Original Article

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Quick Response Code:

Website: http://www.braincirculation.org

DOI: 10.4103/bc.bc_111_23

Investigation of neuroprotective effects of H_2 by CiteSpace-based bibliometric analysis

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Submission: 26-11-2023
Revised: 09-04-2024
Accepted: 10-04-2024
Published: 26-09-2024

Abstract:

BACKGROUND AND AIMS: Neuroprotection plays an important role in the treatment of brain disorders. In recent years, studies using rat models and clinical trials have demonstrated the positive effects of hydrogen treatment on neurological disorders and brain injuries. Hence, it is of great significance to shed light on this issue. In this article, CiteSpace is employed for visualization and bibliometric analysis of the research frontiers and evolving trends related to the neuroprotective effect of hydrogen.

METHODS: All articles published from 2009 to 2023 that discussed the neuroprotective effects of hydrogen in cerebrovascular diseases were retrieved from the Web of Science. Using CiteSpace, a visualization analysis was conducted on aspects such as countries, institutions, authors, keywords, and Co cited references, which enables an intuitive observation of current research hotspots.

RESULTS: After manual screening, a total of 106 articles were retrieved. Over time, The number of publications has increased annually. Regarding national contributions, the top three countries with the highest number of publications include China, the United States, and Japan. The Second Military Medical University is the institution that publishes the most articles and has significant influence in the field of hydrogen neuroprotection. Sun, Xuejun and Domoki, Ferenc were the most productive. The most common keywords include hydrogen, oxidative stress, inflammation, and apoptosis. Potential areas of focus for future research consist of early brain injury, hydrogen, ischemia-reperfusion injury and hypothermia treatment.

CONCLUSION: The bibliometric study presented herein offers insights into the current status and trends of research on hydrogen in the field of cerebrovascular diseases. Future research trends suggest that hydrogen contributes significantly to the cerebrovascular domain through its anti-inflammatory, antioxidative, and anti-apoptotic mechanisms. This study can aid researchers in identifying hot topics and exploring new research directions.

Keywords:

Apoptosis, CiteSpace, hydrogen, hypothermia treatment, inflammation, neuroprotection, neurological diseases, oxidative stress;

Introduction

In recent years, neuroprotective therapy has played an important role in the treatment of ischemic stroke, Alzheimer's disease, Parkinson's disease, subarachnoid hemorrhage, neonatal hypoxic–ischemic encephalopathy, traumatic brain injury, and other neurological diseases.[1-3] Currently, neuroprotective methods mainly include chemical methods, including agents such as edaravone,[4] citicoline,[5] N-butylphthalide,[6] magnesium[7] alongside physical methods like hydrogen gas,[8]

How to cite this article: Feng Y, Wu C, Song B, Zhang Y, Jiang M, Qi Z, *et al*. Investigation of neuroprotective effects of H_2 by CiteSpace-based bibliometric analysis. Brain Circ 2024;10:229-39.

therapeutic hypothermia,[9] and remote ischemic conditioning.[10] Despite years of research dedicated to brain protection, the efficacy of neuroprotective chemical therapies has demonstrated positive results in animal experiments, but not in clinical experiments.[11] The discrepancy underscores the need for novel adjuvant treatment strategies to improve the prognosis of neurological diseases. Notably, the exploration of medical gases is gaining increasing attention in the realm of neuroprotection.[12,13] In particular, hydrogen molecules have become a research hotspot in recent years. Although Li *et al*. conducted a research trend analysis in the field of molecular hydrogen, they mainly focused on its medical applications. In this study, we will shift our attention from clinical needs in cerebrovascular disease to a more specific focus on the field of neuroprotection.[14]

The neuroprotective effects of hydrogen in brain diseases have been reported through anti-inflammatory, antioxidant, and anti-apoptotic pathways.[15] Hydrogen therapy exhibits an anti-inflammatory effect through reducing the number of microglia and astrocytes within damaged brain tissue or by inhibiting the activation of microglia.[16] Hydrogen gas has demonstrated the ability to increase the number of surviving neurons, reduce apoptosis, and inhibit the activities of caspase-3 and caspase-12 to play an anti-apoptotic role.[17] Its antioxidant properties are mainly from the reduction of cytotoxic oxygen-free radicals.[8] In 2007, Ohsawa *et al*. suggested that, in a rat model of acute ischemia/reperfusion injury, inhalation of 2% hydrogen can reduce the oxidative damage induced by cytotoxic oxidative stress and significantly reduce the size of cerebral infarction.[8] This research has aroused widespread concern in the medical community regarding the therapeutical potential of hydrogen. Subsequently, the neuroprotective effects of hydrogen have been confirmed in multiple animal and clinical trials. For example, in an AD rat model, the injection of hydrogen-rich saline in the Aβ side ventricle improved the rat's spatial learning and memory by reducing oxidative stress and neuroinflammatory damage.[18] In subsequent animal studies, hydrogen treatment was found to have beneficial effects on anti-inflammatory, antioxidant, and anti-apoptosis in neonatal hypoxic–ischemic encephalopathy rat models,[17] craniocerebral trauma,[19] delayed encephalopathy caused by carbon monoxide poisoning,[20] and other animal research approaches.

The neuroprotective effects of molecular hydrogen have been successfully translated into clinical practice. Hydrogen gas therapy, as a novel and safe treatment method, holds promising clinical applications in acute cerebral infarction. Hydrogen-saturated saline combined with edaravone has been proven to be beneficial in the treatment of brain stem infarction. It could significantly improve the magnetic resonance imaging indexes of natural disease course in the acute phase of brain stem infarction compared to edaravone alone, suggesting the positive impact of hydrogen therapy on patients with cerebral ischemia.[21] In an open, prospective, nonrandomized study, patients diagnosed with acute ischemic stroke (AIS) were given edaravone in combination with an intravenous solution rich in H_2 immediately. The results demonstrated that the use of H_2-rich intravenous solution in the treatment of acute cerebral infarction patients is a safe practice.[22] Another clinical study investigated the safety and neuroprotective effects of inhaled hydrogen in the treatment of acute cerebral infarction and concluded that inhaled H_2 is both safe and effective for patients.[23] The abovementioned animal experiments and clinical trials indicate that hydrogen intake, whether through inhalation or through intravenous or intraperitoneal injection of hydrogen saline, has neuroprotective effects on neurologic disorders and can improve its prognosis. Consequently, H_2 holds the potential to revolutionize the treatment of cerebrovascular diseases. Therefore, the research hotspot and development trend of H_2 are worthy of discussion.

CiteSpace is a software for data analysis and visualization, which is mainly used to explore cutting-edge areas and trends in specific topics. Therefore, CiteSpace technology is employed in this work to analyze the current research status of hydrogen and brain diseases, aiming to elucidate the future development trends in H_2 neuroprotection.

Materials and Methods

Data collection

The data of this study were sourced from Web of Science Core Collection from 2009 to 2023, the search formula was TS = (H_2 OR hydrogen) AND (neuroprotection OR neuroprotective), the type of literature searched was set as articles or reviews, the language was set as English, and the published time is limited between January 2009 and September 2023 and download in the same day (September 29, 2023). A total of 2,479 articles were searched. Next, manually exclude articles that contain only the subject terms "TS = (H2 OR hydrogen)" or "TS = (neuroprotection OR neuroprotective)" alone, or that are not related to the topic of the article (e.g. hydrogen sulfide and hydrogen peroxide) or repeated content. In total, 106 original English articles (including 80 articles and 26 reviews) were screened. This process resulted in 106 remaining articles.

Data analysis

The processed data were imported into CiteSpace software. In this process, the relevant parameters are set as follows: the time period was set from January 2009 to

September 2023, with the years per slice of 1, selection criteria g-index K was 25, and the node type was selected from the country, institution, author, keywords, and reference. Nodes represent the research objects being analyzed. The size of a node corresponds to its frequency of occurrence; the higher the frequency, the larger the node. Links between nodes indicate collaboration, with wider links signifying stronger collaboration. A higher betweenness centrality is indicated by the purple outer circle around nodes. Centrality reflects the role of nodes in the knowledge network, with nodes having a centrality >0.1 generally regarded as pivotal points with critical roles in the field. CiteSpace provides two metrics, modularity (Q value) and mean silhouette value (S value), based on network structure and clustering clarity in order to assess the effectiveness of the map visualization; in general, Q >0.3 indicates the cluster are significant, S > 0.5 is reasonable, and S > 0.7 indicates high consistency and high confidence. The results are visualized as network analysis diagrams, and the key nodes and features in different analysis diagrams are explained and analyzed. Consequently, these insights aid in understanding the structural and dynamic development of academic research.

Clinical trial registry

Not applicable.

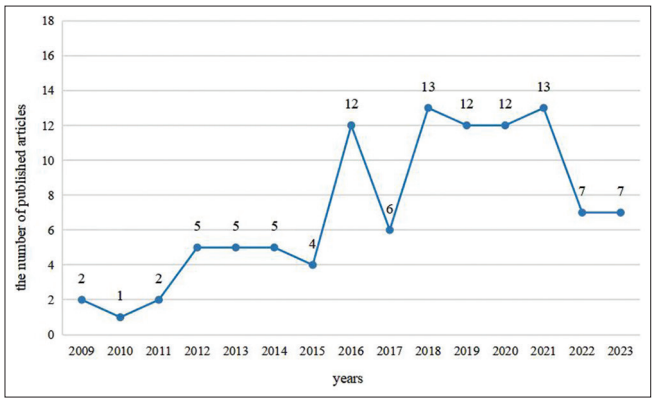


Figure 1: Annual number of published articles from 2009 to 2023

Results

Annual publication trends

In this study, the data of 106 included articles were analyzed from 2009 to 2023, and the annual number of documents issued is an important parameter for evaluating the development of scientific research, which reflects the future research trend in this field to a certain extent. As shown in Figure 1, the annual document volume showed a fluctuating upward trend. The number of publications during 2009–2012 showed an increasing trend, followed by a period of stability from 2012 to 2015. In 2016, a notable inflection point emerged, marked by a substantial increase in the annual publication count. The peak occurred in 2018 and 2021, both with 13 publications. These trends underscore that hydrogen neuroprotection is a hot topic in recent years. Although the number of articles in 2023 is not fully included, it is estimated that the final data in 2023 will show a significant upward trend compared to previous years.

Co-countries/regions and co-institution analysis

A 1-year period was selected for analysis from studies published between 2009 and 2023. Table 1 shows the co-countries/regions that are active in the hydrogen neuroprotection study. Node n = 15, link E = 11. The top three countries with the largest publications are China (68 publications, 54.40%), the United States (23 publications, 18.40%), and Japan (15 publications, 12.00%). The rest ones are Hungary, South Korea, Sweden, Finland, Slovakia, Italy, and New Zealand. We used CiteSpace to visualize these countries, and in Figure 2a, the limited number of nodes suggests minimal international cooperation. However, the United States stands out with the highest centrality of 0.37, signifying its pivotal role in mediating international cooperation within the field of hydrogen neuroprotective therapy over the past 15 years.

According to the classification statistics of the issuing institution, the cooperation map of the issuing institution is obtained, as shown in Figure 2b. Circles represent institutions, and the size of circles represents the number of articles published by institutions, whereas

Table 1: Top 10 countries and institutions in the field

Rank	Country/region	Count, *n* (%)	Centrality	Institution	Count, *n* (%)	Centrality
1	China	68 (54.40)	0	Second Military Medical University	13 (5.88)	0.06
2	USA	23 (18.40)	0.37	Loma Linda University	12 (5.43)	0.02
3	Japan	15 (12.00)	0.13	University Szeged	7 (3.17)	0
4	Hungary	7 (5.60)	0	Kyushu University	5 (2.26)	0
5	South Korea	2 (1.60)	0	Zhejiang University	4 (1.81)	0
6	Sweden	1 (0.80)	0	Tianjin Medical University General Hospital	4 (1.81)	0
7	Finland	1 (0.80)	0	Tianjin Medical University	4 (1.81)	0
8	Slovakia	1 (0.80)	0	Nippon Medical School	3 (1.36)	0
9	Italy	1 (0.80)	0	Shanghai Jiao Tong University	3 (1.36)	0.01
10	New Zealand	1 (0.80)	0	Kagawa University	3 (1.36)	0

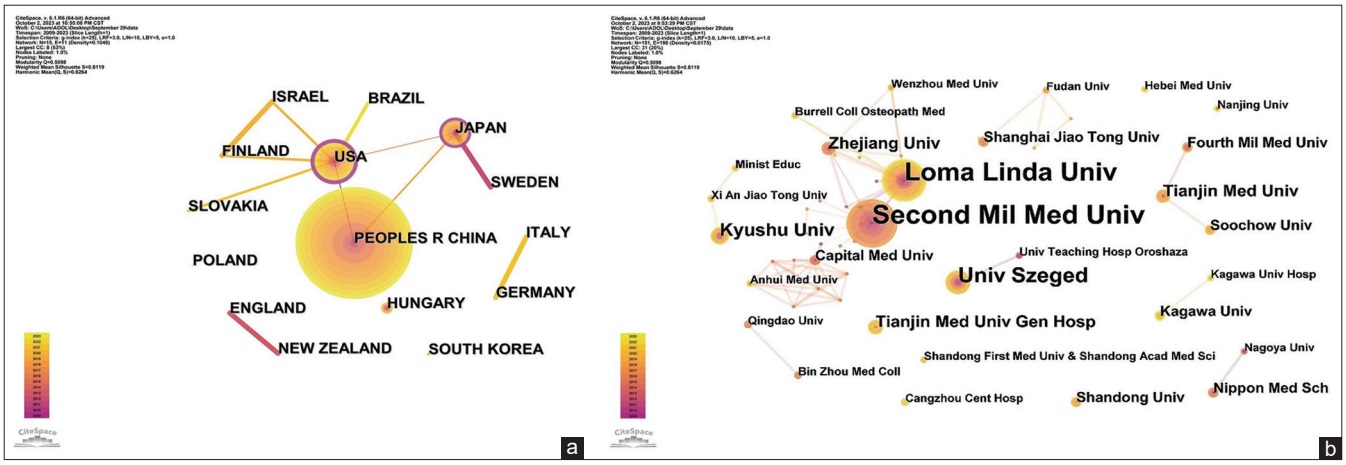


Figure 2: Countries/regions clustering analysis (a), and institution's clustering analysis (b)

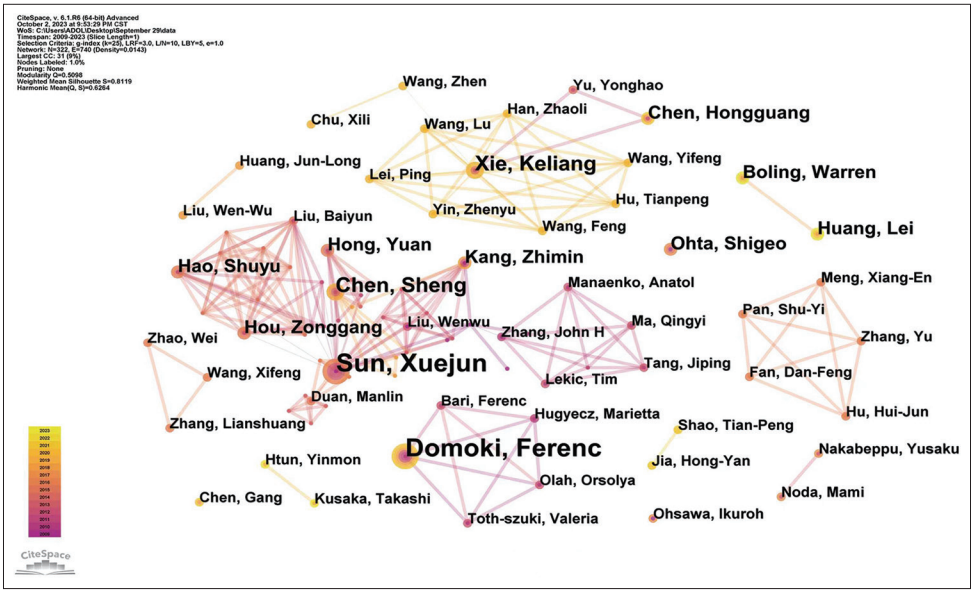


Figure 3: The network of co-authors

Table 2: Top 10 authors and co-cited authors with the highest publications and citations

Rank	Author	Count, *n* (%)	Co-author	Citation	Centrality
1	Sun, Xuejun	6 (1.52)	Ohsawa I	97	0.07
2	Domoki, Ferenc	6 (1.52)	Cai Jm	46	0.33
3	Xie, Keliang	4 (1.02)	Hayashida K	33	0.2
4	Chen, Sheng	4 (1.02)	Ohta S	31	0.05
5	Boling, Warren	3 (0.76)	Ono H	22	0.02
6	Chen, Hongguang	3 (0.76)	Fu Y	20	0.15
7	Ohta, Shigeo	3 (0.76)	Ji Xt	19	0.06
8	Kang, Zhimin	3 (0.76)	Li J	19	0.05
9	Hao, Shuyu	3 (0.76)	Nagatani K	18	0.1
10	Hou, Zonggang	3 (0.76)	Chen Ch	17	0.05

the thickness of lines reflects the intensity of cooperation between institutions. Closer distance between the two circles signifies a stronger academic partnership between the two institutions. The purple circles located outside the main circles represent intermediate centrality. The nodes with high intermediary centrality have great influence in the institutional cooperation network. In Table 1, the leading three institutions by the number of published articles are Second Military Medical University (13 publications, 5.88%), Loma Linda University (12 publications, 5.43%), and University Szeged (7 publications, 3.17%). Among these, Second Military Medical University has the highest number of publications and also the highest centrality of 0.06 among the top 10 institutions, indicating that it holds strong connections to other institutions and has a large impact in this research field, playing a key role.

Authors' and co-cited authors' analysis

The author cooperation analysis diagram is generated and displayed in Figure 3. In general, the connections among the authors in the map are relatively dense, indicating

that there is greater cooperation among the authors in this research field. The size of each circle is proportional to the number of articles published by the author. Lines between the two circles indicate collaborative efforts between these two authors to issue documents, the thickness of the line is positively correlated with the number of cooperation documents issued, and the color of the line corresponds to the year, indicating the time

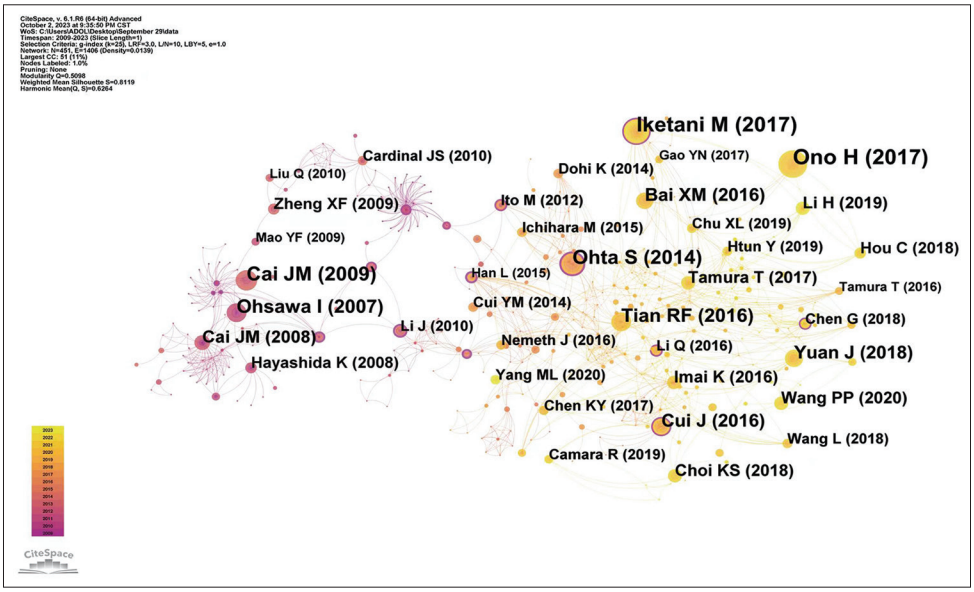


Figure 4: The network of co-cited reference

Table 3: The top 10 co-cited reference

Rank	Title	Author	Source	Impact factor	Year	Citation	Centrality	DOI
1	Hydrogen Gas inhalation treatment in acute cerebral Infarction: A randomized controlled clinical study on safety and neuroprotection	Hirohisa Ono *et al*.[23]	J Stroke Cerebrovasc	2.5	2017	14	0.01	10.1016/j.jstrokecerebrovasdis.2017.06.012
2	Molecular hydrogen as a neuroprotective agent	Masumi Iketani *et al*.[24]	Curr Neuropharmacol	5.3	2017	13	0.12	10.2174/1570159X14666160607205417
3	Neuroprotective effects of hydrogen saline in neonatal hypoxia–ischemia rat model	Jianmei Cai *et al*.[25]	Brain Res	2.9	2009	11	0.01	10.1016/j.brainres.2008.11.048
4	Molecular hydrogen as a preventive and therapeutic medical gas: initiation, development and potential of hydrogen medicine	Shigeo Ohta[26]	Pharmacol Therapeut	13.5	2014	11	0.2	10.1016/j.pharmthera.2014.04.006
5	Hydrogen-rich water attenuates brain damage and inflammation after traumatic brain injury in rats	Runfa Tian *et al*.[27]	Brain Res	2.9	2016	10	0.06	10.1016/j.brainres.2016.01.029
6	Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals	Ikuroh Ohsawa *et al*.[8]	Nat Med	82.9	2007	10	0.07	10.1038/nm1577
7	Inhalation of water electrolysis-derived hydrogen ameliorates cerebral ischemia-reperfusion injury in rats - A possible new hydrogen resource for clinical use	Cui Jin *et al*.[28]	Neuroscience	3.3	2016	9	0.17	10.1016/j.neuroscience.2016.08.021
8	Hydrogen-rich water attenuates oxidative stress in rats with traumatic brain injury via Nrf2 pathway	Jia Yuan *et al*.[29]	J Surg Res	2.2	2018	9	0.04	10.1016/j.jss.2018.03.024
9	Hydrogen-rich saline mediates neuroprotection through the regulation of endoplasmic reticulum stress and autophagy under hypoxia–ischemia neonatal brain injury in mice	Xuemei Bai *et al*.[30]	Brain Res	2.9	2016	9	0.03	10.1016/j.brainres.2016.06.020
10	Hydrogen therapy reduces apoptosis in neonatal hypoxia–ischemia rat model	Jianmei Cai *et al*.[17]	Neurosci Lett	2.5	2008	8	0.09	10.1016/j.neulet.2008.05.077

when the two authors first cooperate to issue documents. Purple represents studies published earlier, whereas yellow represents more recently published studies. As shown in Table 2, the most published authors in the field of hydrogen neuroprotection therapy are Sun, Xuejun (6 publications, 1.52%); Domoki, Ferenc (6 publications, 1.52%); Xie, Keliang (4 publications, 1.02%); and Chen, Sheng (4 publications, 1.02%).

Co-cited authors are defined as at least two authors who were cited simultaneously by at least one article. Ohsawa I was the most cited author (97), followed by Cai Jm (46), with the highest mediating centrality (0.33), and has a significant impact on the research field, providing an important theoretical basis for exploring future research directions.

Co-cited references' analysis

Literature co-citation is defined as two publications cited jointly within a single article. If two articles were frequently cited together by other articles, it signifies a strong correlation between them. CiteSpace software analysis was used to generate a co-citation reference analysis network, which showed n = 451 and E = 1406. As shown in Figure 4, each node represents a co-cited reference, the larger the node, the higher the frequency of citation, and the color of the line corresponds to a color scale, indicating the first co-citation time.

Table 3 lists the top 10 total citations by frequency, and the first high-frequency citation was published in Stroke 2017 by Ono H. In a randomized controlled clinical trial, patients with acute cerebral infarction who inhaled 3% hydrogen had a lighter infarct site and significantly improved prognostic function compared to controls.[23] The second co-cited article published in 2017 was written by Iketani and Ohsawa. In this review, it is proved by experiments that hydrogen has a beneficial effect in cerebrovascular diseases, neurodegenerative diseases, and neonatal encephalopathy through anti-inflammatory and antioxidant mechanisms.[24] In the experiment, a neonatal ischemic and hypoxic rat model was established, and a saturated normal saline solution (5 ml/kg) was injected intraperitoneally immediately after the ischemic and hypoxic injury. We observed that rich-saline treatment reduced the caspase activity, the malondialdehyde (MDA), Iba-1 levels, and infarct ratio and improved long-term neurological function and prognosis.[25] All of the above documents confirm the safety and neurological protective effects of hydrogen.

Co-occurring keywords, clustering, and burst analysis

In Figure 5, keywords serve as the principal feature words in the literature research hotspot, aiding in the identification of research directions and development

Table 4: Top 10 keywords in the field

Rank	Keyword	Occurrences	Centrality
1	Oxidative stress	48	0.14
2	Molecular hydrogen	36	0.33
3	Antioxidant	24	0.13
4	Inhalation	19	0.11
5	Rich saline	19	0.05
6	Brain injury	16	0.17
7	Traumatic brain injury	16	0.09
8	Apoptosis	14	0.06
9	Rat model	14	0.11
10	Damage	13	0.13

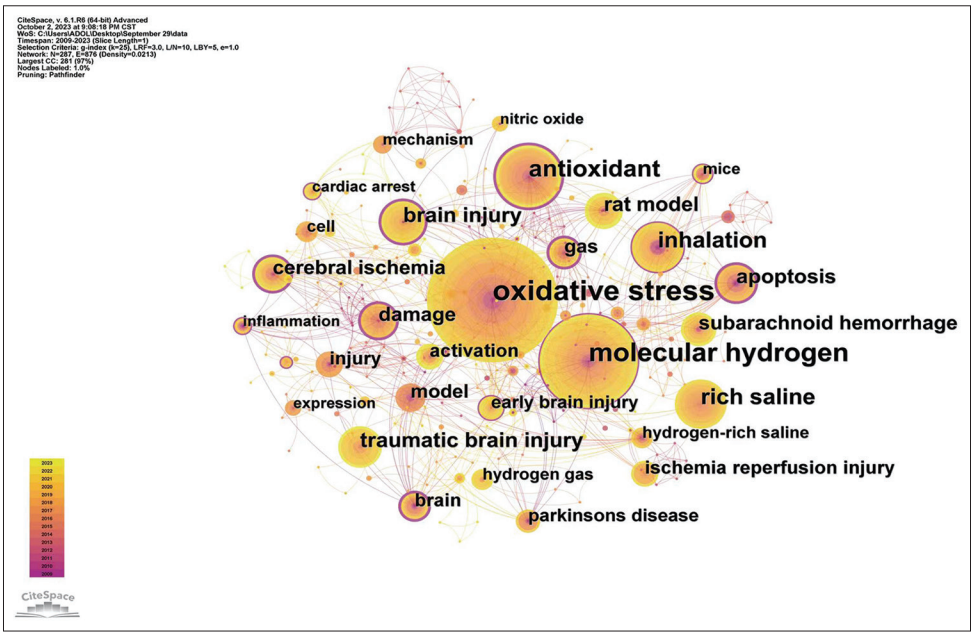


Figure 5: The network of co-occurring keywords

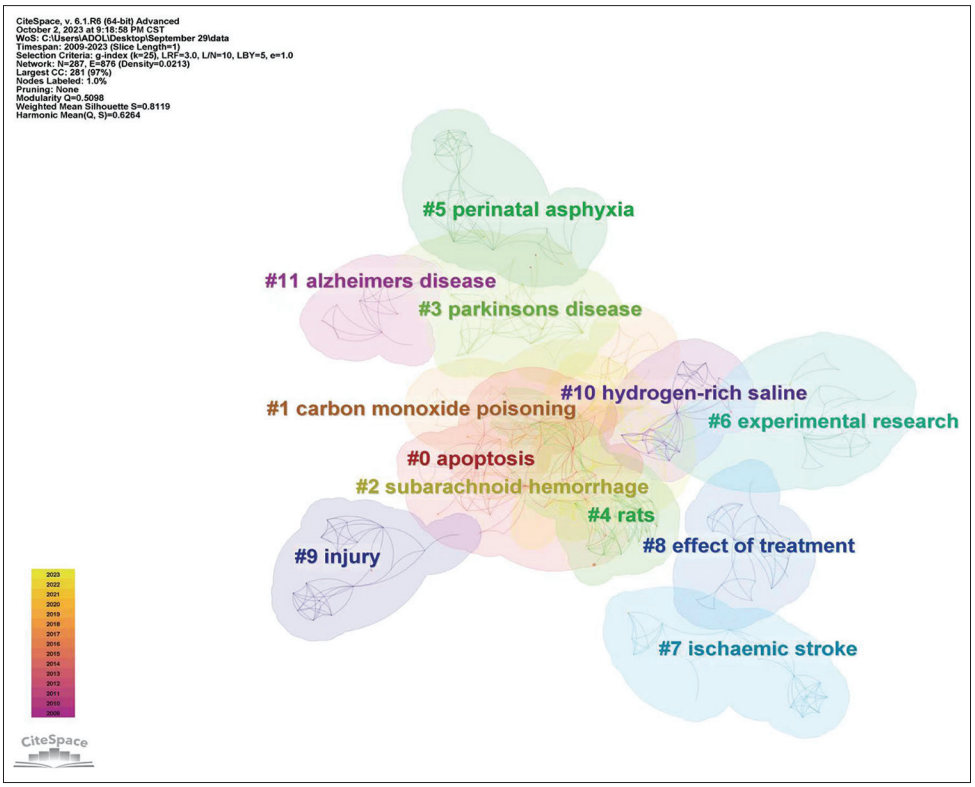


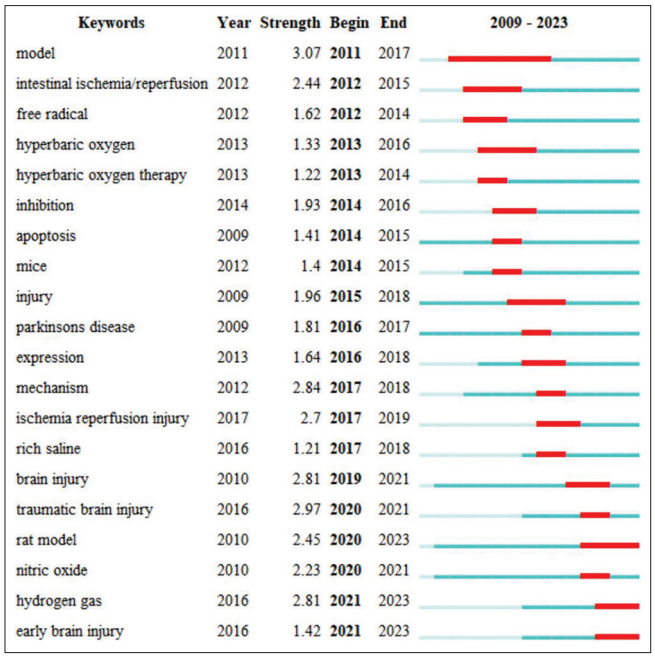
Figure 6: Keywords cluster analysis co-occurrence map

Table 5: Keyword cluster analysis

Cluster-ID	Size	Silhouette	Mean year	Coverage	Label
0	41	0.791	2016	Apoptosis; antioxidant; early brain injury; protect; asphyxia neonatorum	Apoptosis
1	32	0.9	2015	Carbon monoxide poisoning; oxidative stress; caspase; circulatory arrest; neurobehavioral function	Carbon monoxide poisoning
2	29	0.878	2012	Subarachnoid hemorrhage; Parkinson's disease; hypoxia–ischemia; neonatal hypoxia–ischemia; molecular hydrogen (H_2)	Subarachnoid hemorrhage
3	27	0.891	2014	Parkinson's disease; mitochondrial function; NF-kappa B; insulin; inflammatory	Parkinson's disease
4	24	0.903	2012	Rats; cerebral ischemia-reperfusion; water electrolysis; IL-6; firs	Rats
5	22	0.978	2016	Perinatal asphyxia; newborn brain; animal model; hippocalcin; term neuroprotection	Perinatal asphyxia
6	17	0.921	2019	Experimental research; therapeutic implications; vascular dementia; nerve regeneration; GSK-3 beta	Experimental research
7	17	0.987	2015	Ischemic stroke; mechanism; gases; carbon monoxide; diffusion tensor imaging	Ischemic stroke
8	17	0.873	2020	Effect of treatment; noble gases; therapeutic drugs; cardiac arrest; neurodegeneration	Effect of treatment
9	17	0.948	2015	Injury; pial arteriole; blood volume; outcome; brain damage	Injury
10	16	0.897	2016	Hydrogen-rich saline; retinal ischemia-reperfusion injury; poly (ADP-ribose) polymerase-1; autophagy; rostral ventrolateral medulla	Hydrogen-rich saline
11	11	0.939	2019	Alzheimer's disease; female; estrogen; cognitive function; brain disorders	Alzheimer's disease

trends within this field. Mediation centrality reflects the importance of these keyword nodes in the network, and, when combined with word frequency, reflects the hotspot of researchers' common concern and research in a period of time. As shown in Table 4, the mechanisms involved are mainly inflammation, apoptosis, and oxidative stress. Among them, molecular hydrogen, brain injury, and oxidative stress have better centrality.

The software uses LLR algorithm to cluster co-occurrence keywords and identifies each cluster to determine the research hotspots in this field. A total of 12 clusters were obtained, each of which was closely linked and cooperated in a particular domain, as shown in Figure 6. Q= 0.5098 (>0.3), S = 0.8119 (>0.7), indicating that the cluster structure is significant, the data results are credible, and have high certainty and persuasive.



Keywords	Year	Strength	Begin	End	2009 - 2023
model	2011	3.07	2011	2017	
intestinal ischemia/reperfusion	2012	2.44	2012	2015	
free radical	2012	1.62	2012	2014	
hyperbaric oxygen	2013	1.33	2013	2016	
hyperbaric oxygen therapy	2013	1.22	2013	2014	
inhibition	2014	1.93	2014	2016	
apoptosis	2009	1.41	2014	2015	
mice	2012	1.4	2014	2015	
injury	2009	1.96	2015	2018	
parkinsons disease	2009	1.81	2016	2017	
expression	2013	1.64	2016	2018	
mechanism	2012	2.84	2017	2018	
ischemia reperfusion injury	2017	2.7	2017	2019	
rich saline	2016	1.21	2017	2018	
brain injury	2010	2.81	2019	2021	
traumatic brain injury	2016	2.97	2020	2021	
rat model	2010	2.45	2020	2023	
nitric oxide	2010	2.23	2020	2021	
hydrogen gas	2016	2.81	2021	2023	
early brain injury	2016	1.42	2021	2023	

Figure 7: The top 20 keywords with the strongest citation bursts

Specific keywords included in the main clusters are shown in Table 5. The cluster label keywords were extracted: #0 Apoptosis, #1 Carbon monoxide poisoning, #2 Subarachnoid hemorrhage, #3 Parkinson's disease #4 Rats, #5 Perinatal asphyxia, #6 Experimental research, #7 Ischaemic stroke, #8 effect of treatment, #9 Injury, #10 Hydrogen-rich saline, and #11 Alzheimer's disease.

The top 20 keywords with the strongest emergent words from 2009 to 2023 are shown in Figure 7. Bursty words refer to key terms that have significantly increased the number of citations over a period and can be used to highlight research hotspots and research trends during that period. CiteSpace was executed using the "Burtterms" option to retrieve burst graph keywords. As shown, it can predict the cutting-edge development of the field based on the distribution of keywords that cite the strongest outbreak.

Hydrogen neuroprotection research focuses on 2016–2023 and pays more attention to the relationship between hydrogen and Parkinson's disease, ischemia-reperfusion injury, traumatic brain injury, and early brain injury (EBI). Hydrogen plays a neuroprotective role mainly through oxidative stress, inflammation, apoptosis, and other pathological mechanisms.

Discussion

Research progress in neuroprotective effects of H_2

This study conducted a bibliometric analysis of hydrogen's neuroprotection research from 2009 to 2023. Notably, a steady increase in the number of annual publications was observed [Figure 1]. China, the United States, and Japan are the countries with the largest number of publications. While the cooperation map reveals close-knit groups of authors and institutions, small groups work closely together, but there are fewer connections between each group. This highlights the need to strengthen the relevant research of countries, institutions, and authors within this field. According to keyword analysis, oxidative stress, inflammation, and apoptosis are the main research directions at present. EBI, hydrogen gas, and ischemia perfusion injury may become the future research hotspot.

Hot issue of neuroprotective effects of H_2

Hydrogen therapy for ischemia-perfusion injury

The ischemia-reperfusion injury is a long-term issue that is worthy of study. In the course of the disease, ischemic/reperfusion can aggravate nerve cell damage, and among them, oxidative stress is a key factor.[26] In a rat model of focal ischemia/reperfusion, results showed that inhalation of 2% H_2 mitigated OH-induced cytotoxicity without affecting other reactive oxygen species (ROS) and significantly improved oxidative stress damage induced by cerebral ischemia/reperfusion.[8] Then, Nagatani *et al*. established a model of total cerebral ischemia by bilateral common carotid artery embolization. In the treatment group, 1.3% hydrogen was inhaled, the 7-day survival rate was increased by 50% from 8.3%, and it was confirmed that hydrogen could reduce apoptosis by blocking autophagy and significantly improve nerve function.[27] Liu *et al*. found that in the rat model of middle cerebral artery occlusion, after 90 min of ischemia, reperfusion for 24 h, and intraperitoneal injection of hydrogen saline, inflammatory factors (malonaldehyde, interleukin-1β, and tumor necrosis fact-α) decreased, suggesting that hydrogen can reduce nerve damage by alleviating inflammatory response.[28] The above experiments indicated that hydrogen could improve ischemia-reperfusion injury by anti-inflammation, anti-oxidation, and anti-apoptosis.

Hydrogen therapy for early brain injury after subarachnoid hemorrhage

According to the CiteSpace analysis results, EBI began in 2016 and received wide attention in 2021–2023. Subarachnoid hemorrhage, while accounting for only 5% of strokes, presents unique challenges due to its younger patient population and high fatality rate, compounded by the current absence of effective treatment strategies.[29] EBI, a process that occurs within 72 h of Subarachnoid hemorrhage (SAH), is the main cause of poor prognosis in SAH.[30] SAH can cause increased intracranial pressure, decreased cerebral perfusion, neuronal cell death, and endothelial injury and lead to cytotoxic edema and breakdown of the blood–brain barrier.[31] A study has shown that EBI is associated with increased oxidative stress after SAH.[32] In an animal study, a rat

model of subarachnoid hemorrhage was established by intravascular perforation, and it was found that the hydrogen group significantly alleviated brain edema and blood–brain barrier disorders, reduced apoptosis, and improved nervous system function within 24 h.[33] Following a randomized controlled clinical study published by Takeuchi *et al*. in stroke, the Mg + H_2 group had significantly lower rates of cerebral vasospasm and delayed cerebral ischemia than the other groups and improved patient outcomes.[34] The abovementioned animal and clinical experiments have shown that hydrogen plays a neuroprotective role in EBI through antioxidant activity. Based on the association of early severe brain injury after hemorrhage with secondary complications and poor prognosis, more treatment strategies will be needed in the future to slow the severity of EBI to improve the prognosis after SAH.

Hydrogen combined with hypothermia treatment strategy

According to the CiteSpace analysis, the neuroprotection of therapeutic hypothermia in hydrogen is less studied, so it is not shown in the keyword map. However, therapeutic hypothermia is a powerful neuroprotective strategy, which can play a protective role in a number of ways, such as reducing brain metabolism, inhibiting apoptosis, having an anti-inflammatory effect, and maintaining the blood-brain barrier.[35] There are clinical studies showing that therapeutic hypothermia can reduce the prognosis of comatose patients after resuscitation with cardiac arrest.[36] Moreover, it can also produce a neuroprotective effect on neonatal ischemic–hypoxic encephalopathy patients.[37]

It has been found that the combination of medical gas and hypothermia yields a superimposed effect in the treatment of cerebrovascular diseases.[38] In the treatment of cerebrovascular disease, one of the most effective approaches is the endovascular thrombectomy (EVT) after AIS. However, stroke patients have a poor neurological prognosis. Therefore, novel adjuvant treatment strategies are needed to further improve the clinical outcomes in the population of AIS patients receiving EVT. This issue has aroused wide concern among researchers. Hydrogen has demonstrated the neuroprotective effect of ischemic stroke in several basic studies and clinical studies, and basic studies have confirmed that hypothermia therapy has a powerful neuroprotective effect in animal models of stroke.[35] In addition, it has been proven that regional hypothermia is safe and feasible for patients with AIS in clinical studies.[39] While the combination of low temperature and medical gas has shown promising applications in basic experiments, clinical results remain limited.[38] Recent studies have found that animal studies on the use of hydrogen and hypothermia for neonatal cerebral changes following ischemia suggest that hydrogen combined with hypothermia may improve cerebral hemodynamics and oxygenation, thus contributing to reduced brain damage.[40] In a rat model of cardiac arrest, inhalation of 1.3% H_2 combined with hypothermia inhibited neuronal degeneration and microglial activation in ischemic areas and improved neurological outcomes more effectively than hypothermia alone.[41] Based on the above animal experiments, hydrogen combined with low temperature can achieve dual protection to the body by reducing inflammation and reducing ischemia and reperfusion injury.

Although research on hydrogen combined with hypothermia in the field of ischemic stroke is still in its early stages, animal studies have shown that this treatment strategy has neuroprotective effects in cerebrovascular diseases, offering potential prospects for future clinical therapy. However, clinical studies of hypothermia have not confirmed the same effectiveness as basic studies. Currently, several clinical studies focus on systemic hypothermia, where side effects such as shivering and pneumonia can reduce its clinical effect,[42] and relatively selective cooling is considered a better therapeutic hypothermia option through rapid induction of hypothermia and reduction of systemic symptoms.[43] Moreover, despite multiple studies, the duration required for therapeutic hypothermia and the ideal temperature are ambiguous. Therefore, to further improve the neurological outcome of patients with AIS, more clinical studies are necessary on the potential neurological and functional benefits of therapeutic hypothermia in these patients.

The current challenges and future directions of hydrogen therapy

Although hydrogen therapy has demonstrated good neuroprotective effects in ischemia-reperfusion injury and cerebral hemorrhage, it has not shown the same efficacy in other diseases such as Parkinson's disease. A study involving 20 Parkinson's disease patients found that continuous inhalation of 1.2%–1.4% hydrogen gas for 4 weeks did not observe any beneficial effects of hydrogen in the short term.[44] In addition, drinking hydrogen-rich saline for 72 weeks also failed to improve the UPDRS total score of Parkinson's disease patients.[45] These negative results may be related to the concentration and duration of hydrogen gas exposure. Furthermore, although inhalation, oral ingestion, or injection of hydrogen gas can effectively alleviate neurological diseases, the concentration of hydrogen gas in tissues and organs varies significantly due to the choice of intervention in specific diseases, thus different administration routes may have different effects on the same damaged tissue. For example, in a study involving Parkinson's disease rats, drinking hydrogen-rich water was more effective than inhaling hydrogen gas.[46] Therefore, further high-quality

research is needed to determine the most effective hydrogen therapy approach for each disease.

In summary, hydrogen therapy is currently in its early exploration stage. Although some initial studies suggest its potential efficacy in the field of cerebrovascular diseases, integrating it into clinical practice and establishing standardized treatment require further investigation into optimal administration methods, indications, dosage adjustments, and long-term treatment effects. Therefore, to expand the application scope and enhance the clinical efficacy of hydrogen therapy, more support from scientific research and clinical practice is needed. Future research directions for hydrogen should focus on exploring standardized treatments and combining with other adjunctive therapies such as hypothermia to enhance neuroprotection and improve patient outcomes.

Limitation

To our knowledge, this is the first bibliometric analysis of the neuroprotection of hydrogen in the cerebrovascular field using CiteSpace. In WOS, the data obtained after manually eliminating irrelevant articles have a high correlation with the research field. However, our study does have limitations. First, bibliometrics research relies heavily on databases, and the literature data we included only came from the Web of Science. Therefore, the data may not be comprehensive. Second, there is backtracking in CiteSpace, and the analysis results will be biased. However, our findings will ultimately provide valuable information for professionals to identify problems in related fields, providing new directions for further research.

Conclusion

This study uses objective and quantitative methods to discuss the current research status of hydrogen neuroprotection in the past 15 years, aiming to provide researchers with a comprehensive and macro perspective to show the development trend in this field. The research in this field is in the stage of rapid development, and ischemia-reperfusion injury, EBI, and hydrogen combined with a hypothermia treatment strategy may become the research hotspot. However, the current understanding of the neuroprotective effects of hydrogen gas is mainly based on animal studies and preliminary clinical trials. Therefore, its treatment scope may be limited, requiring more research to explore standardized hydrogen therapy. Hydrogen therapy holds potential clinical value in treating and alleviating neurological disorders, promising to become a novel and effective treatment strategy.

Author contributions

Concepts, design, definition of intellectual content and manuscript preparation: YF, CW, BS, YZ; Literature search, data acquisition and data analysis: LC, AL, HY, BL; Manuscript editing: MJ, ZQ, YF; Manuscript review: XJ, ZM, ML.

Ethical policy and institutional review board statement

This study was approved by the Medical Ethics Committee of Affiliated Suzhou Hospital of Anhui Medical University (C2024018, dated on August 23, 2024). All the ethical issues are solved by following the ethical guidelines or principles mentioned in "Declaration of Helsinki" for medical research involving human and other animal subjects originally developed in 1975 and revised in 2000.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship

This work was supported by the National Natural Science Foundation of China (82102220, 82027802, and 61975017), Research Funding on Translational Medicine from Beijing Municipal Science and Technology Commission (Z221100007422023), Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support from Yangfan Project (YGLX202325), the Nonprofit Central Research Institute Fund of Chinese Academy of Medical (2023-JKCS-09), and Outstanding Young Talents Program of Capital Medical University (B2305).

Conflicts of interest

Dr. Xunming Ji is the Editor-in-Chief, Dr. Chuanjie Wu and Dr. Ming Li are Editorial Board members of Brain Circulation. The article was subject to the journal's standard procedures, with peer review handled independently of them and their research groups.

References

1. Ramanathan D, Huang L, Wilson T, Boling W. Molecular hydrogen therapy for neurological diseases: A review of current evidence. Med Gas Res 2023;13:94-8.
2. Wu C, Zou P, Feng S, Zhu L, Li F, Liu TC, *et al*. Molecular hydrogen: An emerging therapeutic medical gas for brain disorders. Mol Neurobiol 2023;60:1749-65.
3. Liu CL, Zhang K, Chen G. Hydrogen therapy: From mechanism to cerebral diseases. Med Gas Res 2016;6:48-54.
4. Kikuchi K, Kawahara K, Miyagi N, Uchikado H, Kuramoto T, Morimoto Y, *et al*. Edaravone: A new therapeutic approach for the treatment of acute stroke. Med Hypotheses 2010;75:583-5.
5. Salamah A, Mehrez M, Faheem A, El Amrousy D. Efficacy of citicoline as a neuroprotector in children with post cardiac arrest: A randomized controlled clinical trial. Eur J Pediatr 2021;180:1249-55.
6. Li Q, Cheng Y, Bi M, Lin H, Chen Y, Zou Y, *et al*. Effects of n-butylphthalide on the activation of keap1/Nrf-2 signal pathway in rats after carbon monoxide poisoning. Environ Toxicol

Pharmacol 2015;40:22-9.
7. Saver JL, Starkman S. Magnesium in clinical stroke. In: Vink R, Nechifor M, editors. Magnesium in the Central Nervous System. Adelaide (AU): University of Adelaide Press; 2011.
8. Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, *et al.* Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. Nat Med 2007;13:688-94.
9. Wu TC, Grotta JC. Hypothermia for acute ischaemic stroke. Lancet Neurol 2013;12:275-84.
10. Chen HS, Cui Y, Li XQ, Wang XH, Ma YT, Zhao Y, *et al.* Effect of remote ischemic conditioning versus usual care on neurologic function in patients with acute moderate ischemic stroke: The RICAMIS randomized clinical trial. JAMA 2022;328:627-36.
11. O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1,026 experimental treatments in acute stroke. Ann Neurol 2006;59:467-77.
12. Zhang ZY, Fang YJ, Luo YJ, Lenahan C, Zhang JM, Chen S. The role of medical gas in stroke: An updated review. Med Gas Res 2019;9:221-8.
13. Wang YZ, Li TT, Cao HL, Yang WC. Recent advances in the neuroprotective effects of medical gases. Med Gas Res 2019;9:80-7.
14. Li H, Ma HY, Hua WL, Zhang YX, Zhang L, Xing PF, *et al.* Trend of research on the medical use of molecular hydrogen: A bibliometric analysis. Med Gas Res 2023;13:212-8.
15. Tan X, Shen F, Dong WL, Yang Y, Chen G. The role of hydrogen in Alzheimer's disease. Med Gas Res 2018;8:176-80.
16. Li J, Dong Y, Chen H, Han H, Yu Y, Wang G, *et al.* Protective effects of hydrogen-rich saline in a rat model of permanent focal cerebral ischemia via reducing oxidative stress and inflammatory cytokines. Brain Res 2012;1486:103-11.
17. Cai J, Kang Z, Liu WW, Luo X, Qiang S, Zhang JH, *et al.* Hydrogen therapy reduces apoptosis in neonatal hypoxia-ischemia rat model. Neurosci Lett 2008;441:167-72.
18. Li J, Wang C, Zhang JH, Cai JM, Cao YP, Sun XJ. Hydrogen-rich saline improves memory function in a rat model of amyloid-beta-induced Alzheimer's disease by reduction of oxidative stress. Brain Res 2010;1328:152-61.
19. Hu Y, Feng X, Chen J, Wu Y, Shen L. Hydrogen-rich saline alleviates early brain injury through inhibition of necroptosis and neuroinflammation via the ROS/HO-1 signaling pathway after traumatic brain injury. Exp Ther Med 2022;23:126.
20. Sun Q, Cai J, Zhou J, Tao H, Zhang JH, Zhang W, *et al.* Hydrogen-rich saline reduces delayed neurologic sequelae in experimental carbon monoxide toxicity. Crit Care Med 2011;39:765-9.
21. Ono H, Nishijima Y, Adachi N, Tachibana S, Chitoku S, Mukaihara S, *et al.* Improved brain MRI indices in the acute brain stem infarct sites treated with hydroxyl radical scavengers, edaravone and hydrogen, as compared to edaravone alone. A non-controlled study. Med Gas Res 2011;1:12.
22. Nagatani K, Nawashiro H, Takeuchi S, Tomura S, Otani N, Osada H, *et al.* Safety of intravenous administration of hydrogen-enriched fluid in patients with acute cerebral ischemia: Initial clinical studies. Med Gas Res 2013;3:13.
23. Ono H, Nishijima Y, Ohta S, Sakamoto M, Kinone K, Horikosi T, *et al.* Hydrogen gas inhalation treatment in acute cerebral infarction: A randomized controlled clinical study on safety and neuroprotection. J Stroke Cerebrovasc Dis 2017;26:2587-94.
24. Iketani M, Ohsawa I. Molecular hydrogen as a neuroprotective agent. Curr Neuropharmacol 2017;15:324-31.
25. Cai J, Kang Z, Liu K, Liu W, Li R, Zhang JH, *et al.* Neuroprotective effects of hydrogen saline in neonatal hypoxia-ischemia rat model. Brain Res 2009;1256:129-37.
26. Allen CL, Bayraktutan U. Oxidative stress and its role in the pathogenesis of ischaemic stroke. Int J Stroke 2009;4:461-70.
27. Nagatani K, Wada K, Takeuchi S, Kobayashi H, Uozumi Y, Otani N, *et al.* Effect of hydrogen gas on the survival rate of mice following global cerebral ischemia. Shock 2012;37:645-52.
28. Liu Y, Liu W, Sun X, Li R, Sun Q, Cai J, *et al.* Hydrogen saline offers neuroprotection by reducing oxidative stress in a focal cerebral ischemia-reperfusion rat model. Med Gas Res 2011;1:15.
29. Bederson JB, Connolly ES Jr., Batjer HH, Dacey RG, Dion JE, Diringer MN, *et al.* Guidelines for the management of aneurysmal subarachnoid hemorrhage: A statement for healthcare professionals from a special writing group of the stroke council, American Heart Association. Stroke 2009;40:994-1025.
30. Broderick JP, Brott TG, Duldner JE, Tomsick T, Leach A. Initial and recurrent bleeding are the major causes of death following subarachnoid hemorrhage. Stroke 1994;25:1342-7.
31. de Oliveira Manoel AL, Goffi A, Marotta TR, Schweizer TA, Abrahamson S, Macdonald RL. The critical care management of poor-grade subarachnoid haemorrhage. Crit Care 2016;20:21.
32. Ayer RE, Zhang JH. Oxidative stress in subarachnoid haemorrhage: Significance in acute brain injury and vasospasm. Acta Neurochir Suppl 2008;104:33-41.
33. Zhan Y, Chen C, Suzuki H, Hu Q, Zhi X, Zhang JH. Hydrogen gas ameliorates oxidative stress in early brain injury after subarachnoid hemorrhage in rats. Crit Care Med 2012;40:1291-6.
34. Takeuchi S, Kumagai K, Toyooka T, Otani N, Wada K, Mori K. Intravenous hydrogen therapy with intracisternal magnesium sulfate infusion in severe aneurysmal subarachnoid hemorrhage. Stroke 2021;52:20-7.
35. Yenari MA, Han HS. Neuroprotective mechanisms of hypothermia in brain ischaemia. Nat Rev Neurosci 2012;13:267-78.
36. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, *et al.* Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557-63.
37. Yildiz EP, Ekici B, Tatlı B. Neonatal hypoxic ischemic encephalopathy: An update on disease pathogenesis and treatment. Expert Rev Neurother 2017;17:449-59.
38. Li H, Tan X, Xue Q, Zhu JH, Chen G. Combined application of hypothermia and medical gases in cerebrovascular diseases. Med Gas Res 2018;8:172-5.
39. Wu C, Zhao W, An H, Wu L, Chen J, Hussain M, *et al.* Safety, feasibility, and potential efficacy of intraarterial selective cooling infusion for stroke patients treated with mechanical thrombectomy. J Cereb Blood Flow Metab 2018;38:2251-60.
40. Nakamura S, Nakao Y, Htun Y, Mitsuie T, Koyano K, Morimoto A, *et al.* Impact of hydrogen gas inhalation during therapeutic hypothermia on cerebral hemodynamics and oxygenation in the asphyxiated piglet. Sci Rep 2023;13:1615.
41. Hayashida K, Sano M, Kamimura N, Yokota T, Suzuki M, Ohta S, *et al.* Hydrogen inhalation during normoxic resuscitation improves neurological outcome in a rat model of cardiac arrest independently of targeted temperature management. Circulation 2014;130:2173-80.
42. Li F, Gao J, Kohls W, Geng X, Ding Y. Perspectives on benefit of early and prereperfusion hypothermia by pharmacological approach in stroke. Brain Circ 2022;8:69-75.
43. Huber C, Huber M, Ding Y. Evidence and opportunities of hypothermia in acute ischemic stroke: Clinical trials of systemic versus selective hypothermia. Brain Circ 2019;5:195-202.
44. Hirayama M, Ito M, Minato T, Yoritaka A, LeBaron TW, Ohno K. Inhalation of hydrogen gas elevates urinary 8-hydroxy-2'-deoxyguanine in Parkinson's disease. Med Gas Res 2018;8:144-9.
45. Yoritaka A, Ohtsuka C, Maeda T, Hirayama M, Abe T, Watanabe H, *et al.* Randomized, double-blind, multicenter trial of hydrogen water for Parkinson's disease. Mov Disord 2018;33:1505-7.
46. Ito M, Hirayama M, Yamai K, Goto S, Ito M, Ichihara M, *et al.* Drinking hydrogen water and intermittent hydrogen gas exposure, but not lactulose or continuous hydrogen gas exposure, prevent 6-hydorxydopamine-induced Parkinson's disease in rats. Med Gas Res 2012;2:15.