

ORIGINAL RESEARCH

Effects of Hydrogen Inhalation on Neurological Function Indicators, Oxidative Stress Markers, and E-Cadherin Levels in Patients with Brain Glioma

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ABSTRACT

Objective • This study aims to evaluate the effects of hydrogen therapy on nerve function and tumor progression markers in glioma patients, focusing on the modulation of oxidative stress and cadherin expression to establish its potential as a complementary treatment.

Methods • 100 glioma patients were enrolled and divided into two groups using the random number table: routine treatment (50) and hydrogen inhalation plus routine treatment (50). After 2 weeks of treatment, clinical curative effect, levels of nerve function indexes [national institute of health stroke scale (NIHSS), central nervous specific protein (S100 β), neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP)], oxidative stress indexes [malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT)] and E-cadherin before and after treatment, and occurrence of adverse reactions during treatment were compared between the two groups.

Results • After treatment, the overall effect of the hydrogen inhalation group (90.00%) was significantly better than that of the conventional group (72.00%), which was statistically significant ($P = .022$). In terms of specific biomarkers, post-treatment levels of E-cadherin were elevated to 0.84 ± 0.05 ng/mL in the hydrogen group compared to 0.72 ± 0.06 ng/

mL in the routine group. SOD and CAT levels rose to 63.21 ± 5.36 U/L and 8.01 ± 0.54 U/mL, respectively, versus 52.31 ± 5.24 U/L and 5.25 ± 0.59 U/mL in the routine group ($P < .05$ for both). Conversely, the NIHSS scores decreased significantly to 12.19 ± 2.08 in the hydrogen group, compared to 16.92 ± 2.23 in the routine group. Similarly, S100 β , NSE, GFAP, and MDA levels were found to be lower in the hydrogen group (0.41 ± 0.09 μ g/L, 8.24 ± 1.64 ng/mL, 0.71 ± 0.23 pg/mL, and 6.05 ± 1.08 mmol/L respectively) than in the routine group (0.66 ± 0.12 μ g/L, 10.67 ± 1.83 ng/mL, 0.93 ± 0.29 pg/mL, and 7.21 ± 1.12 mmol/L respectively) with $P < .05$ for all comparisons. The total incidence of adverse reactions was slightly lower in the hydrogen group (64.00%) compared to the routine group (68.00%), but this difference was not statistically significant ($\chi^2 = 0.178$, $P = .673$).

Conclusion • Hydrogen inhalation therapy significantly enhances nerve function, reduces local oxidative stress levels, and increases E-cadherin levels in patients with brain glioma, suggesting its potential as an adjunct treatment. The findings underscore the therapy's role in enhancing patient recovery and guiding future research and treatment strategies. (*Altern Ther Health Med.* 2025;31(2):384-388).

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INTRODUCTION

Gliomas are the most common malignant tumours in the central nervous system, posing a major threat to the survival and quality of life of patients. Due to their aggressive nature, lethality is high.¹ Glioma cells are markedly aggressive,

characterised by diffuse infiltrative growth, unrestricted proliferation and a high tendency to recur after treatment, severely impairing cognitive function and lowering patients' quality of life.² Statistics in recent years have shown that glioma morbidity and mortality rates have continued to rise, highlighting the urgency to intensify research and therapeutic strategies. Although a variety of therapeutic options are available, including surgery, radiotherapy and chemotherapy, these traditional treatments are often limited by the complexity and high recurrence rate of gliomas.³ Specific shortcomings of these treatments include limited improvement in survival, significant side effects, and reduced quality of life following treatment.

Hydrogen therapy, explored in this study, demonstrates therapeutic potential that is different from existing treatments

due to its unique antioxidant and anti-inflammatory effects.⁴ Hydrogen has been found to have the potential to ameliorate cerebral ischemia/reperfusion injuries, which opens the way to exploring the therapeutic and protective roles of hydrogen. Hydrogen is the most abundant element in the universe and has been shown to have protective effects on human organs, tissues and cells.⁵⁻⁷ Hydrogen therapy is unique in its ability to directly eliminate harmful free radicals and reduce oxidative stress without affecting normal cell function.

Previous studies have demonstrated the protective effects of hydrogen, but there is still a dearth of research that combines these findings with glioma therapy. This study aims to fill this gap and provide new hope for patients by delving into the use of hydrogen therapy in glioma treatment. By directly correlating the limitations of current treatments with the specific goals of this study, this paper highlights the importance of exploring hydrogen as a potential therapeutic tool. By improving treatment outcomes and patient quality of life, this study is expected to make a meaningful contribution to the field of glioma treatment.

MATERIALS AND METHODS

Baseline information

This study enrolled 100 patients with brain glioma at our hospital between January and December 2022. Using the random number table method, they were divided into two groups: the routine group (50 cases receiving routine treatment) and the hydrogen inhalation group (50 cases receiving hydrogen inhalation in addition to routine treatment). The control group comprised 27 males and 23 females, aged 35 to 72 years (mean age: 44.63 ± 4.18 years). Tumor locations included 25 cases in the temporal lobe, 21 in the frontal lobe, and 4 in the occipital lobe. Clinical staging revealed 34 cases in stage I, 13 cases in stage II, and 3 cases in stage III. Pathological types included 12 cases of glioblastoma and 38 cases of astrocytoma. The average duration of illness ranged from 1 to 6 years (mean duration: 3.09 ± 0.48 years). The hydrogen inhalation group consisted of 26 males and 24 females, aged 35 to 72 years (mean age: 45.02 ± 4.17 years). Tumor locations were distributed as follows: 24 cases in the temporal lobe, 20 in the frontal lobe, and 6 in the occipital lobe. Clinical staging revealed 35 cases in stage I, 11 cases in stage II, and 4 cases in stage III. Pathological types included 14 cases of glioblastoma and 36 cases of astrocytoma. The average duration of illness ranged from 1 to 6 years (mean duration: 3.13 ± 0.51 years).

The study received approval from the hospital's ethics committee. Patients and their families were provided with information and gave informed consent.

Inclusion Criteria: (1) All patients met the diagnostic criteria for glioma according to the World Health Organization Classification of Tumors of the Central Nervous System (5th edition) and were diagnosed with glioma by head CT or MRI. (2) Patients were 18 years of age or older. (3) Patients were newly diagnosed. (4) Patients were eligible for surgical treatment.

Exclusion Criteria: (1) Presence of cardiovascular system diseases. (2) Presence of mental consciousness disorders. (3) Presence of digestive system diseases. (4) Presence of hematologic system diseases. (5) Presence of infectious diseases.

Each inclusion and exclusion criteria were carefully selected to ensure the integrity of the study and the reliability of the results. For example, inclusion criteria are limited to specific pathology types to ensure applicability and comparability of study findings. Patients with severe complications are excluded from the exclusion criteria to reduce potential bias in treatment response.

Treatment methods

Routine group: Patients in the routine group received postoperative chemotherapy in combination with conventional oral temozolomide (Beijing Shuanglu Pharmaceutical Co., Ltd; State Drug License: H20110153, Beijing, China) treatment. Specifically, temozolomide was administered at a dosage of 150 mg/m^2 per day for 14 days, constituting one course of treatment. This regimen involved 7 days of continuous administration followed by a 7-day discontinuation period, repeated for a total of 14 consecutive weeks.

Hydrogen Inhalation Group: Patients in the hydrogen inhalation group received mechanical hydrogen therapy in addition to the routine treatment. The ventilation mode employed synchronized intermittent ventilation with a frequency range of 12-20 breaths per minute and a stable respiratory ratio of 3/2 to 2/1. Ventilation mode was adjusted to pressure support ventilation, providing expiratory positive pressure ventilation ranging from 3 to $10 \text{ cm H}_2\text{O}$ ($1 \text{ cm H}_2\text{O} = 0.098 \text{ kPa}$) based on individual patient conditions. Airway peak pressure was set between 30 to $45 \text{ cmH}_2\text{O}$, and tidal volume was maintained at 6-8 mL/kg. Patients inhaled hydrogen for 2 hours each day, once a day, for a total of 28 days as one course of treatment. The treatment was administered continuously for 14 weeks.

The technical details of hydrogen therapy are described in detail, including the pressure-supported ventilation Settings used, which are based on preliminary research and generally accepted practice. At the same time, the dose of temozolomide conforms to the standard treatment protocol, ensuring the effectiveness and safety of the treatment.

Observation indicators

Overall efficiency. The total effective rate of clinical treatment was assessed after the completion of treatment. The evaluation criteria were categorized as follows: Obvious Effect (Significant Rate): Patients falling into this category experienced a significant reduction in clinical symptoms during the treatment period, with their symptoms decreasing by approximately 50% compared to the original symptoms. Furthermore, these improvements remained stable for about 28 days, and no new symptoms emerged during this period. Effective Rate (Effective): Patients categorized as effective experienced a reduction in clinical symptoms, albeit to a

lesser extent, approximately a 10% reduction compared to the original symptoms. These improvements also continued to remain stable for about 28 days. Ineffective: Patients in this category did not exhibit any reduction in clinical symptoms, and there was an observable tendency for their symptoms to deteriorate. The overall effective rate was calculated as the sum of the significant rate and effective rate, providing a comprehensive measure of the treatment's effectiveness.

Degree of neurological deficit scale score. The neurological function of the patients was evaluated by the National Institute of Health Stroke Scale (NIHSS) score before and after treatment.⁹ The scale consists of 11 entries with a score of 42 out of a possible 42 points, and the lower the score, the better the neurological function of the patient.

Biochemical indicators

The patients' fasting vein 3 mL venous blood was extracted before and after treatment, respectively, and centrifuged for 10 min by 3000r/min 10 cm radius centrifuge (purchased from Lianyungang Depon Chemical Machinery Co., Ltd., Lianyungang, China), and the serum was retained. Enzyme-linked immunosorbent assay (ELISA) was used to detect the patients' neurological function indexes [S100 β , neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP)], oxidative stress indexes [malondialdehyde (malondialdehyde), and other oxidative stress indexes. Malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT)] and E- cadherin levels. The main outcome measures in this study included clinical efficacy assessment (such as changes in NIHSS score) and biochemical changes (including S100 β , NSE, GFAP, MDA, SOD, CAT and E-cadherin). These indicators were chosen because they could reflect the effects of treatment on neurological recovery and oxidative stress status in glioma patients.

Adverse reactions

The occurrence of adverse reactions (vomiting, hypertension, malaise, bleeding) was recorded and compared between patients in the routine and hydrogen inhalation groups, respectively, during the treatment period. The monitoring of adverse reactions was assessed using a standardized scale (e.g. CTCAE v5.0) to ensure consistency of assessment. All adverse events were recorded and assessed for their relevance to treatment.

Statistical analysis

Our study utilized SPSS software (version 22.0, IBM) for data processing. The t-test was employed for comparing continuous variables like NIHSS scores, which were presented as mean $\pm$ SD. This method was chosen for its ability to assess differences in means of normally distributed datasets. For categorical variables like the incidence of adverse reactions, we used the chi-square (χ^2) test, ideal for comparing proportions, and presented results as percentages. Both tests were selected for their appropriateness in analyzing medical data and their widespread acceptance in biomedical research. Data normality was evaluated by Shapiro-Wilk test and histogram. Independent

Table 1. Comparison of total effective rate between routine and hydrogen inhalation groups (%).

Group	n	Significant effective	Effective	Ineffective	Total incidence
Routine group	50	27 (54.00)	9 (18.00)	14 (28.00)	36 (72.00)
Hydrogen inhalation group	50	32 (64.00)	13 (26.00)	5 (10.00)	45 (90.00)
χ^2					5.263
P value					.022

Figure 1. Comparison of total effective rate between routine and hydrogen inhalation groups

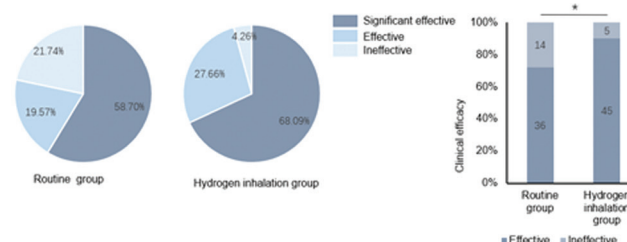
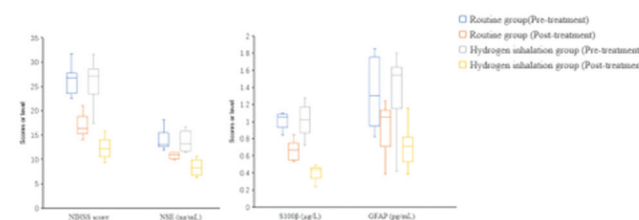


Table 2. Comparison of neurological function indicators between the two groups ($\bar{x} \pm s$)

Indicator	Timing	Routine group (n=50)	Hydrogen inhalation group (n=50)	t	P value
NIHSS score	Pre-treatment	25.63 $\pm$ 4.11	26.07 $\pm$ 4.13	0.534	.595
	Post-treatment	16.92 $\pm$ 2.23	12.19 $\pm$ 2.08	10.968	.000
S100 β (μ g/L)	Pre-treatment	1.05 $\pm$ 0.17	1.03 $\pm$ 0.18	0.571	.569
	Post-treatment	0.66 $\pm$ 0.12	0.41 $\pm$ 0.09	11.785	.000
NSE (ng/mL)	Pre-treatment	14.01 $\pm$ 2.09	13.57 $\pm$ 2.05	1.063	.291
	Post-treatment	10.67 $\pm$ 1.83	8.24 $\pm$ 1.64	6.992	.000
GFAP (pg/mL)	Pre-treatment	1.34 $\pm$ 0.42	1.38 $\pm$ 0.45	0.459	.647
	Post-treatment	0.93 $\pm$ 0.29	0.71 $\pm$ 0.23	4.203	.000

Note: Compared with pre-treatment, $P < .05$.

Figure 2. Comparison of neurological function indicators between the two groups.



sample t test was used for comparison between groups, and $P < .05$ was considered as statistically significant difference.

RESULTS

Comparison of overall efficiency

At the conclusion of the treatment period, the total effective rate among patients in the hydrogen inhalation group was notably higher at 90.00% compared to 72.00% in the routine group. This difference was statistically significant ($P < .05$). Detailed data can be found in Table 1 and Figure 1.

Comparison of Neurological Function Indicators

Upon completion of the treatment, patients in the hydrogen inhalation group exhibited lower NIHSS scores, as well as reduced levels of S100 β , NSE, and GFAP, in contrast to those in the routine group. These differences were statistically significant ($P < .05$). Refer to Table 2 and Figure

Table 3. Comparison of oxidative stress indicators and E-cadherin levels in patients ($\bar{x} \pm s$)

Norm	Timing	Routine group (n=50)	Hydrogen inhalation group (n=50)	t	P value
SOD (U/L)	Pre-treatment	40.28±4.15	40.69±4.17	0.493	.623
	Post-treatment	52.31±5.24	63.21±5.36	10.282	.000
CAT (U/mL)	Pre-treatment	4.27±0.53	4.23±0.48	0.396	.693
	Post-treatment	5.25±0.59	8.01±0.54	24.401	.000
MDA (mmol/L)	Pre-treatment	10.04±2.62	10.23±2.67	0.359	.720
	Post-treatment	7.21±1.12	6.05±1.08	5.272	.000
E-cadherin (ng/mL)	Pre-treatment	0.33±0.04	0.34±0.06	0.981	.329
	Post-treatment	0.72±0.06	0.84±0.05	10.864	.000

Note: Compared with pre-treatment, $P < .05$.

Figure 3. Comparison of oxidative stress indicators and E-cadherin levels between the two groups.**Table 4.** Comparison of the occurrence of adverse reactions in the routine and hydrogen inhalation groups (%)

Group	n	Vomit	Hypertension	Fatigue	Hemorrhage	Total incidence
Routine group	50	20 (40.00)	1 (2.00)	13 (26.00)	0 (0.00)	34 (68.00)
Hydrogen inhalation group	50	17 (34.00)	0 (0.00)	15 (30.00)	0 (0.00)	32 (64.00)
χ^2						0.178
P value						.673

2 for specific data. The improvement in the NIHSS score in the hydrogen inhalation treatment group was significantly greater than that in the conventional treatment group, indicating the effectiveness of hydrogen therapy in improving patients' neurological function.

Comparison of oxidative stress indicators and E-cadherin levels

At the end of the treatment period, patients in the hydrogen inhalation group demonstrated higher levels of therapeutic E-cadherin, as well as increased levels of SOD and CAT, while showing lower levels of MDA compared to the routine group. These disparities were statistically significant ($P < .05$). Detailed data are available in Table 3 and Figure 3. These improvements suggest that hydrogen therapy may improve patient health by reducing nerve damage and promoting nerve cell repair. At the same time, our findings suggest that hydrogen therapy helps reduce oxidative stress and may affect glioma progression by improving cell adhesion properties.

Comparison of the occurrence of adverse reactions

Throughout the treatment period, the total incidence of adverse reactions in the hydrogen inhalation group was 64.00%. However, this occurrence did not show a statistically significant difference when compared to the 68.00% observed in the routine group ($P > .05$). Please refer to Table 4 for further details. This suggests that the safety and tolerability of hydrogen inhalation therapy is comparable to conventional treatment.

DISCUSSION

Gliomas are malignant tumors that progress rapidly and have a poor prognosis and, in most cases, cannot be removed completely by surgery. The immune microenvironment of the central nervous system is at the baseline level; the brain is in an immunological quiescent state, and together with the existence of the blood-brain barrier, most peripheral immune cells cannot enter the brain. In addition, the individual antigen specificity of glioma is strong, which makes the clinical treatment of brain glioma patients difficult.¹¹ At the same time, it is difficult for chemotherapeutic drugs to cross the blood-brain barrier to reach the tumor site, which makes the clinical treatment of glioma patients much more difficult. Therefore, it is urgent to seek an efficient and convenient treatment for glioma.¹² Currently, studies have shown that hydrogen has a certain protective effect on brain injury. Hydrogen is colorless and odorless and can reduce the inflammatory reaction in the brain, inhibit oxidative stress, improve nerve function and protect the nervous system.¹³ In exploring the potential of hydrogen therapy in glioma management, this study found that hydrogen inhalation significantly improved neurological function and reduced oxidative stress, findings that support the potential of hydrogen therapy as a promising adjunct therapy. In particular, hydrogen therapy has shown particular advantages in overcoming the blood-brain barrier and reducing damage to surrounding healthy brain cells, which is a significant challenge to conventional treatments. The work of Ohsawa et al. highlights the potential of molecular hydrogen in reducing oxidative stress and neuroprotection due to its antioxidant properties. In addition, by delving into how hydrogen interacts with glioma cells at the molecular level, for example by regulating specific signaling pathways to inhibit tumor growth or promote apoptosis, this study provides further insights into the mechanism of action of hydrogen therapy.

The results of this study showed that at the end of the treatment, the total effective rate of treatment of glioma patients in the hydrogen inhalation group was higher than that of the routine group, and the NIHSS score, serum S100 β , NSE, and GFAP levels were lower than those of the routine group. S100 β is widely distributed in the neuronal cells, and when neurons are destroyed, it can enter the blood circulation. NSE enters the cerebrospinal fluid through the blood-brain barrier after the nerve damage and the elevation of GFAP. The elevation of GFAP suggests that the spinal cord has received damage.¹⁴ The present results suggest that patients with gliomas can improve with routine combined hydrogen inhalation therapy. Conventional chemotherapy combined with drugs kills cancer cells and also causes damage to normal cells in the body. However, the physical and chemical properties of hydrogen gas give it a natural advantage in targeting brain system diseases. Hydrogen has a small molecular weight, strong dispersing ability, easy diffusion, fast onset of action, stable nature and no obvious toxic side effects. Its small molecular structure makes it easier to pass through the blood-brain barrier. The hydrogen molecules entering the human brain have a certain degree of reducibility, which can quickly neutralize a large number of free radicals

produced by cancer cells, reduce the invasion of free radicals on normal cells, hinder their continued growth, and thus improve the body's neurological function and autoimmune ability. Hydrogen inhalation therapy not only can fundamentally hinder the proliferation of tumor cells but also will not harm the normal cells of the human body.

The results of this study showed that at the end of treatment, the levels of E-cadherin, SOD and CAT in the hydrogen inhalation group were higher than those in the routine group, and the levels of MDA were lower than those in the routine group. E-cadherin can be used as an indicator of the degree of malignancy of tumors. In normal physiological state, E-cadherin contributes to the correct localization of the cells and is responsible for the recognition of adhesion and separation of different tissue layers for migration. In the microenvironment of the tumors, the hypoxia prompts the Dysregulation of epithelial calreticulin in cancer cells, leads to disruption of contact inhibition, epithelial-mesenchymal transition occurs, and cancer cells spread to distant sites.¹⁵ SOD and CAT are a key antioxidant enzyme in the cell, and MDA is a metabolic product of lipid peroxidation.¹⁶ The results suggest that hydrogen inhalation therapy can reduce the level of oxidative stress and inhibit the malignant biological behavior of tumor cells in patients with glioma. This may be due to the fact that the tumor microenvironment is a mixture of fluid, immune cells, and blood vessels encasing the tumor, and tumor cells can continue to survive under hypoxic conditions by activating adaptive responses.¹⁷ On the one hand, the oncogenes of cancer cells cannot be expressed normally, and their metabolism is overactive, which generates a large number of free radicals; on the other hand, under the attack of a large number of free radicals, the antioxidant defense system of cancer cells is impaired, and they cannot scavenge these free radicals effectively. On the other hand, hydrogen can effectively antagonize inflammatory and oxidative reactions, plays a significant role in signal regulation, and also protects the nervous system of patients.¹⁸

The results of this study indicate that hydrogen inhalation therapy does not significantly increase the total incidence of adverse effects compared to the control group during treatment, suggesting its relative safety. The therapy shows promise in improving neurological function, reducing oxidative stress, and increasing E-calcium mucin levels in patients with glioma. However, this study has limitations that should be considered. First, the sample size was relatively small, which may limit the generalizability of the findings. Additionally, the study's duration was short-term, and the long-term effects of hydrogen therapy remain unknown. Further research should also investigate the underlying mechanisms of hydrogen's therapeutic effects in glioma patients. Future studies should validate these initial findings by expanding the sample size and extending the study period, and explore the long-term effects of hydrogen therapy on survival, quality of life improvement, and its potential resistance mechanisms.

Based on our findings, future research should focus on larger, multi-center trials to validate these results and assess the long-term safety and efficacy of hydrogen inhalation therapy. Exploring the molecular pathways involved in hydrogen's

effects on glioma cells can also provide deeper insights into its potential as a therapeutic agent. In addition, comparing hydrogen therapy with other emerging treatments could help determine its place in a comprehensive glioma treatment strategy. By comparing the efficacy and safety of hydrogen therapy with other treatments such as targeted therapy and immunotherapy, it can provide important guidance for future clinical practice. Finally, all conclusions and mechanisms discussed in this study are based on currently available scientific literature and research data, which ensures the credibility and practicability of the discussion. Future research will require further experiments and clinical trials to deepen our understanding of the potential of hydrogen therapy, particularly in exploring its effects on specific molecular pathways and as part of glioma treatment regimens.

ETHICAL COMPLIANCE

The study received approval from the Ethics Committee of Xingtai Third Hospital, adhering to the principles of the Declaration of Helsinki. Detailed informed consent was obtained from all participants or their guardians, ensuring a clear understanding of the study's purpose, risks, and benefits. This process was thoroughly documented. Ethical guidelines for human research were rigorously followed, including maintaining participant confidentiality and using data exclusively for research purposes. The study's protocol, including ethical considerations, was overseen by an independent committee to ensure transparency and uphold the highest ethical standards in all aspects of the research.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

YL and JH designed the study and performed the experiments LZ and SW collected the data YF, ZP and WZ analyzed the data, and YL and JH prepared the manuscript. All authors read and approved the final manuscript.

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REFERENCES

- Urbanaviciūtė R, Skauminas K, Skiriūtė D. The Evaluation of AREG, MMP-2, CH3L1, GFAP, and OPN Serum Combined Value in Astrocytic Glioma Patients' Diagnosis and Prognosis. *Brain Sci*. 2020;10(11):872. doi:10.3390/brainsci10110872
- Jan HJ, Lee CC, Shih YL, et al. Osteopontin regulates human glioma cell invasiveness and tumor growth in mice. *Neuro-oncol*. 2010;12(1):58-70. doi:10.1093/neuonc/nop013
- Wen PY, Stein A, van den Bent M, et al. Dabrafenib plus trametinib in patients with BRAF^{V600E} mutant low-grade and high-grade glioma (ROAR): a multicenter, open-label, single-arm, phase 2, basket trial. *Lancet Oncol*. 2022;23(1):53-64. doi:10.1016/S1470-2045(21)00578-7
- Yuan T, Zhao JN, Bao NR. Hydrogen applications: advances in the field of medical therapy. *Med Gas Res*. 2023;13(3):99-107. doi:10.4103/2045-9912.344978
- Zheng ZG, Sun WZ, Hu JY, et al. Hydrogen/oxygen therapy for the treatment of an acute exacerbation of chronic obstructive pulmonary disease: results of a multicenter, randomized, double-blind, parallel-group controlled trial. *Respir Res*. 2021;22(1):149. doi:10.1186/s12931-021-01740-w
- Giovinazzo D, Bursac B, Shodjo JL, et al. Hydrogen sulfide is neuroprotective in Alzheimer's disease by sulphydrating GSK3 β and inhibiting Tau hyperphosphorylation. *Proc Natl Acad Sci USA*. 2021;118(4):e2017225118. doi:10.1073/pnas.2017225118
- Ramanathan D, Huang L, Wilson T, Boling W. Molecular hydrogen therapy for neurological diseases: a review of current evidence. *Med Gas Res*. 2023;13(3):94-98. doi:10.4103/2045-9912.359677
- Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro-oncol*. 2021;23(8):1231-1251. doi:10.1093/neuonc/noab106
- Saposnik G, Guzik AK, Reeves M, Ovbiagele B, Johnston SC. Stroke Prognostication using Age and NIH Stroke Scale: SPAN-100. *Neurology*. 2013;80(1):21-28. doi:10.1212/WNL.0b013e31827b1ace
- Song Y, Li C, Jin L, et al. R10K2 is negatively regulated by miR-4744 and promotes glioma cell migration/invasion through epithelial-mesenchymal transition. *J Cell Mol Med*. 2020;24(8):4494-4509. doi:10.1111/jcmm.15107
- Zhong H, Liu S, Cao F, et al. Dissecting Tumor Antigens and Immune Subtypes of Glioma to Develop mRNA Vaccine. *Front Immunol*. 2021;12:709986. doi:10.3389/fimmu.2021.709986
- Fuchs Q, Pierrelvein M, Messe M, et al. Hypoxia Inducible Factors' Signaling in Pediatric High-Grade Gliomas: Role, Modelization and Innovative Targeted Approaches. *Cancers (Basel)*. 2020;12(4):979. doi:10.3390/cancers12040979
- Huang JL, Liu WW, Sun XJ. Hydrogen inhalation improves mouse neurological outcomes after cerebral ischemia/reperfusion independent of anti-necroptosis. *Med Gas Res*. 2018;8(1):1-5. doi:10.4103/2045-9912.229596
- Huang JL, Liu WW, Manaenko A, Sun XJ, Mei QY, Hu Q. Hydrogen inhibits microglial activation and regulates microglial phenotype in a mouse middle cerebral artery occlusion model. *Med Gas Res*. 2019;9(3):127-132. doi:10.4103/2045-9912.266987
- Liu N, Yang C, Bai W, et al. CADM2 inhibits human glioma proliferation, migration and invasion. *Oncol Rep*. 2019;41(4):2273-2280. doi:10.3892/or.2019.7010
- Nawwar DA, Zaki HF, Sayed RH. Role of the NRG1/ErbB4 and PI3K/AKT/mTOR signaling pathways in the anti-psychotic effects of aripiprazole and sertindole in ketamine-induced schizophrenia-like behaviors in rats. *Inflammopharmacology*. 2022;30(5):1891-1907. doi:10.1007/s10787-022-01031-w
- Egal ESA, Jancenik D, Soares HP, Beswick EJ. Translational challenges in pancreatic neuroendocrine tumor immunotherapy. *Biochim Biophys Acta Rev Cancer*. 2021;1876(2):188640. doi:10.1016/j.bbcan.2021.188640
- Lin H, Du J, Tian Z, Yu Y, Cui Y, Xie K. Hydrogen Gas Treatment Improves Postoperative Delirium and Cognitive Dysfunction in Elderly Noncardiac Patients. *J Pers Med*. 2022;13(1):67. doi:10.3390/jpm13010067