



Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Molecular Hydrogen

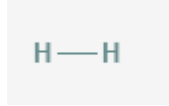
Evidence Summary

Hydrogen can protect against minor oxidative stress and inflammation-associated tissue damage, but cannot repair existing damage.

Neuroprotective Benefit: No cognitive benefits were seen in a clinical trial of MCI patients. Hydrogen may be clinically useful to mitigate oxidative damage associated with mild brain trauma when administered close to time of injury, but cannot repair existing damage or reverse neuropathology.

Aging and related health concerns: Hydrogen-rich water is protective against mild oxidative stress, has anti-inflammatory properties, and may regulate blood lipids and metabolism. May help protect the liver.

Safety: Hydrogen therapy has a strong safety profile, but hydrogen is a very mild antioxidant and has a short half-life, so chronic treatment is likely needed for therapeutic benefit.

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| <p>Availability: OTC as hydrogen-rich water</p> | <p>Dose: 1-3 ppm H₂ water (drink) daily 1-3% H₂ gas (inhalation) (in surgical setting). Based on clinical trials.</p> | <p>Chemical formula: H₂ MW: 2.016 g/mol</p> |
| <p>Half-life: ~2 hours after exposure to air (H₂ water)</p> | <p>BBB: Penetrant</p> |  |
| <p>Clinical trials: Parkinson's disease (n=18, 178), MCI (n=73), stroke (n=34, 38, 50), metabolic disorders (n=10, 20, 30, 68), UV-skin damage (n=6, 11), myopathy (n=12, 10), inflammatory autoimmune disease (n=20, 75), chemoprotection (n=136), hepatitis (n=60)</p> | <p>Observational studies: One study (n=309) revealed benefits in dialysis patients.</p> | <p>Source: Pubchem</p> |

What is it? Molecular hydrogen is a gas which can be used therapeutically to **help prevent oxidative stress damage**. Molecular hydrogen can be inhaled as a gas at concentrations of 1-3% (plus 20-30% oxygen, and nitrogen making up the remainder) or it can be dissolved into water or saline under pressure to create saturated (1.6 mg/L= 1.6 ppm= 0.8 mM) and supersaturated solutions (>1.6 ppm) [1]. Hydrogen gas inhalation has been tested for the mitigation of acute neurological impairment associated with stroke/heart attack or surgery. Hydrogen-rich water has been used to protect against oxidative stress and inflammation in a variety of conditions, including Parkinson's disease, diabetes and metabolic dysregulation, kidney disease, hepatitis rheumatoid arthritis, and chemotherapy. Hydrogen water bathing is also popular in Japan for the maintenance of youthful skin and preventing wrinkles. Molecular hydrogen acts as an antioxidant to reduce hydroxyl radicals and peroxynitrite (ONOO-), but does not neutralize potentially beneficial free radicals, such as nitric oxide. Hydrogen can also modulate miRNA expression and signal transduction pathways [2]. Some of the protective benefits appear to be related to induction of the Nrf2 antioxidant pathway and the fatty acid metabolism regulator FGF21. However, the exact mechanisms mediating its beneficial effects are not fully understood.



Neuroprotective Benefit: No cognitive benefits were seen in a clinical trial of MCI patients. Hydrogen may be clinically useful to mitigate oxidative damage associated with mild brain trauma when administered close to time of injury, but cannot repair existing damage or reverse neuropathology.

Types of evidence:

- 7 clinical trials (2 RCT for stroke, 1 non-controlled study for stroke, 2 RCT for Parkinson's disease, 1 RCT for MCI, 1 RCT in healthy volunteers)
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? Molecular hydrogen therapy may be helpful for **mitigating oxidative stress** and neurological impairment when administered close to the time of neurological damage, but offers only marginal benefits and is **most effective when used in combination with other antioxidant or neuroprotective agents**.

Preventing dementia progression: Potential minor/no benefit (Hydrogen-rich WATER)

In a one-year study of 73 patients with mild cognitive impairment (MCI) (>67 years old), drinking 300 mL of hydrogen-rich water per day did not significantly affect Alzheimer's Disease Assessment Scale -Cog (ADAS-cog) scores relative to those who drank placebo water [3]. Upon subset analysis, ApoE4 carriers, specifically, showed improvements on the total ADAS-cog score (P=0.037) and the word recall task score (P=0.036), but could represent a small sample size artifact. The hydrogen water was obtained from Blue Mercury, Inc, and contained at least 0.6mM (1.2 ppm) of hydrogen. It is likely that due to the rapid clearance of hydrogen from tissues, hydrogen water would need to be administered throughout the day to maintain antioxidant activity, and once daily administration is unlikely to produce clinically significant benefits.

Preclinical models

Hydrogen-rich water consumption has been shown to suppress oxidative stress, reduce neuronal loss, and provide modest cognition protecting benefits in models of neurodegenerative dementia. In mice expressing a mutant form of aldehyde dehydrogenase 2 (DAL101), hydrogen-rich water consumption decreased oxidative stress markers and mitigated the decline in cognitive impairment in aged mice (novel object recognition task) [3]. The hydrogen water was beneficial when administered beginning in youth (1-month-old) or middle age (8 months-old). In senescence accelerated mice (SAMP8), hydrogen-rich water consumption for 10 weeks, starting at 2 months old reduced oxidative stress markers (TBARS, TRAP) but only provided minor cognitive benefits [4]. Similarly, in a vascular dementia model, hydrogen-



rich water (>1.6 ppm H₂ for 28 days) suppressed the activation of autophagy signaling (FOXO and Atg7) toward levels detected in sham animals, but was only moderately effective in improving performance on spatial memory tasks [5]. These studies suggest that hydrogen water may be most effective at mitigating oxidative stress-associated cognitive decline when used continuously as a preventative measure, before the onset of pathology.

Improved mood: Potential minor benefit (Hydrogen-rich WATER)

In a small RCT (n=26), healthy volunteers (34.4 ± 9.9 years old) drank 600 mL of hydrogen-rich or placebo water every day for 4 weeks (300 mL 2x/day) [6]. The hydrogen water was stored in aluminum pouches supplied by the Melodian Corporation (Japan) and contained 0.8–1.2 ppm of hydrogen. The hydrogen-water group demonstrated a slight improvement on the psychophysiological K6 score for mood and anxiety levels from baseline compared to the placebo water group. However, the levels remained within the range of normal variation, thus the slight shift could have been related to personal experiences outside the realm of the study. No other significant changes were found with respect to autonomic function, blood parameters (hs-CRP, d-ROMs, BAP, and OSI) or cognitive function (mATMT task E). This suggests that hydrogen water has minimal effects on young healthy adults, which is not unexpected from an antioxidant therapy.

Prevention of stroke-related cognitive impairment: Potential benefit (Hydrogen GAS),

Unclear benefit (Hydrogen-rich saline/water)

Hydrogen therapy has been tested for its ability to protect against neurological damage in the context of stroke, either in relation to the antioxidant edavarone, or in conjunction with it. Based on the limited clinical studies conducted so far, hydrogen gas inhalation was more therapeutically beneficial than i.v. infusion of hydrogen-rich saline. In all studies, the stroke patients were still in the acute phase, and treatment was administered within 3-24 hours of the onset of symptoms for a total of 7 days.

In a small RCT, stroke patients (n=50) with mild to moderate neurological impairment based on the NIH Stroke Scale (NIHSS) (scores 2-6), were treated with 3% hydrogen gas (1-hour 2X/day) or i.v. edavarone [7]. Hydrogen-treated patients had lower stroke severity based on MRI (P<0.05) and NIHSS scores (P<0.01) at days 7 and 14, compared to edavarone-treated controls.

Patients with brainstem-localized stroke (n=34) receiving hydrogen-rich saline infusions and edavarone infusions 2X daily showed evidence of faster recovery on MRI measures (rDWI, rADC) than those receiving only edavarone, though the benefit was small, and of unclear clinical significance [8]. In a separate non-controlled study, patients with acute ischemic stroke (n=38) receiving tPA, edavarone



infusion, and hydrogen-rich saline infusion did not show a significant reduction in oxidative stress (MDA levels) or neurological improvement (based on NIHSS and the Barthel index) [9].

Preclinical models

Hydrogen therapy, particularly hydrogen gas treatment, has shown small benefits in reducing neurological disability associated with surgery, stress, stroke, and traumatic brain injury. The neuroprotective effects were related to the **mitigation of oxidative stress and inflammation**, and preservation of the blood brain barrier (BBB).

Hydrogen GAS

Hydrogen gas (2% H₂ for 3 hours) starting one hour after surgery was able to **reduce postoperative cognitive impairment in rats**, as measured by performance on a fear conditioning task [10]. This was associated with decreased levels of pro-inflammatory cytokines in the brain (IL-1 β , IL-6, TNF- α , HMGB1), less neuronal loss, and improved BBB integrity. Following mild blast induced traumatic brain injury in mice, hydrogen gas treatment (4% H₂ for 7 days) mitigated blast-induced vascular leakage and oxidative stress (ROS levels), and prevented induction of depression-like behaviors [11].

Hydrogen WATER/SALINE

Hydrogen-rich water has also been shown to be beneficial in animal models of brain injury, but may be less practical in a clinical setting. Hydrogen-rich water (1.2 ppm H₂) consumption ad lib was able to prevent stress induced declines in hippocampal proliferation and performance on spatial memory tasks, but did not prevent a stress-induced decline in body weight in mice [12]. Administration of hydrogen-rich water (i.p. 5 mL/kg) 5 min after traumatic brain injury, improved 7-day survival from 30% to 65% (P<0.05), **induced the Nrf2 antioxidant response**, and partially reduced neurological deficits [13]. In a stroke model, infusion of hydrogen-rich saline (1.6 ppm H₂) had a strong anti-inflammatory response involving the induction of T regulatory cells, but only slightly reduced the neurological severity score [14].

The efficacy of hydrogen therapy may depend on the nature and severity of the brain injury. In an intracerebral hemorrhage model, both hydrogen gas (1.3% for 3 hours) or hydrogen-rich saline (5 ml/kg i.v.) daily for 3 days was able to significantly reduce oxidative stress in the brain (8-OHdG), but neither had any meaningful effects on hematoma volume or functional outcome [15]. This suggests that hydrogen may be most beneficial when used as an adjunct to other therapies, for mild brain insults.



Human research to suggest benefits to patients with dementia:

Parkinson's disease: Unclear benefit (Hydrogen WATER)

The results from a small (n=18) RCT of patients with mild to moderate severity Parkinson's disease (PD), who were taking L-DOPA, suggested that hydrogen water may be beneficial in reducing disease severity [16]. Total Unified Parkinson's Disease Rating Scale (UPDRS) scores improved in the hydrogen water group (-5.7±8.4), whereas UPDRS scores in the placebo group worsened (4.1±9.2, P<0.05). In this study, patients drank 1L /day of saturated hydrogen water prepared by dissolving 0.8 mM H₂ using AqueraBlue (Ecomo International). A larger RCT (n=179) failed to find any significant differences between the hydrogen and placebo water groups, however, this finding is not unexpected, considering the 'hydrogen-rich water' used in the study did not contain appreciable levels of hydrogen [17]. A new trial would need to be conducted in order to validate or counter the results of the original study.

Preclinical models

Molecular hydrogen therapy has been found to be beneficial in animal models of PD, **by protecting mitochondria from oxidative stress damage**. Dopaminergic neuron-like SH-SY5Y cells pre-treated with hydrogen gas (50%) were protected from hydrogen peroxide-induced oxidative stress through the induction of the Nrf2 antioxidant signaling pathway [18]. The hydrogen treatment also increased the mitochondrial membrane potential and the cellular ATP level, which were accompanied by a decrease in the reduced glutathione level and an increase in the superoxide level. It should be noted that the **effects were transient** and wore off rapidly (within 6 hours) after hydrogen administration.

Pre-treatment with hydrogen water (0.8 ppm H₂) was beneficial in reducing oxidative stress (8-oxoG and 4-HNE) and protecting against the loss of dopaminergic neurons (8117 ± 589 vs 5927 ± 240) in the MPTP model [19; 20; 21]. It is unclear whether ghrelin is involved in this protective effect since the protective effects of hydrogen water were abolished in animals treated with a ghrelin receptor antagonist [20], but not in the ghrelin knockout [21]. There was a greater effect on oxidative stress reduction than on improving behavioral motor performance (ambulation score 54±4% vs. 40±4%, P<0.05), suggesting that hydrogen water may only provide minor benefits of clinical significance.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Alzheimer's Disease: Potential minor/no benefit based on rodent studies (Hydrogen-rich WATER)

In rodent models of AD, hydrogen treatment was capable of **reducing markers of oxidative stress and enhancing synaptic plasticity, but was ineffective in reducing Aβ or tau related pathology**. In APP/PS1



mice, daily hydrogen water (1.2 ppm H₂, Hanqing Biotech Co) for 3 months, enhanced antioxidants SOD and glutathione, increased the neurotrophic factor BDNF, reduced inflammation (IL-6, NLRP3), and improved cognitive function on spatial memory tasks, but had no effect on APP processing or clearance [22]. The beneficial effects were stronger in females. In an A β injection model, hydrogen-rich saline post-treatment (5 ml/kg, i.p. daily for 10 days, 1.2 ppm H₂) slightly enhanced hippocampal synaptic plasticity (LTP), reduced oxidative stress (MDA, 4-HNE), reduced inflammatory markers (IL-6, TNF- α), and improved performance on the Morris water maze [23; 24]. However, on all measures the hydrogen-treated animals were more like the untreated A β animals than the sham controls, indicating that the benefits were of statistical, but likely not clinical, significance.

Neuropathic pain: Potential minor benefit based on rodent studies (Hydrogen-rich WATER)

In a rat model of constriction-injury induced neuropathic pain, hydrogen-rich saline administered intrathecally (1.2 ppm H₂, 100 μ l/kg for 8 days) greatly reduced oxidative stress markers (protein carbonyls, MDA, MPO) and levels of BDNF, but only had a minor effect on pain in terms of reducing the sensitivity to painful stimuli (elevating pain threshold). Overall, hydrogen was more effective at reducing oxidative stress than providing clinical benefits [25].

Hearing loss: Potential minor benefit based on rodent studies [prevention] (Hydrogen-rich WATER)

In a guinea pig model of noise-induced hearing loss, pre-treatment with hydrogen-rich water (> 0.8 ppm, ad lib for 14 days), led to accelerated recovery for some frequencies, although the effect was quite modest [26].

Retina protection: Potential benefit based on rodent studies [prevention] (Hydrogen-rich eye drops)

Hydrogen rich saline was found to have retinal protective effects in male rats when administered at the time of injury. In an ischemia-reperfusion model, eye drops containing saturated hydrogen (1.6 ppm) were able to reduce neuronal apoptosis by 77% ($P < 0.0001$), and prevent retinal thinning by >70% ($102.6 \pm 3.8 \mu\text{m}$ vs $66.9 \pm 7.8 \mu\text{m}$, $P < 0.0001$) when administered during the ischemia-reperfusion event [27]. Protective effects were not detected in retinas that received the eye drops as a post-treatment. The protective effects of hydrogen-rich saline (i.p injection >1.2 ppm H₂) immediately following high-intensity light exposure have been attributed to its antioxidant capacity and ability to activate Sirt1, leading to the suppression of neuronal apoptosis [28]. These studies suggest that hydrogen-containing eye drops may help protect against oxidative stress-associated retinal damage, but will not repair damaged tissue.



APOE4 interactions: Unclear. The small study in MCI patients suggests that ApoE4 carriers may preferentially benefit from hydrogen-rich water [3], perhaps due to increased baseline oxidative stress in this population.

Aging and related health concerns: Hydrogen-rich water is protective against mild oxidative stress, has anti-inflammatory properties, and may regulate blood lipids and metabolism. May help protect the liver.

Types of evidence:

- 17 clinical trials (1 RCT myopathy, 1 RCT healthy volunteers (blood flow), 1 open-label myocardial infarction, 1 RCT dialysis patients, 1 RCT cancer patients undergoing chemotherapy, 1 RCT hepatitis, 1 RCT diabetes, 2 non-controlled studies metabolic syndrome, 1 RCT hypercholesterolemia, 2 clinical studies athletic performance, 1 RCT overweight women, 1 RCT rheumatoid arthritis, 1 RCT psoriasis, 2 studies on skin aging)
- 1 observational study (Dialysis patients)
- Numerous laboratory studies

Metabolic Regulation: Potential minor benefit (Hydrogen-rich WATER)

Hydrogen-rich water has been shown to be mildly beneficial in regulating oxidative stress and blood lipid profiles in certain populations of patients. However, the potential benefits/effects may be dependent on an individual's baseline characteristics in terms of level of oxidative stress, weight, and lipid profile. The effects appear to be related to the ability of molecular hydrogen to induce hepatic FGF21 and enhance PPAR- α mediated fatty acid metabolism.

Metabolic Syndrome:

Two small non-placebo-controlled trials of patients with potential metabolic syndrome (n=20) for 8 or 10 weeks found that consumption of hydrogen-rich water reduced markers of oxidative stress (reduced TBARS 43%, increased SOD 39%), and altered some blood lipids [29; 30]. In the 8-week study, consumption of 1.5-2L of hydrogen water prepared using a magnesium stick to contain 1.1-1.2 ppm H₂, lead to an 8% increase in HDL levels [29]. In the 10-week study, patients who drank 1L of hydrogen water also produced by a magnesium stick, but only containing 0.4-0.5 ppm H₂, **decreased total cholesterol, LDL-cholesterol, and apoB100 levels** [30]. ApoA1 levels were not affected. While these changes were relative to baseline, similar effects seen in a placebo-controlled trial suggest that they may be meaningful.



Overweight

In a very small RCT ([NCT02832219](#)) of overweight women (n=10, age 56.4 ± 12.6 years; body mass index (BMI) 29.3 ± 3.2 kg/m²), hydrogen therapy for 4 weeks reduced overall body fat percentage (by 3.2 vs. 0.9%, P = 0.05) and reduced serum triglycerides (by 21.3 vs. 6.5%; P = 0.04) compared to placebo [31]. However, there were no differences in overall weight, BMI, or other blood lipids. Since the statistics were not corrected for multiple comparisons, a larger study would be needed to confirm these results. This study used oral caplets (from SevenPoint2) containing hydrogen-generating minerals (46 mg Ca²⁺ and 40 mg Mg²⁺) supplying ~6 ppm of H₂ per day.

Hypercholesterolemia

In a small RCT in China, patients with hypercholesterolemia (n=68, 35-60 years old) drank 0.3L of hydrogen-rich water (1.0-1.2 ppm H₂, from Beijing Hydrovita Biotechnology Company) 3X per day for 10 weeks [32]. Hydrogen treatment increased the effective rate in **down-regulating plasma levels of total cholesterol** (47.06% vs 17.65%), **LDL cholesterol** (47.06% vs 23.53%), and **apoB100**.

Diabetes

A small RCT of patients with Type 2 diabetes (n=30, age 58.6 ± 4.7 years; BMI, 23.4 ± 3.5 kg/m²), found that hydrogen-rich water consumption **reduced oxidative stress (isoP) and LDL levels**, but had no significant effects on BMI, other blood lipids, glucose, insulin, or blood pressure measures [33]. Patients drank 0.3 L of hydrogen-rich water (from I'rom Pharmaceutical Co.) 3X daily for 8 weeks. It is unclear whether these minor changes are clinically relevant.

Preclinical

In high-fat diet and db/db models of diabetes, hydrogen-rich water reduced the level of serum triglycerides, decrease plasma glucose, and enhanced fatty acid metabolism [34; 35]. The effect of hydrogen therapy on gene expression is relatively minor. Based on a microarray study in the hepatic cells of diabetic mice, all gene changes were less than 2-fold following administration of hydrogen-rich water for 2 weeks [35]. The significantly changed pathways include fatty acid metabolism, steroid biosynthesis, peroxisome, and PPAR signaling. Hydrogen-rich water increases hepatic FGF21, which induces PGC-1 α (via regulation of Foxo1/Akt), which in turn activates PPAR- γ and enhances fatty acid metabolism [34; 35]. Similar induction of hepatic PPAR- γ , along with improved glucose tolerance, decreased inflammation and oxidative stress was also seen in response to hydrogen-rich saline (5 mL/kg 2x daily i.p. >1.2 ppm H₂) in a high fat and sugar diet model of non-alcoholic fatty liver disease [36].



Cardiovascular: Potential minor/no benefit

In preclinical models, hydrogen therapy has been shown to be protective against vascular cellular senescence, but this has **not translated into clinically meaningful effects** in human studies.

Myocardial infarction:

Patients with myocardial infarction treated with hydrogen gas (1.3% H₂ with 26% oxygen from Taiyo Nippon Sanso Corporation) during coronary angiography did not experience any significant improvement in terms of ventricular remodeling based on MRI compared to controls, although there were some improvements in surrogate markers, such as the ventricular stroke volume index (H₂: 9.2±7.1 mL/m²; control: -1.4±7.2 mL/m²; P=0.03) [37]. Based on these results, hydrogen therapy during surgery is likely not harmful, and may offer some benefits to patients, though further studies are needed to determine optimal concentration and duration.

Blood vessel function: No benefit (humans)/Minor benefit (preclinical)

Hydrogen-rich water (500 mL, 7ppm H₂, Hydrogen water 7.0 from Ecomo Int.) consumption did not significantly affect acute blood vessel function compared to placebo in terms of blood flow, blood pressure, or heart rate in healthy volunteers (n=34) [38]. These results are unsurprising, as these measures have also not been significantly affected by hydrogen therapy in other human studies.

Preclinical

In culture, hydrogen treatment can protect cells against: induction of oxidative stress (8-OHdG), loss of NAD⁺, impaired Sirt1 activity, and enhanced senescence-associated β-galactosidase [39; 40]. Hydrogen-rich water consumption also protected high-fat diet fed mice against induction of vascular endothelial cell senescence (p16INK4a and p21) [41]. Notably, hydrogen reduced macrophage infiltration, but had no effect on blood lipid profiles, suggesting that the protective effects were due to antioxidant and anti-inflammatory activity.

Muscle Function: Potential minor benefit

Although preclinical studies have suggested that molecular hydrogen may regulate mitochondrial homeostasis and function, hydrogen therapy **has not been able to significantly improve short-term muscle function** in patients with muscular disease or elite athletes.



Myopathy: No benefit

In open label and placebo-controlled clinical trials of patients with myopathy or muscular dystrophy, consumption of hydrogen-rich water (1L or 0.5L per day, 0.5 ppm H₂ from Blue Mercury Inc.) for 8 or 12 weeks led to no objective improvement or worsening of clinical symptoms [42].

Athletic performance: Minor benefit

Two small studies examined the effect of hydrogen-rich water consumption on exercise intensity by elite athletes. In one study (n=8) male soccer players drank three bottles of 0.5mL (Doctor SUIOSUI®, one the night before, and two the morning of testing) [43]. The hydrogen water reduced blood lactate levels during heavy exercise, but only led to a very minor improvement in peak torque during a knee extension exercise. In the other study (n=10) elite cyclists drank 2L of hydrogen-rich water (0.45 ppm H₂) per day for 2 weeks, and showed an improvement in peak power output relative to placebo [44]. In both studies, other measures including the fatigue index and mean power were not affected by the hydrogen water. This suggests that there is **no athletic performance-enhancing effect** of hydrogen-rich water.

Kidney disease: Potential benefit (Dialysis patients)

The incorporation of hydrogen into dialysis solution may help mitigate the decline in kidney function, and reduce the risk for premature mortality. These benefits may be related to the ability of molecular hydrogen to preserve Klotho levels in response to kidney damage.

In one small clinical trial, treatment of dialysis patients with H₂ containing peritoneal dialysis solution for 2 weeks lead to improvements in surrogate kidney function markers, including increased CA125 and mesothelin, suggestive of enhanced mesothelial regeneration [45]. A separate prospective observational study (n=309) found that patients receiving H₂ containing (30-80 ppb) dialysis solution were able to reduce their use of anti-hypertensive agents and had decreased all-cause mortality (Hazard ratio (HR):0.593, 95% Confidence Interval (CI), 0.384–0.916, P=0.019) over the 3-year observation period [46]. However, the difference in mortality could be related to patient-selection bias, as it was a non-randomized, non-blinded study.

Preclinical

In a mouse model of acute kidney injury, administration of hydrogen-rich saline (1.2 ppm H₂, 1 mg/kg i.p) was shown to significantly decrease fibrosis in the kidney and reduced levels of BUN (8.9 ± 0.6 vs. 9.9 ± 0.1 mmol/l) and creatine (51 ± 6.5 vs. 60 ± 5.8 μmol/l), which are markers of kidney dysfunction [47].



These improvements were associated with a protection of Klotho levels stemming from reduced methylation of the Klotho promoter.

Inflammation: Potential benefit (Hydrogen-rich WATER)

Molecular hydrogen has been shown to reduce inflammation in the context of two inflammatory autoimmune diseases and several preclinical models. Hydrogen-rich water **may be useful as a preventative measure to mitigate inflammation associated with daily-living**, while hydrogen gas may be useful in a hospital setting for mitigating inflammatory damage in the context of surgery or trauma.

Autoimmune disease

In a small RCT (n=20), patients with rheumatoid arthritis receiving a daily infusion of hydrogen-rich saline (1.6 ppm H₂) for 5 days showed improvement on the DAS28 joint inflammation score (decreased from 5.18 ± 1.16 to 3.74 ± 1.22, P<0.01) and decreased levels of pro-inflammatory cytokine IL-6 by 37.3 ± 62.0%, while placebo-treated patients showed worsening of inflammation [48]. The beneficial effects appear to have been mediated by the reduction of oxidative stress (8-OHdG) and MMP3 (by 19.2% ± 24.6%), which promotes joint inflammation.

In patients with psoriasis (n=74) unresponsive to concomitant therapy, daily hydrogen-water bathing for 8 weeks was beneficial for reducing severity of the skin-inflammation disease [49]. 24.4% of patients receiving hydrogen-water bathing achieved the end point of at least 75% improvement in Psoriasis Area Severity Index (PASI) score compared with 2.9% of patients of the control group (P_c = 0.022, Odds ratio (OR) = 0.094, 95%CI 0.011 - 0.777), and 56.1% achieved at least 50% improvement in PASI compared with 17.7% of the control group (P = 0.001, OR = 0.168, 95%CI 0.057 - 0.492).

These studies suggest that hydrogen-water can help mitigate inflammation, and may be beneficial when used in addition to standard-of-care anti-inflammatory drugs.

Preclinical

In rodent models, hydrogen therapy has been able to **protect against inflammation and oxidative stress-associated tissue damage**. In the context of LPS-induced inflammation, 6 hours of 2% hydrogen gas prevented fever (increased temperature), and increased the anti-inflammatory cytokine IL-10 [50], while pre-treatment with 80% saturated (1.28 ppm) hydrogen-water for 3 days reduced oxidative stress, suppressed liver damage, and prolonged survival (57.7% vs 26.9%, P<0.05) [51]. Notably, hydrogen-water post-treatment offered no protection against LPS-induced sepsis. Chronic consumption of hydrogen-rich water (Aquila Legend (AL-036A), conc >500 µg/L) starting at 4 months of age, prevented



age-induced increases in oxidative stress, inflammation and associated periodontal tissue damage [52]. Hydrogen-water (from MiZ Co. Ltd, 7 ppm H₂) treatment was also able to reduce oxidative stress levels and cigarette smoke-induced lung tissue damage in a rodent COPD model [53].

Skin aging: Potential benefit (Hydrogen-rich WATER)

Bathing with hydrogen-rich water is a beauty trend in Asia that claims to help protect against skin aging and the formation of wrinkles. A few clinical studies have been conducted which offer moderate support to this claim, although, the methods and measures used were highly unconventional.

UV skin damage

Hydrogen therapy was found to **protect against UV-induced skin damage** in young (age 24-47) and old (age 65-81) Korean volunteers [54]. Atomic hydrogen treatment for 2 hours **reduced the induction of inflammatory mediators** (MMP-1, COX-2, IL-6, IL-1 β) and increased procollagen expression in intrinsically aged skin. Hydrogen also reduced UV-induced skin redness (by 22.8 \pm 5.8%) and thymine-dimer formation (by 56.7 \pm 11.8%). Beneficial effects were not seen with less than 2 hours of treatment. The treatment involved the use of atomic hydrogen surrounded by water, applied with a device developed for topical application of the hydrogen water. Similarly, in cell culture, hydrogen-rich water (1.13 ppm) was able to improve skin cell (keratinocyte) viability (from 29% to 35%), prevent DNA damage (nuclear fragmentation and condensation), suppress ROS formation, and enhance collagen synthesis (2.03 fold) following UVA exposure [55].

Wrinkles

Wrinkle improvement was assessed via image analysis in six volunteers in Japan (aged 14-65) who bathed in hydrogen water containing 0.2–0.4 ppm of H₂ daily for 3 months [55]. The hydrogen water was produced by the electrolysis of tap-water using a hydrogen-water generating device (The Chugoku Electric manufacturing Co. Inc). In the four youngest participants (aged 14–46 years, average 31.5 \pm 11.4 years), the wrinkle-area ratio improved from 3041.7 \pm 151.6 to 1770.7 \pm 547.7 $\mu\text{m}^2/\text{mm}^2/100$ by the end of the study, but there were no improvements found in the two oldest participants (ages 55 and 65), and the study lacked a control group. This suggests that hydrogen therapy may be most useful as a preventative measure to protect against UVA damage, and is not effective for reversing prior skin damage. Additionally, due to increased levels of oxidative stress and/or a decline in the induction of endogenous antioxidant pathways, the protection offered by hydrogen may lessen with age.



Liver Protection: Potential benefit

Hydrogen-rich water has been shown to help protect against liver damage, most likely through induction of antioxidant pathways, possibly through regulation of FGF21.

Chemoprotection: Potential benefit (Hydrogen-rich WATER)

In an RCT of colorectal cancer patients treated with chemotherapy (mFOLFOX6) in China (n=136), consumption of hydrogen-rich water (0.25 L 4X) for 4 days starting 1 day prior to the chemotherapy session helped **protect against chemotherapy-induced liver damage** without negatively impacting the efficacy of the chemotherapy treatment [56]. Hydrogen treatment protected against elevations in liver enzymes (ALT, AST, IBIL) and reduced the hepatic damage mean rank (58.13 vs 81.63, P=0.00). The protection is expected to be mediated by the antioxidant activity of the hydrogen.

Hepatitis: Potential benefit (Hydrogen-rich WATER)

In a small RCT, patients with chronic hepatitis B (n=60) who drank 1.2-1.8 L of hydrogen-rich water prepared using a magnesium stick (1.1-1.3 ppm H₂) twice daily for 6 weeks experienced improvements in liver function based on liver enzyme levels (ALT: from 220.5 ± 95.0 to 54.8 ± 34.6, Tbil: from 34.9 ± 33.9 to 16.7 ± 9.6, ChE: from 6.7 ± 1.5 to 7.7 ± 1.4, P<0.05) [57]. These improvements were comparable to the comparator group receiving routine treatment. Those in the hydrogen group also showed reductions in oxidative stress through reductions in serum MDA and increases in levels of SOD and glutathione.

Safety: Hydrogen therapy has a strong safety profile, but hydrogen is a very mild antioxidant and has a short half-life, so chronic treatment is likely needed for therapeutic benefit.

Types of evidence:

- 24 clinical studies
- Numerous laboratory studies

Hydrogen therapy has an excellent safety profile. Animal studies involving life-long consumption of hydrogen-rich water have not reported any adverse effects on the animals. Hydrogen infused water has been granted [GRAS](#) (generally recognized as safe) status from the FDA. In the vast majority of clinical studies, hydrogen therapy was not associated with any adverse events. A few patients consuming hydrogen-rich water experienced mild gastrointestinal problems, but it could not be clearly tied to the



hydrogen itself [29]. The only reported severe adverse event was cardiac failure in a stroke patient with prior heart damage receiving an infusion of hydrogen-rich water, and was not related to the hydrogen itself, but rather, was attributed to the excess fluid [9]. The use of hydrogen gas in a clinical setting (1-3% H₂) is considered safe because hydrogen cannot burn or explode at concentrations under 4%.

Sources and dosing:

Based on clinical trials and preclinical studies, hydrogen gas inhalation at 1-3% may be beneficial for patients in the hospital undergoing surgery or experiencing acute trauma, while consumption of hydrogen-rich water at 1-3 ppm (1-3 mg/L = 0.5-1.5 mM) may be beneficial for protection against mild inflammatory and oxidative stress damage.

The hydrogen does not last long in the body. Following consumption of 0.5L of saturated hydrogen-rich water, the H₂ content of exhaled breath peaks after 10 minutes, and returns to baseline within 1 hour [58]. 59% was exhaled and 41% was consumed or lost. Additionally, hydrogen has a very short half-life when exposed to air (~2 hours), and when hydrogen-water is poured into a cup 2-5% of it is lost within the first 3 minutes. Consequently, in order to achieve the maximal protective benefits, one may need to consume hydrogen-rich water throughout the day, and consume the water shortly after it has been infused with hydrogen.

Hydrogen inhalation devices are available for home use, but there is not enough evidence to support them. There are several options for obtaining hydrogen-rich water, including in pre-packaged aluminum bottles or pouches, or it can be produced at home using hydrogen tablets, hydrogen sticks, water ionizers, or hydrogen infusion machines.

Research underway:

According to [Clinicaltrials.gov](https://clinicaltrials.gov), hydrogen-rich water is being tested for Steroid-refractory chronic graft-versus-host disease in a Phase 2 trial ([NCT02918188](https://clinicaltrials.gov/ct2/show/study/NCT02918188)) and Non-alcoholic fatty liver disease ([NCT03625362](https://clinicaltrials.gov/ct2/show/study/NCT03625362)). A hydrogen/oxygen nebulizer is being tested for Bronchiectasis ([NCT02765295](https://clinicaltrials.gov/ct2/show/study/NCT02765295)), and hydrogen saline infusion plus minocycline is being tested for ischemic stroke in a Phase2/3 trial ([NCT03320018](https://clinicaltrials.gov/ct2/show/study/NCT03320018)). Inhaled hydrogen gas (2% H₂) is also being tested for comatose out-of-hospital cardiac arrest survivors in the HYBRID II trial (UMIN 000019820) [60].



Search terms:

Pubmed, Google: Molecular Hydrogen OR Hydrogen-rich water OR Hydrogen-rich saline OR Hydrogen gas +

Dementia, Alzheimer's disease, Parkinson's disease, cognitive, neurodegeneration, neuroprotection, aging, lifespan, metabolism, diabetes, cardiovascular, inflammation, klotho, cancer, liver, skin, clinical trial, safety, meta-analysis, antioxidant

Websites visited for Molecular Hydrogen:

- Clinicaltrials.gov
- PubChem

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