Trend of research on the medical use of molecular hydrogen: a bibliometric analysis

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Abstract

The medical use of molecular hydrogen, including hydrogen-rich water and hydrogen gas, has been extensively explored since 2007. This article aimed to demonstrate the trend in medical research on molecular hydrogen. A total of 1126 publications on hydrogen therapy were retrieved from the PubMed database until July 30, 2021. From 2007 to 2020, the number of publications in this field had been on an upward trend. *Medical Gas Research*, *Scientific Report* and *Shock* have contributed the largest number of publications on this topic. Researchers by the name of Xue-Jun Sun, Ke-Liang Xie and Yong-Hao Yu published the most studies in the field. Analysis of the co-occurrence of key words indicated that the key words "molecular hydrogen," "hydrogen-rich water," "oxidative stress," "hydrogen gas," and "inflammation" occurred most frequently in these articles. "Gut microbiota," "pyroptosis," and "COVID-19" occurred the most recently among the key-words. In summary, the therapeutic application of molecular hydrogen had attracted much attention in these years. The advance in this field could be caught up by subscribing to relevant journals or following experienced scholars. Oxidative stress and inflammation were the most important research directions currently, and gut microbiota, pyroptosis, and coronavirus disease 2019 might become hotspots in the future.

Key words: molecular hydrogen; bibliometric analysis; oxidative stress; inflammation; gut microbiota; pyroptosis; COVID-19; autophagy

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Introduction

Molecular hydrogen, or hydrogen gas, is the simplest molecule in the world with the smallest molecular weight, which is transparent, odorless, tasteless and non-toxic. The medical safety of hydrogen inhalation has been proven in terms of diving medicine in the last century, but hydrogen was always considered to have no significant biomedical effect.[1,2] In 2007, Shigeo Ohta, a Japanese researcher, identified the selective anti-oxidative effect of hydrogen, which launched the upsurge of medical research into molecular hydrogen.[3]

With the progression of this research field, many other mechanisms of molecular hydrogen in addition to anti-oxidation have been identified, including anti-inflammation, anti-apoptosis, and multiple cellular pathways adjustment.[4] Molecular hydrogen was also used to treat various diseases or pathological changes, such as ischemia-reperfusion injury, sepsis, liver injury, kidney injury, lung injury, and brain injury.[5-9] On the basis of these studies, numerous relevant products emerged, for instance, medical hydrogen gas generator, hydrogen-rich water, and hydrogen-rich saline, and several clinical investigations were conducted. The safety and efficacy of molecular hydrogen have been demonstrated in several clinical trials focusing on cerebral ischemia, kidney failure, acute lung injury, and lung cancer.[10-13] Researchers are currently making efforts to expand the clinical application scope of molecular hydrogen by translating the results of basic medical research into clinical practice.

Thus, it is necessary to systematically summarize the existing knowledge and find future research orientations on molecular hydrogen. Bibliometric analysis is a way to comprehensively review the development trend of a research field.[14] In this study, a bibliometric analysis was conducted using published data on the medical use of molecular hydrogen extracted from the PubMed database. The trend of the publication, the contribution of the authors or journals, as well as current and future research hotspots were demonstrated and discussed.

Data and Methods

Data sources and search strategy

PubMed is a free database for medical research publications mainly based on Medline, one of the most authoritative medical literature databases. The major strength of the PubMed database is that it mainly included medical research rather than any other scientific field. An exhaustive literature search basing on PubMed was carried out until July 30, 2021. The search strategies were presented as follows: ("molecular hydrogen"[tiab] OR "hydrogen-rich saline"[tiab] OR "hydrogen-rich fluid"[tiab] OR "hydrogen gas inhalation"[tiab] OR "hydrogen-rich water"[tiab] OR "hydrogen inhalation"[tiab] OR "hydrogen gas"[tiab] OR "hydrogen therapy"[tiab] OR "hydrogen/oxygen mixed" [tiab] OR "hydrogen/oxygen therapy"[tiab]) AND ("treatment"[tiab] OR "therapy"[tiab] OR "therapeutic"[tiab] OR "disease"[tiab] OR "injury"[tiab] OR "injuries"[tiab] OR "impairment"[tiab] OR "dysfunction"[tiab] OR "disfunction"[tiab] OR "clinical"[tiab] OR "medical"[tiab] OR "medicine"[tiab]). Doctor YXZ and HYM were responsible for literature retrieval.

Data extraction

Data were extracted from all included publications, and the

elements included titles, keywords, publication dates, authors, and resource journals. The data were subsequently analyzed by Microsoft Excel (Microsoft, Seattle, WA, USA), Graphpad Prism 9.0 (GraphPad Software, LLC, San Diego, CA, USA), and VOSviewer 1.6.[16] (Centre for Science and Technology Studies, Leiden University, the Netherlands).

Bibliometric analysis

The publication dates were extracted to analyze the publication trend from 2007 to 2021. The data of authors' names were input into VOSViewer to generate the cooperation network, which demonstrated the numbers of relevant publications published by each author and their cooperation status. Journal name and publication data were also inputted into VOSViewer to show which journal published the most relevant studies. The co-occurrence of each article's keywords was also analyzed by VOSViewer, and a co-occurrence network was generated. Keywords that occurred more than three times in all the articles were included in the network, and the occurrence time and the average occurrence year (AOY) of each keyword were listed.

Results

Growth trends of publications related to molecular hydrogen

Until July 30, 2021, there were 1123 publications related to the medical use of molecular hydrogen (**Figure 1A**). The articles published prior to 2007 were of less relevance to current research directions. Thus, the publication trend from 2007 to 2021 was demonstrated. Generally, the number of annual publications was increasing. A total of 104 relevant articles were published in 2021 until July 30, and the number of publications was presumed to be 178 in 2021.

Contribution analysis of authors in molecular hydrogen

The cooperation network of authors was demonstrated as follows (**Figure 1B**). As shown on the graph, the size of a circle indicated the number of publications by the represented authors. The links between the two authors represented their cooperation, and the thickness of each link reflected the frequency of the cooperation. According to the results, the top 10 authors who published the most articles about the medical use of molecular hydrogen were Xue-Jun Sun, Ke-Liang Xie, Yong-Hao Yu, Shigeo Ohta, Hong-Guang Chen, John H. Zhang, Nakao Atsunori, Yang Yu, Guo-Lin Wang, and Ohsawa Ikuroh. The top 10 authors with the highest link strength were Ke-Liang Xie, Yong-Hao Yu, Xue-Jun Sun, Hong-Guang Chen, Yang Yu, Shigeo Ohta, Ohno Kinji, Nakao Atsunori, Guo-Lin Wang, and Ishibashi Toru. Among them, Xue-Jun Sun, Ke-Liang Xie, Yong-Hao Yu, Ohta Shigeo, Hong-Guang Chen, Nakao Atsunori, Yang Yu, and Guo-Lin Wang appeared in both two lists.

The cooperation network was further divided into several clusters according to the association strength algorithm, with which the closely cooperating authors were included in the same cluster. The first to the eleventh clusters respectively included 16, 15, 12, 11, 9, 8, 8, 7, 7, 5, and 5 authors, and headed by Xue-Jun Sun, Ohta Shigeo, Ke-Liang Xie, Ostojic Sergej M, Hirano Shinichi, Ohno Kinji, Nakao Atsunori, Lei Zhang, Jian-Ming Cai, John H. Zhang, and Pan Yu.

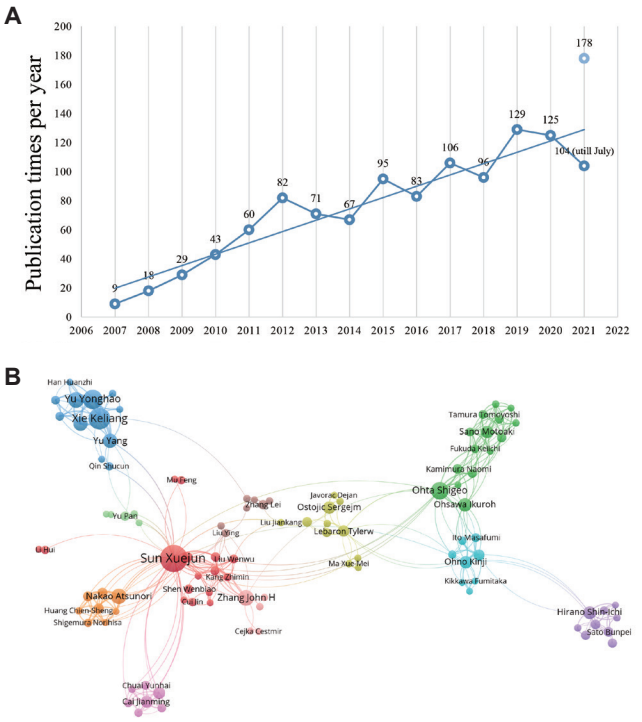

Figure 1: Overall research trend and author cooperation network.
Note: (A) The increasing trend of publication numbers from 2007 to 2021. The circles of each year indicated the number of publications in that year. The blue line was the regression line that indicated the upward tendency. (B) The cooperation network of the authors in this field. The size of each circle represented the number of publications published by the authors. The lines between two circles represented the cooperation between two authors.

Journal focusing analysis in molecular hydrogen

The top 10 journals which published the most articles in this field were listed as follows: *Medical Gas Research* (ESCI, 48 times), *Scientific Reports* [impact factor (IF) = 4.379, 22 times], *Shock* (IF = 3.454, 21 times), *Journal of Surgical Research* (IF = 2.192, 21 times), *Current Pharmaceutical Design* (IF = 3.116, 20 times), *PLoS One* (IF = 3.24, 20 times), *Brain Research* (IF = 3.252, 15 times), *International Immunopharmacology* (IF = 4.932, 13 times), *Oxidative Medicine and Cellular Longevity* (IF = 6.543, 12 times), and *Digestive Diseases and Sciences* (IF = 3.119, 12 times). The annual publication status was demonstrated in **Figure 2**. Accordingly, the top three journals in the last 5 years are *Medical Gas Research*, *Current Pharmaceutical Design*, and *Scientific Reports*.

Keywords analysis in molecular hydrogen

A total of 89 keywords that occurred more than 3 times were included in the co-occurrence network (**Figure 3** and **Additional Table 1**). Accordingly, the top 10 keywords that occurred the most included "molecular hydrogen" (161 times), "hydrogen-rich water" (66 times), "oxidative stress" (58 times), "hydrogen gas" (50 times), "inflammation" (32 times), "anti-oxidation" (31 times), "reactive oxygen species" (30 times), "ischemia-reperfusion injury" (30 times), "apoptosis" (14 times), and "autophagy" (11 times) (**Table 1**). On the other hand, the top 10 keywords that occurred the most recently included "gut microbiota" (AOY 2021.3, 3 times), "pyroptosis" (AOY 2020.7, 3 times), "COVID-19" (AOY

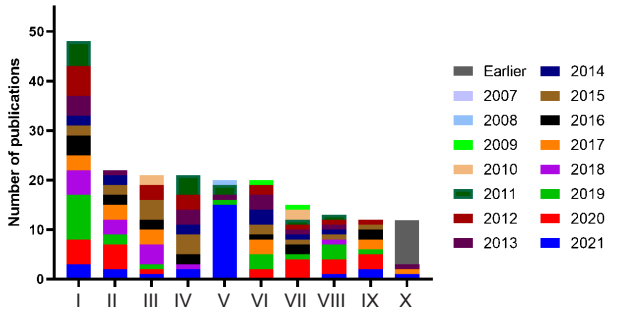

Figure 2: The top 10 journals with most publications in molecular hydrogen and their publication numbers each year.
Note: (I–X) *Medical Gas Research*, *Scientific Reports*, *Shock*, *Journal of Surgical Research*, *Current Pharmaceutical Design*, *PLoS One*, *Brain Research*, *International Immunopharmacology*, *Oxidative Medicine* and *Cellular Longevity*, and *Digestive Diseases and Sciences*.

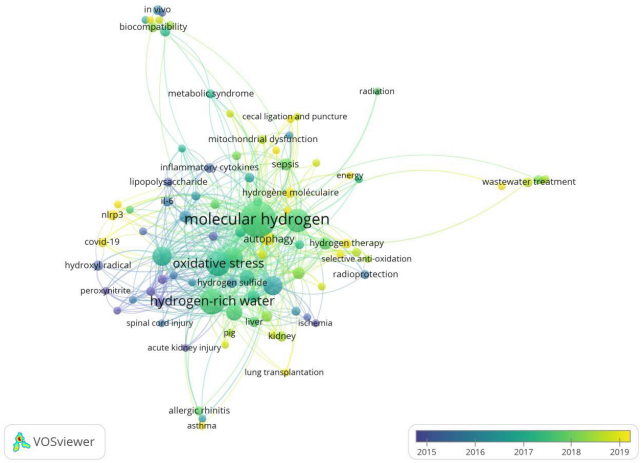

Figure 3: The co-occurrence network of the keywords in molecular hydrogen.
Note: The size of a circle represented the occurrence time of a keyword, and the links between two circles indicated the co-occurrence of two keywords. The color of each circle reflected the average occurrence year of the keyword.

Table 1: The top 10 keywords with the most occurrence time in molecular hydrogen

ID	Keywords
1	Molecular hydrogen
2	Hydrogen-rich water
3	Oxidative stress
4	Hydrogen gas
5	Inflammation
6	Anti-oxidation
7	Reactive oxygen species
8	Ischemia-reperfusion injury
9	Apoptosis
10	Autophagy

2020.6, 5 times), "sepsis-associated encephalopathy" (AOY 2020.3, 3 times), "energy" (AOY 2020, 3 times), "asthma" (AOY 2019.6, 3 times), "neuroinflammation" (AOY 2019.7, 3 times), "nlrp3" (AOY 2019.5, 6 times), "hydrogen therapy" (AOY 2019.4, 5 times), and "autophagy" (AOY 2019.4, 11 times) (**Table 2**). Autophagy was the only keyword that occurred in both of the top 10 lists.

Table 2: The top 10 keywords with the most recent average occurrence year in molecular hydrogen

ID	Keywords	Occurrence	Average occurrence year
1	Gut microbiota	3	2021.3333
2	Pyroptosis	3	2020.6667
3	COVID-19	5	2020.6
4	Sepsis-associated encephalopathy	3	2020.3333
5	Energy	3	2020
6	Asthma	3	2019.6667
7	Neuroinflammation	3	2019.6667
8	Nlrp3	6	2019.5
9	Hydrogen therapy	5	2019.4
10	Autophagy	11	2019.3636

Note: COVID-19: Coronavirus disease 2019.

Many included keywords were relevant to the basic biological mechanisms of molecular hydrogen. Keywords such as "oxidative stress" (58 times), "anti-oxidation" (31 times), "reactive oxygen species" (30 times), "nitric oxide" (9 times), and "nrf2" (9 times) were relevant to the anti-oxidative effect of hydrogen. Keywords including "inflammation" (32 times), "anti-inflammation" (10 times), "nlrp3" (6 times), "il-6" (5 times), and "inflammatory cytokines" (5 times) were relevant to anti-inflammation. Some keywords could reflex the targeted diseases or pathological changes of molecular hydrogen, for instance, "ischemia-reperfusion injury" (19 times), "neuroprotection" (9 times), "sepsis" (9 times), "kidney" (6 times), "liver" (6 times), "COVID-19" (5 times), "traumatic brain injury" (4 times), "lung injury" (4 times), "allergic rhinitis" (4 times), "metabolic syndrome" (4 times), and "cardiac arrest" (4 times) (**Additional Table 1**).

Discussion

General trend in molecular hydrogen research

Medical research on molecular hydrogen is thriving during these years. From 2007 to 2020, the annual number of publications increased from 9 to 125, and the total number of publications amounted to 1123. The prosperity of this innovative field of research comes from the contribution of researchers. The top 10 authors who published the most papers were assumed to be the experts who paid much attention to this field. The beginners of this field can review the articles from them to grasp the basic knowledge. Some of their representative works were listed here (**Table 3**). The most influential article in the list, which had been cited 1233 times, was the one published on *Nature Medicine* (IF = 53.44) by Ohta's team[3] in 2007. This article firstly discovered the selective anti-oxidative effect of molecular hydrogen and its potential medical value in the treatment of cerebral ischemia-reperfusion injury. The second one was published on *Free Radical Research* (IF = 4.148) by Atsunori's team[4] in 2010. This article systematically summarized the mechanisms and potential target organs or diseases of molecular hydrogen, which was a good guide for beginners in this field. The third article was published on *Neuroscience Letters* in 2008 by Sun's team,[15] which introduced hydrogen

Table 3: Representative works in molecular hydrogen of the top-10 authors with the most publications

Authors*	Year	Title of representative works	Journals	Citation times**
Shigeo Ohta	2007	Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals	*Nature Medicine*	1233
Nakao Atsunori	2010	Recent advances in hydrogen research as a therapeutic medical gas	*Free Radical Research*	203
Xue-Jun Sun	2008	Hydrogen therapy reduces apoptosis in neonatal hypoxia-ischemia rat model	*Neuroscience Letters*	172
Ke-Liang Xie	2010	Protective effects of hydrogen gas on murine polymicrobial sepsis via reducing oxidative stress and hmgb1 release	*Shock*	150
Ohsawa Ikuroh	2008	Consumption of hydrogen water prevents atherosclerosis in apolipoprotein E knockout mice	*Biochemical And Biophysical Research Communications*	131
Ke-Liang Xie	2012	Molecular hydrogen ameliorates lipopolysaccharide-induced acute lung injury in mice through reducing inflammation and apoptosis	*Shock*	125
Yonghao Yu	2014	Inhalation of hydrogen gas attenuates brain injury in mice with cecal ligation and puncture via inhibiting neuroinflammation, oxidative stress and neuronal apoptosis	*Brain Research*	64
John H. Zhang	2012	Hydrogen gas ameliorates oxidative stress in early brain injury after subarachnoid hemorrhage in rats	*Critical Care Medicine*	52
Hongguang Chen	2012	Molecular hydrogen protects mice against polymicrobial sepsis by ameliorating endothelial dysfunction via an Nrf2/Ho-1 signaling pathway	*International Immunopharmacology*	36
Yang Yu	2019	Hydrogen gas reduces hmgb1 release in lung tissues of septic mice in an Nrf2/Ho-1-dependent pathway	*International Immunopharmacology*	20

Note: *The names of the first authors or the corresponding authors. **The citation times of the articles in the core index of Web of Science on July 30, 2021.

therapy into the treatment of neonatal hypoxia-ischemia brain injury. Other articles in the list focused on the protective effect of hydrogen against sepsis, atherosclerosis, acute lung injury, brain injury induced by systemic inflammation, and subarachnoid hemorrhage.[16-20] Thus, the articles of these influential authors were highly appreciated and comprehensive, which deserved to be studied. On the other hand, the cooperation among the authors was common, and many authors who frequently collaborated with others also had many publications. This phenomenon emphasized the importance of cooperation and teamwork. According to the cooperation network, the clusters could be a reflection of the research teams and their leaders. Other researchers may collaborate with these teams in order to enhance their research capacity and academic influence.

Subscribing to journals that have published many articles about the medical use of molecular hydrogen is another way to comprehend this field. The journals that published numerous relevant articles were listed in the result section, in which three journals published the most articles in the last 5 years, including *Medical Gas Research*, *Current Pharmaceutical Design*, and *Scientific Reports*. *Medical Gas Research* is a journal specializing in the medical application of various gases such as oxygen, hydrogen, carbon monoxide, carbon dioxide, nitrogen, xenon, and so on. This journal publishes basic, translational, and clinical medical researches on the therapeutic effects of gases, and it has been included in the Emerging Source Citation Index. As a journal specializing in medical gas, *Medical Gas Research* is worthy of the name, and we look forward to other publications on medical gas from this journal. *Current Pharmaceutical Design* primarily publishes reviews and research articles in the field of drug design and other relevant topics, such as medicinal chemistry, pharmaceutical targets, pharmacology, and pathophysiology. Recently, this journal published a special issue on the development of hydrogen medicine and biology, which made them become one of the top three journals that published the most relative articles. The publication of this special issue revealed that hydrogen therapy has attracted the attention of pharmacological researchers, reflecting the increasing influence of hydrogen medicine. Another journal in the top three list was *Scientific Reports*, a comprehensive journal relevant to nearly all scientific fields. Although the degree of professional focus of *Scientific Reports* was relatively low, the number of relevant articles in this journal was numerous in these years owing to the high total publication number and the growing recognition of molecular hydrogen. The wide attention given by journals with different aims and scopes reflected the growing influence of hydrogen therapy in different fields, from biological research to engineering and drug design.

Current and future research hotspots on molecular hydrogen

The keywords of an article can reflect its main topic and purpose, and the bibliometrics analysis of the keywords can illustrate the research hotspots. The co-occurrence of the keywords can reflect the cumulative attention degree of different topics. The keywords "molecular hydrogen," "hydrogen-rich water," and "hydrogen gas" were included in the top 10 co-occurrence list. The presentation of these keywords showed that the hydrogen therapy was based on molecular hydrogen, rather than hydrogen ion or hydrogen atoms in other compounds. And the most common delivery routes for hydrogen included inhalation of hydrogen gas and drinking or dripping water rich (or saline) in hydrogen.[21,22] Three keywords in the top 10 co-occurrence list, such as "oxidative stress," "anti-oxidant," and "reactive oxygen species," were related to the anti-oxidative effect of molecular hydrogen, and the total co-occurrence time of key-

words relative to anti-oxidation was 169. Similarly, the total times of co-occurrence of keywords pertinent to inflammation were up to 72 times. Other mechanism-related keywords, such as "apoptosis" and "autophagy," were included in the top 10 co-occurrence list. This result indicated that the mechanism of molecular hydrogen was the hotspot for research at the moment, and it also clearly demonstrated the classical and novel mechanisms of molecular hydrogen, including anti-oxidation, anti-inflammation, anti-apoptosis, and autophagy.

Based on the AOY data of each keyword, future research hotspots could be assumed. The keyword with a recent AOY partially indicated that the corresponding topic was concentrated on recently. According to the results, the keyword "gut microbiota" appeared most recently. Gut microbiota had become a hotspot in many fields of biological research, having significant relevance with the generation of multiple metabolic diseases, inflammatory diseases, and some systemic diseases.[23-25] The function of gut microbiotas predominantly depended on their production, including molecular hydrogen. For instance, several researches indicated that the insufficient production of hydrogen gas by gut microbiotas might result in Parkinson's disease because of the absence of its anti-oxidative, anti-inflammatory, and cytoprotective effect. Conversely, hydrogen could also ameliorate diseases by adjusting the activity of gut microbiota. It was illustrated that the consumption of hydrogen-rich saline decreased the incidence of gut microbial translocation in mice after cecal ligation and puncture, which further inhibited the development of sepsis.[26] The keyword appearing the second earlier was "pyroptosis," a pathological process known as inflammatory death. It was a novel concept defined in 2005, which has become a research hotspot in the last 5 years. Several studies reported that inhalation of hydrogen gas inhibited NLR family pyrin domain containing 3 mediated pyroptosis, additionally ameliorating myocardial ischemia-reperfusion injury and post-ischemia cardiac remodeling.[27] The third keyword in the AOY list was "COVID-19," a notorious virus that has caused the global pandemic of new coronavirus pneumonia since 2020. The research team of Zhong published an article demonstrating the therapeutic effect of hydrogen/oxygen mixed gas inhalation against coronavirus disease 2019 (COVID-19), and hydrogen therapy was introduced in China's COVID-19 treatment guidelines since then.[12] Thus, the keywords in this top 10 AOY list could be the research hotspots in the future.

The keyword "autophagy" was the only keyword in both top 10 co-occurrence and AOY lists. Autophagy refers to the process by which a cell degrades its own proteins or organelles by the lysosomes, which occurs during many physiological or pathological processes. Hydrogen also influenced the autophagy process, and the actual effect of hydrogen on autophagy depended on the type of targeted pathological change. For example, it was reported that inhalation of hydrogen gas or intake hydrogen-rich water alleviated myocardial ischemia-reperfusion injury, hypoxia-ischemia neonatal brain injury, and sepsis by activating autophagy.[28-30] However, another research indicated that hydrogen inhibited autophagy in acute carbon monoxide poisoning and lipopolysaccharide-induced acute lung injury and presented the protective effect.[31] These results revealed the diverse effect of molecular hydrogen on autophagy, which merits further investigation.

To sum up, the anti-oxidative, anti-inflammatory, and anti-apoptotic effects of hydrogen were the eternal topics for the mechanism study of molecular hydrogen. Gut microbiota, pyroptosis, and COVID-19 might be novel research directions in this field. Autophagy was a promising research direction for the mechanism study, which might become the research hotspot in the future.

Translational directions of molecular hydrogen

The keyword remaining in the top 10 co-occurrence list not mentioned above was "ischemia-reperfusion injury" (23 times), a pathophysiological change targeted by molecular hydrogen. The molecular basis of ischemia-reperfusion injury included the generation of reactive oxygen species, calcium influx, activation of inflammatory immune cells, and apoptotic pathways.[32] These pathological changes were the appropriate targets of hydrogen therapy. Likewise, many other diseases or pathological changes related to these mechanisms could become the potential targets for hydrogen. For instance, the presentation of the keyword "neuroprotection" (9 times) indicated the protective effect of hydrogen on cerebral, spinal, or peripheral nerve injuries. In addition to the article by Shigeo Ohta published in 2007,[3] many other basic medical studies had demonstrated that molecular hydrogen exerted neuroprotective on intracerebral hemorrhage, traumatic brain injury, subarachnoid hemorrhage, spinal cord injury, and Parkinson's disease.[33-37] The neuroprotective effect of molecular hydrogen was successfully translated into clinical practice in these years. Ono et al.[10] designed a randomized controlled clinical trial and found that inhalation of hydrogen reduced the relative signal intensity of infarcted territories, NIHSS scores, and increased Barthel prognosis indexes. Another study by Takeuchi et al.[38] published in 2021 indicated that intravenous hydrogen therapy with magnesium sulfate infusion attenuated the incidence of cerebral vasospasm and delayed cerebral ischemia, and partially improved the prognosis of patients.

Similarly, the studies on molecular hydrogen dealing with other diseases continued to emerge these years. A pilot study of a clinical trial reported that hydrogen-rich water ameliorated liver fat accumulation and abnormal levels of liver enzymes in patients with non-alcoholic fatty liver disease. Another clinical trial focusing on metabolic syndrome showed that high-concentration hydrogen-rich water reduced blood cholesterol and glucose levels, the serum amount of glycosylated hemoglobin, and ameliorated the disorder of inflammatory and redox homeostasis biomarkers. A multi-center clinical trial, including 108 patients, illustrated the therapeutic effect of hydrogen/oxygen therapy on chronic obstructive pulmonary disease. Hydrogen and oxygen that were mixed in a 2:1 manner and inhaled by patients significantly improved their Breathlessness, Cough, and Sputum Scale scores. Their Cough Assessment Test scores were also reduced by inhalation of hydrogen/oxygen mixture.

In short, just as the keyword analysis showed, the clinical studies of molecular hydrogen were relevant to chronic obstructive pulmonary disease, subarachnoid hemorrhage,

sleep-deprivation, Parkinson's disease, muscular damage, graft-*versus*-host-disease, metabolic diseases, vascular endothelial dysfunction, dermatosis, allergic reaction, non-small cell lung cancer, nasopharyngeal cancer, and even daily health care. It was manifest that there were numerous translation directions for the medical use of molecular hydrogen. However, only about 50 clinical studies were published up to now, many of which were pilot studies or open-labeled trials with lower scientific reliability. So, the primary mission for researchers in this field was not to discover new translation directions but to verify the clinical effect of hydrogen by multi-center, randomized, double-blind clinical research with more subjects.

Limitations

The main limitation of this research was that the conventional data search tool, Web of Science, could not be used when searching for publications in this field. Because of the large scope of Web of Science, many articles searched from the Web of Science were not relevant to medical treatment but relevant to engineering or agriculture. Therefore, we used a more pertinent database, PubMed, to make sure that the searching results were primarily relevant to medicine. But this compromise made it impossible to analyze citations, which crippled the quality of the results. Even so, this research was the first bibliometric analysis about the medical use of molecular hydrogen. The quality of analysis could be improved by a better search strategy and data filters in the future.

Conclusion

The bibliometric analysis showed a significant thriving trend of medical research on molecular hydrogen. Many productive authors contributed a lot to this field, and some of their articles were influencing and deserving of reading. Anti-oxidative, anti-inflammatory, and anti-apoptotic effects of molecular hydrogen were the classical mechanisms of molecular hydrogen, which were the basis of further research on mechanisms. Gut microbiota, pyroptosis, COVID-19, especially autophagy may be the hotspots for future research. The translational directions of basic research were multiple, and more high-standard clinical research was necessary for the future development of this field.

Author contributions

HL: composed the introduction and discussion parts of the manuscript; HYM: composed the abstract, method, and results parts of the manuscript; WLH: carried out the figures and Additional table; YXZ: searched for the literature; LZ: carried out Tables 1 and 2; PFX: carried out Table 3; PFY: raised the idea and modified the manuscript; JML: screened the literature and gave writing advise for discussion part. All authors revised the manuscript and approved the final version.

Conflicts of interest

All the authors declare no conflicts of interests.

Additional file

Additional Table 1: This table listed all the keywords in molecular hydrogen occurred more than three times in the included articles.

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