. According to these co-citation clusters, the research front of nimodipine neuroprotection is the use of randomized controlled trials to study nimodipine intervention of subarachnoid hemorrhage. Using time zone view analysis on hot spots labeled with a key word, the areas of interest in the field of nimodipine neuroprotection are nimodipine pharmacology and therapeutics, blood-brain barrier, trials, and anti-angiospasm. Our findings indicate that, increasing evidence has emphasized on the neuroprotection of nimodipine, which is mainly applied in the treatment of subarachnoid hemorrhage and at the same time, pharmacology is another hot spot.

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