antioxidants

Review

Redox-Mechanisms of Molecular Hydrogen Promote Healthful Longevity

Md. Habibur Rahman [1], Eun-Sook Jeong [1], Hae Sun You [2,*], Cheol-Su Kim [1] and Kyu-Jae Lee [1,*]

[1] Department of Convergence Medicine, Wonju College of Medicine, Yonsei University, Wonju 26426, Republic of Korea; cs-kim@yonsei.ac.kr (C.-S.K.)
[2] Department of Anesthesiology & Pain Medicine, Anam Hospital, Korea University College of Medicine, Seoul 02841, Republic of Korea
* Correspondence: sunhae67@korea.ac.kr (H.S.Y.); medbio@yonsei.ac.kr (K.-J.L.); Tel.: +82-2-10-5664-1160 (H.S.Y.); +82-33-741-0331 (K.-J.L.)

Abstract: Age-related diseases represent the largest threat to public health. Aging is a degenerative, systemic, multifactorial and progressive process, coupled with progressive loss of function and eventually leading to high mortality rates. Excessive levels of both pro- and anti-oxidant species qualify as oxidative stress (OS) and result in damage to molecules and cells. OS plays a crucial role in the development of age-related diseases. In fact, damage due to oxidation depends strongly on the inherited or acquired defects of the redox-mediated enzymes. Molecular hydrogen (H_2) has recently been reported to function as an anti-oxidant and anti-inflammatory agent for the treatment of several oxidative stress and aging-related diseases, including Alzheimer's, Parkinson's, cancer and osteoporosis. Additionally, H_2 promotes healthy aging, increases the number of good germs in the intestine that produce more intestinal hydrogen and reduces oxidative stress through its anti-oxidant and anti-inflammatory activities. This review focuses on the therapeutic role of H_2 in the treatment of neurological diseases. This review manuscript would be useful in knowing the role of H_2 in the redox mechanisms for promoting healthful longevity.

Keywords: aging; molecular hydrogen; reactive oxygen species; oxidative stress; therapeutic effects; redox mechanism; antioxidant; longevity

check for updates

Citation: Rahman, M.H.; Jeong, E.-S.; You, H.S.; Kim, C.-S.; Lee, K.-J. Redox-Mechanisms of Molecular Hydrogen Promote Healthful Longevity. *Antioxidants* **2023**, *12*, 988. https://doi.org/10.3390/antiox12050988

Academic Editor: Stanley Omaye

Received: 20 March 2023
Revised: 7 April 2023
Accepted: 21 April 2023
Published: 24 April 2023

Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Almost all major human diseases, including atherosclerosis, cancer, cardiovascular disease, metabolic syndrome, dementia, hypertension, and other neurodegenerative diseases have aging, a biosocial concern, as their underlying basis. To help older people maintain their health for as long as possible and to deal with an ever-increasing population, it is essential for healthcare providers to improve the prevention and control of age-related disorders. Diet is a useful and reasonably priced approach to helping seniors live longer and healthier lives [1]. Aging is seen mainly in protected settings as an evolving phenomenon that enables longevity in the wild beyond the normal lifespan. Aging is characterized by the accumulation of nucleic acids, proteins and lipids formed as a result of molecular damage. The free-radical rationale of aging has long been established among the theories explaining the aging process [1]. Aging occurs when several defense mechanisms fail to respond to the damage caused by reactive oxygen species (ROS), particularly in the mitochondria [2]. The key causes of aging-induced damages are the ineffectiveness and inability of the maintenance, repair, and turnover pathways [3]. Aging is related to the propensity for adverse water balance and makes older subjects more vulnerable to dehydration [4]. Water accounts for approximately half the weight of the human body and is necessary for human life and health [5,6]. There is growing evidence that even mild dehydration (determined to be 1–2% body mass loss due to fluid deficit) may lead to various age-related diseases, including arthritis, cataracts, osteoporosis, type 2 diabetes (T2D), hypertension

and Alzheimer's disease (AD) [7]. The type of water supplied as drinking water plays an important role in determining the safety and health issues because tap water quality continues to cause public concern [8,9], with some countries demanding the derogation from European water quality standards [10]. Groundwater is the Earth's most abundant and important freshwater resource [11]. Although dietary food components have been shown to improve cognitive function in older people [2], the effects of different nutritional compounds on other biomarkers of aging are much less understood. A dietary supplement, which has a direct impact on telomere metabolism, slows telomere decline and reduces aging and might expand life and improve health [3]. Nowadays, molecular hydrogen (H_2) can be used safely in the air at body temperature and at concentrations less than 4.7%. H_2 selectively quenches toxic ROS and has an anti-apoptotic, anti-oxidant, anti-inflammatory and anti-allergic impact, and it has become a new non-oxidant [12]. H_2 has recently been studied in preclinical and clinical studies under various conditions linked to oxidative and inflammatory stress, such as heart failure due to radiation, ischemia-reperfusion (I/R), myocardial infarction, brain infarction, heart storage and heart transplants [13]. Hydrogen-rich water (HRW) has recently come to light as a novel dietary beverage that may improve several aging-related characteristics in interventional trials, reducing different inflammatory responses that may help prevent programmed cell death [4], improve nutrient metabolism, repress wrinkle formation and increase other physiological activities [5]. Japanese centenarians were discovered to have higher levels of H_2 gas, which indicated that the intestinal production of H_2 gas may have conferred upon them longevity and reduced oxidative stress [6,7]. Increase in longevity was also reported by another study, stating intestinal production of H_2 gas as the apparent reason [8]. Cardiovascular and oncological disorders, the primary cause of morbidity and mortality worldwide, are more than 93% [14,15]. Pathological disorders, such as cardiac fibrosis, liver injury, neuronal diseases, and diabetes, causally involving free radicals have been investigated for the protective effects of H_2 [13]. Ischemia and subsequent heart reperfusion are other disorders in which a large number of tissue-damaging free radicals are formed [16]. One study revealed that drinking HRW for 6 months favorably affected different age-related features, including general pain, telomere strength and brain metabolism—indices that helped to increase anti-oxidant activity; HRW also enhanced sleep quality [9]. It has been reported that increased H_2 gas generation in the intestine depends on the presence of undigested carbohydrates and hydrogen-producing bacteria that are affected by some environmental conditions [10,11]. Over a thousand peer-reviewed study papers have been published thus far, demonstrating the wide-ranging interest in H_2 biomedical research.

In this review, we highlight the emerging role of H_2 in the prevention of age-related diseases, Alzheimer's, Parkinson's, cancer and osteoporosis, etc. This review manuscript would be useful in knowing the role of H_2 in the redox mechanisms for promoting healthful longevity.

2. The Mechanism of Action of H_2

H_2 suppresses the allergic [12] and inflammatory signaling pathways [13]. The anti-oxidative stress effect of H_2 was initially thought to be conferred upon by the direct elimination of hydroxyl radicals and peroxynitrite. Subsequent studies reported that H_2 activated the system nuclear factor erythroid 2–related factor 2 (Nrf2) [14,15] and its downstream heme oxygenase-1 (HO-1) [16]. Kawamura et al. (2013) suggested that H_2 in Nrf2-knockout mice did not relieve hyperoxic lung injury [17]. In addition, at the Medical H_2 Symposia in 2012 and 2013, Ohsawa et al. (2012) stated that H_2 enhanced mitochondrial functions and induced Nrf2 nuclear translocation. Furthermore, Matsumoto et al. reported that oral H_2 water intake increased ghrelin gastric expression and secretion and that the ghrelin receptor-antagonist and ghrelin secretion-antagonist abolished the neuroprotective effects of H_2 water [18]. At the 5th Medical H_2 Symposium in Nagoya, Japan, in 2015, Ohta et al. demonstrated that H_2 affects the free radical chain reaction of unsaturated fatty acids on the cell membrane and modifies the lipid peroxidation process [12]. This irregular

oxidation of the phospholipids at low levels of H_2 (at least 1.3%) has also been reported indicating that the biological effects of H_2 can be explained by the aberrant oxidation of the phospholipids upon exposure to H_2. Among the many molecules altered by H_2, most molecules were predicted to be "passengers" (downstream regulators), secondarily modulated by the pilot (master regulator) [12]. Proving the effect of H_2 in an in vitro setting would be the best way to classify the master regulator. While nothing is known about the lipid peroxidation analysis, the second master control body for H_2, next to the radical scavenging effect, may be the free chain response to lipid peroxidation [12]. Intracellular signal transduction systems are modulated by H_2, and the downstream gene expression is regulated to alleviate disease processes. Moreover, biologically active substances, which modulate signaling molecules, damage our bodies [19]. Inhaling a gas mixture containing H_2 (less than 4%) is effective in protecting against acute oxidative stress, according to one research study [20]. Another research study showed that it is safe and more practical to dissolve H_2 in water up to 0.8 mM under atmospheric pressure at room temperature [21]. H_2 also mitigates surgery-induced cognitive impairment [22]. Following 4% H_2 inhalation, the liver's H_2 concentration rose quickly and reached balance in about 5 min at 20 mol/L. HRW consumption resulted in sporadic availability to H_2. One study revealed that, even after 8 h, supersaturated H_2 in HRW (1000 mol/L) was maintained at a high content and was still above 600 mol/L [23].

Remarkably, the effects of saturated HW were virtually identical to those of H_2 concentrations as low as 0.08 ppm. (1.5 ppmH_2). Within 30 min of consuming HW, the majority of H_2 in the blood is invisible [24]. Another example would be that the amount of H_2 exposed to a 60-kg individual for 24 h as a 2% gas would be at least 104 times greater than what would be consumed by drinking saturated HW. However, HW is sometimes even more efficient than H_2 at achieving its goals [25]. Drinking H_2-rich water reduced fatigue in healthy people, according to one research [26]. Additionally, blood flow-dependent vasodilatory responses in people were enhanced by H_2-rich water [27]. In radiotherapy patients with liver cancer, it helped appetite and taste issues and reduced oxidative stress in the blood [28]. It was reported that H_2-rich water improved cognitive impairment [29]. In addition, drinking H_2-rich water improved neuropsychiatric and endocrine metabolic disorders in vivo study [29].

3. The Anti-Oxidative Effects of H_2 That Extend Life Span

Although H_2 has long been assumed to be an inert gas for living organisms, an animal study found that owing to its anti-oxidant properties, inhalation of H_2 gas reduced oxidative stress and stifled the brain damage caused by I/R injury. Among several proposed biological activities, the function of H_2 as an anti-oxidant has received the greatest attention. Furthermore, even after elimination of H_2 from the body, especially at low concentrations, its biological and anti-oxidant benefits continue to exist, implying that the mechanism may include modulation of anti-oxidant signaling rather than actual free radical scavenging [24]. H_2 is a specific scavenger of hydroxyl radical and peroxynitrite, powerful oxidants that interact without distinction with nucleic acids, lipids and proteins leading to DNA breakage, lipid peroxidation and protein inactivation [25,26]. In both human diseases and rodent models, H_2 administration reduces the expression of various oxidative stress markers, such as myeloperoxidase, malondialdehyde (MDA) and 8-hydroxy-desoxyguanosine (8-OHdG) [27,28]. In addition, H_2 can also minimize myeloperoxidase expression [29], decrease the function of mitochondrial oxidoreductase and stabilize the mitochondrial membrane potential to reduce the tissue damage caused by oxidative stress [30]. In 2016, researchers proposed that H_2 may reduce the ROS content depending on the endogenous glutathione peroxidase in *Ganoderma lucidum* [31]. Another study demonstrated that HRW intake affected different aging-related characteristics in aged people, such as extension of telomeres and improvement in DNA methylation [9]. Several studies have shown that H_2 is not cytotoxic even at high concentrations [32,33]. H_2-water consumption reduced the development of oxidative stress and avoided cognitive decline; therefore, it can play a role

in extending the life span [34]. In rats, H_2-water stopped the onset and spread of nigrostriatal degeneration [35]. Numerous studies have shown that H_2 reduces apoptosis during the treatment of septic injury in rodents [36,37]. Many studies have demonstrated that H_2 reduces ROS, increases anti-oxidant enzyme activity and inhibits pro-oxidant enzyme activity to mitigate the tissue damage caused by lipopolysaccharides [38].

4. The Anti-Inflammatory Effects of H_2

A study reported that H_2 breathing capacity could cure liver inflammation caused by parasites and was the first to demonstrate the anti-inflammatory properties of H_2 [39]. Hydrogen has been shown to exhibit anti-inflammatory activity in multiple injury models. H_2 is known to prevent the oxidative stress-induced inflammatory tissue damage by downregulating pro-inflammatory and inflammatory cytokines [40], such as interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α) [41]. H_2 can also drastically decrease NF-kB expression post-liver damage [42]. In animal models of allergic rhinitis or I/R cerebral injury, H_2 also has anti-inflammatory effects via upregulation of regulatory T cells (Tregs), which have an immunosuppressive effect and reduction in the expression of NF-kB [43]. Similarly, a study found that increasing the expression of the heat stress protein Hsp60, which is stimulated at high temperatures to protect itself, may successfully prevent acute pancreatitis in mice in the early stages through pre-inhalation of H_2 [44].

5. H_2 and Redox Mechanism of Oxidative Stress

The anti-oxidant effects of H_2 are primarily expressed in certain ways. First, H_2 was discovered to specifically eliminate hydroxyl radicals and peroxynitrite. H_2 can readily penetrate biofilms compared to standard anti-oxidants, such as superoxide dismutase (SOD), catalase and alpha-tocopherol, and does not influence the usual metabolic redox reaction, owing to its small molecular weight and anti-oxidant activity, which selectively affects only the strongest oxidant [45]. H_2 can also directly downregulate ROS or act as a gas-mediated signal regulator. Recently, a study [46] showed that H_2 in the urine, a marker of oxidative stress, can increase quickly and approximately to the same level as that induced by exercise. During cell adaptation, the production of exercise-induced ROS is necessary, and short-term ROS exposure can protect neurons from oxidative stress [47]. H_2 can mediate beneficial effects of the mitohormetic effectors of hormone processes on the body [46]. However, the anti-oxidative mechanism of H_2 may affect the free radical chain reaction of lipid peroxidation. Many studies have shown that H_2 protects cells by preventing the peroxidation of lipids and fatty acids [48]. According to wear-and-tear theory, aging is the slow deterioration of the body's cells and tissues due to oxidative stress, radiation exposure, exposure to toxins or other deteriorating processes [49]. Denham Harman [50] introduced the free radical theory of aging [51] in the 1950s. Numerous studies have shown that oxidative damage and ROS levels rise with aging [52], that reducing oxidative damage increases lifespan in a variety of model organisms (such as yeast, nematodes, fruit flies, mice, etc.) and that both higher ROS production and oxidative damage have detrimental effects on lifespan [53]. In addition, H_2 can reduce myeloperoxidase expression [46], decrease mitochondrial oxidoreductase activity [54] and stabilize mitochondrial membrane potential [55], thus enhancing tissue damage resulting from oxidative stress. The protective mechanism of H_2 in treating different age-related diseases is shown in Figure 1.

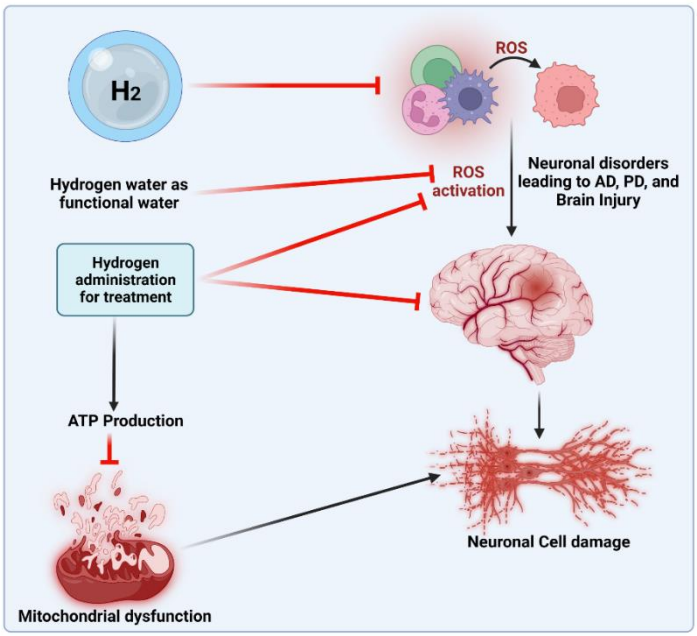

Figure 1. Protective effects of H_2 in treating different age-related diseases.

6. Age-Related Diseases and Redox Mechanisms

Over the last few decades, several models have been suggested to define the relationships and biopathways of aging [56]. The generally accepted theory is the "oxidative stress hypothesis", which advances and improves upon the free radical aging theory [57,58]. The oxidative stress theory underlines the crucial role of anti-oxidant defenders in the overall redox balance [59]. Ito et al. (2011) performed an open-label H_2-water analysis (1.0 L/day) for 12 weeks in 14 patients with muscle disorders, including muscular dystrophy and mitochondrial myopathies. This open-label research showed significant improvements in the lactate: pyruvate ratio, fasting blood glucose, serum matrix metalloproteinase-3 (MMP3) and triglyceride levels [60,61]. In mitochondrial myopathies, the lactate: pyruvate ratio, a responsive biomarker of a weakened mitochondrial electron transportation system, decreased by 28%. In addition, MMP3, the marker of inflammation, decreased by 27% in dermatomyositis. Then, for eight weeks, 22 people with dermatomyositis and mitochondrial myopathies were recruited for a randomized double-blind, placebo-controlled, crossover H_2-water or placebo dehydrogenated water (0.5 L/day) examination [60]. H_2 may provide an interpretation of multiple energy booster advantages seen in H_2 intervention studies that are not due to H_2 but which do not control the growth hormone secretagogue receptor (GHS-R1α) in tissues rich in mitochondria (including breast, skeletal muscle, myocardium, testis or liver) [62]. Mitochondria are the most important organelles responsible for energy production via oxidative phosphorylation, which is essential for cellular behavior and adenosine triphosphate (ATP) generation [63]. The formation and oxidation of ROS occurs under normal, healthy conditions in a regulated manner. Changes in the redox state and immune system dysregulation may result in increased systems inflammatory status during aging. Both processes induce inflammatory mediators to stimulate redox imbalances through oxidative stress [64]. The net effects of poor protection by anti-oxidant systems and aggression by reactive species, such as superoxide, hydroxyl radicals, peroxynitrite and H_2 peroxide, are most likely to cause age-related redox imbalances [65,66]. Functional shifts may be seen as pathophysiological connections to degenerative disorders correlated with age and unresolved chronic inflammation throughout aging [67]. The functional activities of certain proteins require certain prosthetic groups to be covalently connected to the polypeptide chain. These normally involve the conversion of inactive apoproteins into enzymes through complex organic molecules that, for example, engage in protein activity. In addition, some of the posttranslational changes influence biochemical processes through

different enzyme operations [68]. To improve homeostatic cell operation, the preservation of a healthy redox balance is essential for a physiological acid-base buffer system in the body. Modernization of the redox balance would greatly impact transcription and mobile signal pathways because most activations and reactions rely on reduction/oxidation processes [55]. Figure 2 shows the effects of oxidative stress and the associations between aging and age-related diseases [56].

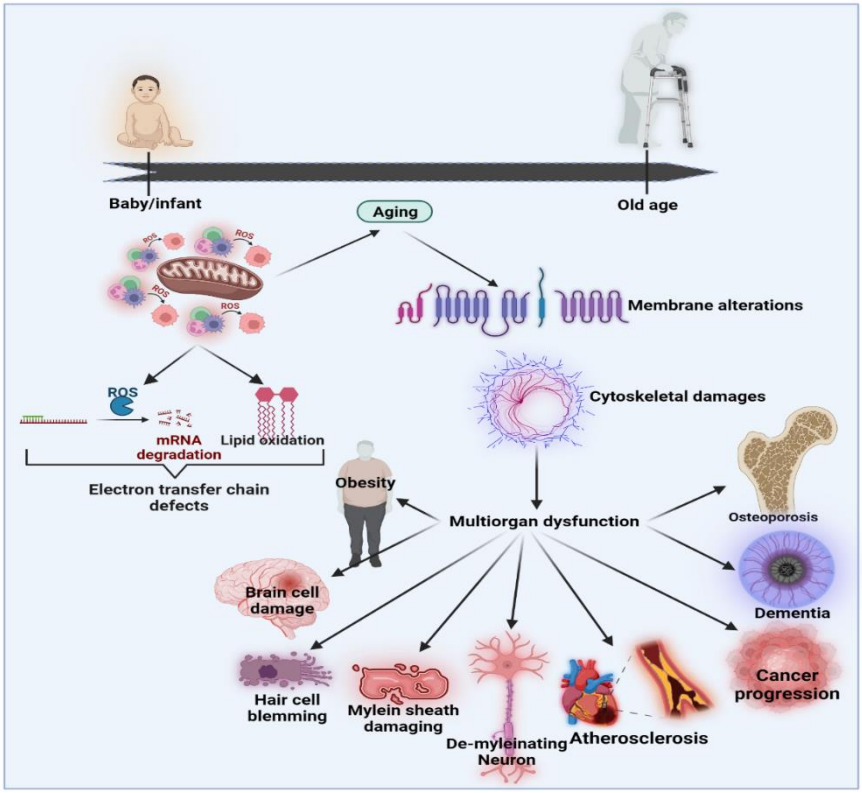

Figure 2. Effects of oxidative stress and the associations between aging and age-related diseases modified from [56].

7. Effects of Hydrogen Gas on Inflammatory Cytokines

Inflammatory cytokines affect a number of signals, which mediate an innate immune response and can aid dysregulation in many diseases, including cancer [69,70]. Common inflammatory cytokines include white blood cell-secreted ILs and macrophage-secreted TNFs, both of which have been closely correlated with cancer initiation and progression [71,72]; both ILs and TNFs can be blocked by H_2 gas [73]. In cancer patients, chemotherapy-induced inflammation not only causes adverse events [74,75], it also promotes cancer metastasis and treatment failure [76]. By regulating inflammation, H_2 gas may prevent tumor development, progression and decrease the side effects of chemotherapy and radiation therapy [73].

8. Hydrogen Gas Relieves Adverse Effects of Chemotherapy

The leading methods for treating cancer are chemotherapy and radiotherapy [77,78]. However, cancer patients are frequently fatigued, and their quality of life is compromised [79,80]. During cancer, the generation of ROS skyrockets and contributes to adverse outcomes, which lead to severe oxidative stress and inflammation [81]. Therefore, H_2 gas, on account of its anti-oxidant, anti-inflammatory and other cell-defensive characteristics, can be used to suppress these adverse effects. Doxorubicin, a fatal dilated cardiomyopathy and hepatotoxicity causing antibiotic, is also an important cancer antibiotic used in the treatment of various cancers [82,83]. An in vivo study showed that intraperitoneal injections of saline rich in H_2 decreased mortality and doxorubicin-led cardiovascular dysfunction. H_2 rich water has also been shown to exert renal protective effect against cisplatin-induced

nephrotoxicity in rats. Treatment with hydrogen rich water can significantly reverse the toxic effects, and it demonstrated a significantly higher rate of cross-relation by the removal of oxygen radicals [84,85]. In another study, the inhalation of H_2 gas (1% hydrogen in air) and the use of water rich in hydrogen (0.8 mM Hydrogen in water) reversed the body-weight loss and the mortality caused by cisplatin due to the antioxidant property of H_2 [73]. Similar findings were also reported by Meng et al. (2015), who showed that hydrogen-rich saline could mitigate follicle-stimulated hormone release, increase estrogen levels, improve follicle growth and reduce cisplatin-induced ovarian cortex damage [86]. In a previous study, cisplatin induced higher oxidation levels during therapy and suppressed the activity of antioxidant enzymes. In another study, a six-week intake of H_2 rich water in patients with malignant liver tumors minimized reactive oxygen metabolites and increased antioxidant activity [87]. Remarkably, the quality of life during radiotherapy was found to be greatly improved in the H_2-rich water consuming group in comparison to the placebo groups. Both groups showed similar tumor reactions to radiation therapy, indicating that the ingestion of water rich in H_2 decreased the oxidative stress due to radiation without undermining the antitumor effect of radiation therapy [87]. The various routes of administration, application and mechanisms of action of H_2 molecules in cancer treatment are listed in Table 1.

Table 1. Various routes of administration, application and mechanisms of action of H_2 in cancer treatment.

Route of Administration Category	Application Purpose	Function	Reference
H_2-rich saline	Cisplatin-induced damage to ovarian cortex	Stimulation of Nrf2 pathway	[86]
	Improvement of cardiac dysfunction caused by Doxorubicin	Inhibition of ROS, Inflammatory cytokines and apoptosis	[88]
H_2 Pd nanocrystals	synergistic impact with thermal therapy	Provocation of ROS	[89]
H_2 inhalation	Development of inhibition and improvement of survival rate in glioblastoma	Inhibition of cancer stem cell properties	[90]
	Reversal of renal toxicity due to cisplatin	Inhibition of apoptosis and ROS	[91]
	suppression of tumor growth	Arrest and induction of apoptosis	[92]
H_2-rich water	Improvement of mFOLFOX6 regimen-induced liver toxicity	Inhibition of oxidative stress	[93]
	44Gy electronic beam reversal of skin damage created	Inflammatory cytokines and oxidative stress reduction	[94]
	inhibition of cancer stem cells	Inhibition of angiogenesis	[92]
	Prevention of gefitinib-induced lung injury	Cytokines inflammatory and oxidative stress reduction	[95]
	Prevention of cisplatin-induced nephrotoxicity	Elimination of oxygen radicals	[73]
	Reversal of mortality and body-weight loss caused by cisplatin	Inhibition of ROS	[73]
	Incidence of tumors and suppression of growth	Inhibition of inflammatory cytokines and oxidative stress, Induction of apoptosis	[96]
	Improved quality of life	Action of antioxidants	[73]

9. Hydrogen and Intestinal Microbiome

In recent years, gut microbiota brain axis (GMBA) has been recommended as an important therapeutic target for neurological disorders affecting the central nervous system, such as AD [97,98]. Several mechanisms play a key role in preventing bacterial overgrowth in the proximal gut, including migrating motor complex, gastric acid, gut immune system and biliary secretions [99]. During fermentation, H_2 is produced in the large intestine; this

may be excreted through the breath and flatus or metabolized by the flora [100]. Moreover, the proportion of H_2 excreted in the breath varies depending on its production rate. In addition, the fermentation of lactulose generated more H_2 than that generated by resistant starch or pectin. HRW is a promising functional drink with positive effects on human health. Over the past decade, the publication of approximately 150 papers related to HRW in human trials, have shown multiple advantageous effects of HRW consumption [101]. According to a study, H_2 delivered by HRW could affect the gut microbiota, a community of 100 trillion microbial cells that can enhance human metabolism, immune function, nutrition and other physiological activities [102]. A Chinese research team's first investigation of HRW, released in January 2018, showed that HRW administration in an animal model affected radiation-induced small intestine toxicity [103]. Ikeda et al. investigated the effects of HRW treatment as preventive measure against bacterial translocation in a murine model of sepsis. Zheng et al. (2018) studied the intestinal microbiota response to 25 d oral administration of HRW and lactulose in female piglets fed *Fusarium* mycotoxin-contaminated maize [104]. The results of this study also showed that HRW treatment affected various intestinal segments, with fewer *Escherichia coli* and more *Bifidobacterium* in the HRW group than in the control group. A 15 d HRW therapy reportedly restored the intestinal barrier that had been damaged by permethrin and increased the amount of butyric acid in the feces. Moreover, a first-in-human trial supported HRW consumption and its positive impact on gut microbiota [105]. According to another study, HRW protected against inflammatory bowel disease (IBD) in an animal model [106]. Following oral administration, HRW demonstrated positive effects by decreasing epithelial cell apoptosis in the small intestine, maintaining the intestinal barrier and tight junctions and restoring the protein expression and distribution of CLDN3 in the small intestine of female piglets fed food contaminated with *Fusarium* toxins [107]. HRW intake improved glucose tolerance that might be decreased in *Bacteroides* levels [108]. Another clinical study reported that drinking alkaline electrolyzed water for two weeks increased *Bifidobacterium* in healthy volunteers [109]. Jin et al. reported that H_2 released from the gut by hydrogen nanocapsules could induce an abundance of *Akkermansia muciniphila* and reduce metabolic dysfunction-associated fatty liver diseases [110]. However, the gut microbiota may be the major contributors of the biological effects of exogenous hydrogen consumption. Another study revealed that H_2 saline therapy modulated the abundance of *Bacteroides* and *Lactobacillus* in feces, which might account for the increase in lipid metabolism in mice fed a high fat diet [111]. A previous study reported that acute exercise augments breathing of H_2 after the lactulose test [112], and the results, corroborated through a recent gut-exercise, implied that colonic bacteria are an endogenous H_2 source during exercise [113]. The degree of obesity and leanness has a contributory impact on the gut microbiota, and this was observed in the gut flora of bariatric surgery patients [114]. Therefore, HRW might become an upcoming functional water drink that could enhance and adjust endogenous gut microbiota; however, it should be administered as an experimental drink and not suggested for the general population. Interestingly, the function and composition of the intestinal microbiota that routinely produces H_2 gas fluctuate throughout the day, and the quantity of H_2 produced varies depending on the person and time of day. One study revealed H_2S as a new endogenous factor for regulating the circadian clock [115].

10. Protective Effects of H_2 on the Cardiovascular System

The essential gas signaling molecule nitric oxide (NO) can usually be recognized for inducing vasodilatation, reducing the production of superoxide, decreasing inflammation and improving the production of mitochondrial energy. I/R lung damage reduces by ventilation during warm ischemia, ex-vivo infusion and post-transplantation with NO nonheart-beating lung grafts [116]. Carbon monoxide (CO) has a high affinity for the heme prosthetic community in laboratory studies and has also been shown to enhance the graft function in combination with preservation solutions [117,118]. Ohsawa et al. (2008) found that oral H_2 water prevented the development of atherosclerosis in an apolipoprotein E

knockout mouse model [119]. H_2S is known to induce smooth muscle relaxation, apoptosis, inflammatory response regulation and oxidative stress relief [120]. Although not a gas transmitter, H_2 is now called a gaseous signal molecule [118]. The advantages are similar to those of NO, CO and H_2 sulfide (H_2S), both physiologically and therapeutically [121,122]. Myocardial damage to the mouse caused by radiation was reduced by H_2 water [123]. Inhalation of H_2 in a rat model of post-cardiac arrest syndrome also improved survival and functional performance [124]. Researchers have concluded that improved cold-rat ischemia-reperfusion injuries and frequent drinking of H_2 water could protect beneficiaries from inflammatory heart and aortic allograft degradation [125]. H_2 is beneficial in terms of toxicity; it shows no cytotoxicity even at high concentrations. For inhalation, high levels of H_2 gas are defined as high-pressure. In deep-diving gas blends, H_2 gas is used to prevent the oxidation and thrombosis of arterial gas [126]. Given that H_2 is an inert and nonfunctional gas in the body, it is understandable that it has no toxic effects. As described above, the inhalation of 1–4% H_2 gas is highly effective [20]. Basic and clinical research over the past ten years has shown that H_2 is a major regulatory pathophysiological factor with anti-oxidative, anti-inflammatory and anti-apoptotic effects on cells and organs [127]. Myocardial transmission releases H_2 through inhalation or injection with [128], injection with H_2-rich saline [129], drinking H_2-rich water [127], taking an H_2-rich bath and increasing the development of intestinal H_2 through bacteria [130]. Table 2 summarizes the effects of H_2 on age-related clinical studies in human diseases.

Table 2. Effect of H_2 on age-related clinical studies in human diseases.

Authors	Category of Disease	Sample Size	Route of Administration	Application	Reference
Sakai et al.	Vascular feature of the endothelium	34	Water	Vasomotor activity	[131]
Ostojic et al.	Metabolic acidosis caused by exercise	52	Water	Increased alkalinity of blood in men who are physically active	[132]
Kajiyama et al.	Type II diabetes mellitus	30	Water	Improvement in LDL-cholesterol fractions and glucose tolerance test	[133]
Nakao et al.	Metabolic Syndrome	20	Water	Enhancement of oxidative stress urinary markers	[125]
Yoritaka et al.	PD	17	Water	Improvement of Total Unified PD	[134]
Nakayama et al.	Chronic renal insufficiency	29	Dialysis	Improved markers for inflammation and oxidative stress	[61]
Kang et al.	Adverse effects of radiation-induced liver tumors	49	Water	Improved quality of life ratings during radiotherapy	[87]
Xia et al.	Chronic hepatitis B	60	Water	Reduced oxidative stress	[135]
Ishibashi et al.	Rheumatoid arthritis	20	Water	Improved rheumatoid arthritis activity score	[136]
Aoki et al.	Fatigue in the muscles	10	Water	Improvement in muscle tiredness among young athletes	[137]
Nagatani et al.	Ischemia of the cerebrum	38	Intravenous infusion	Decrease in a subset of patients of MDA-LDL, an oxidative stress serum marker	[138]
Li et al.	Skin pressure ulcer	22	Water	Reduction in wound size and early recovery from skin pressure ulcers	[139]
Ostojic et al.	Soft tissue damage linked to sports	36	H_2-rich tablets and topical H_2 packs	Decrease in the viscosity of plasma	[140]

11. Therapeutic Effects of H_2 on Parkinson's Disease (PD) and Co-Relation with Intestinal Microbiome

PD of the substantia nigra with extrapyramidal symptoms is a disorder induced by the degeneration and loss of dopamine-producing cells. However, aggregation of α-synuclein in the intestinal mucosa may be caused by oxidative stress produced by macrophages in the luminal wall due to a hyperpermeable intestinal wall, where the intestinal microbiota significantly affects hyperpermeability-induced oxidative stress that may be linked to synuclein pathology in the enteric nervous system in PD [141]. In a study the breath H_2 concentrations were analyzed in 28 healthy controls and 37 PD patients after consumption of 6 g lactulose [142].

The clinical manifestation of PD is associated with oxidative stress [143]. In addition, studies have been conducted on the involvement of PD with mitochondrial dysfunction [12,143]. Both animal PD models and clinical trials have reported the effects of H_2 on PD [12]. Oxidative stress was inhibited in the nigrostriatal pathway with the intake of H_2-rich- drinking water, and the loss of dopamine cells was reduced. These findings indicated that consuming water rich in H_2 may influence the onset of PD [134]. A randomized double-blind study found that 48 weeks of intake of H_2-rich water (1000 mL/day) substantially increased the overall Unified PD Rating Scale (UPDRS) score for levodopa-treated PD patients. A double-blind, multicenter H_2 water study is currently underway [144]. According to one study, intestinal permeability increased in PD, and its level favorably correlated with intestinal staining for *Escherichia coli*, nitrotyrosine and other proteins subjected to protein oxidation [145]. However, another study demonstrated that decreased H_2 production by the intestinal microbiota is associated with the development and progression of PD [146]. One study also showed how much H_2 was produced by the seven bacterial strains representing the main bacterial species and groups in the intestine [146]. According to Scheperjans et al., on analysis of the 16S ribosomal RNA genes of the gut microbiota in 72 PD patients and 72 controls, the degree of postural instability was favorably correlated with the relative abundance of Enterobacteriaceae [147].

12. Therapeutic and Preventive Effect of H_2 on AD and Co-Relation with Intestinal Microbiome

The term "gut microbiota" refers to the microbial community that inhabits the gastrointestinal system and may include bacteria, fungi, and protozoans that coexist harmoniously within our intestine [148,149]. This microbiota regulates host homeostasis and many diseases and may play a significant pathogenic role in neurodegenerative disorders, including AD [150,151]. The therapeutic and preventive applications of H_2 have been confirmed in more animal and human studies, such as in neurodegeneration [152], inflammation [153], and I/R injuries [154]. The gut microbiota, however, has recently been shown to play a significant role in the development of host immunity, in controlling gut endocrine functions and in controlling other neurological signaling [155]. Moreover, the gut microbiome and H_2 consumption relationship is quite limited. One study found that HRW could improve the structural integrity of the butyrate-producing bacteria in the gut, along with the clinical symptoms of disturbed gut microbiota [156]. Another study demonstrated that HRW intake induced a significant increase in the relative abundance of *Lactobacillus* and a decrease in *Bacteroides* and *Bifidobacterium*. Additionally, because the gut microbiota is important for both health and disease, the impact of HRW on the gut microbiota may greatly improve these diseases. One study revealed that patients with AD showed an increased proinflammatory endobacteria species of *Escherichia coli* and decreased anti-inflammatory taxon, such as *E. rectale*, which may result in microbiota modification, amyloidosis and peripheral inflammation [152].

The deposition of amyloid beta (Aβ) protein outside nerve cells and the accumulated tau phosphorylated protein inside nerve cells are characteristic of the pathology of Aβ protein deposition. Oxidative stress and neuroinflammation have in recent years been documented to be correlated with AD [157]. To date, studies have focused on the role

of oxidative stress in the brain parenchyma [158,159]. Aβ protein accumulation is highly linked to the absence of Aβ clearance, which is intricately linked to AD's pathogenesis [160,161]. It is understood that Aβ protein removal requires low-density lipoprotein receptor 1 (LRP1). The onset of AD involves LRP dysfunction due to oxidative stress and neuroinflammation [161]. The initiation and progression of AD can be prevented by regulating oxidative stress and neuroinflammation. The effect of H_2 on AD prevention has been investigated in several studies [162]. A rat AD model has been identified in the hippocampus and cerebral cortex; herein, memory was enhanced using H_2-rich saline (5 mL/kg, i.p., daily) as an inhibitor of oxidative stress, cytokine development and NF-κB production [163]. H_2-rich water consumption has also been reported to prevent changes in the brain age and decline in spatial memory [164]. Moreover, H_2 water also exhibited the potential to control dementia at the mild cognitive impairment stage of AD [165]. Safety is a primary concern with respect to H_2 transportation, storage and administration. H_2 is flammable only at temperatures greater than 527 °C and explodes by rapid chain reaction with oxygen in the H_2 concentration range of 4–75% (vol/vol) [166,167]. Because inhaling 1–4% H_2 has demonstrated great efficacy in medical applications, the use of H_2 at such low concentrations has been deemed feasible and safe [168].

13. Effects of H_2 in Heart Diseases

Ventricular remodeling contributes to several molecular and cellular pathways in response to pathophysiological stimuli, such as myocardial I/R, hypertension or neurohumoral triggers [169,170]. Endothelin-1 (ET-1) innovations are increased, and Ang II, catecholamines and proinflammatory cytokines activate the receptors and downstream signaling events of their cognates, leading to apoptosis or hypertrophy [169,170]. Until the coronary blood flow was restored in the occluded region, the inhaled H_2 was rapidly brought into the ischemic myocardial system, and 2% H_2 was inhaled at the time of ischemia and persisted for 60 min after reperfusion decreased the duration of infarction [169]. In H_2, for example, the myocardial I/R injury infarction scale is reduced by NO also [169]. In addition to H_2 inhalation, intraperitoneal saline injection has been shown to reduce the effects of myocardial I/R and also improve heart activity through its anti-oxidant, anti-apoptotic and anti-inflammatory effects [171]. Inhalation of H_2 at low levels in the C57BL/6J left ventricular myocardial mice (1.3 vol/100 vol) decreased transient dyslipidemia caused by hypoxia, oxidative stress and preventive cardiomyocyte and perivascular fibrosis [145]. Neurohumoral activation, such as β-adrenoceptor and Ang II enhancement, not only results in hypertension, but also leads to ischemic heart diseases as well as sleep apnea syndrome [172]. Direct inhibition of NADPH oxidase expression and decrease in mitochondrial damage leads to ROS inhibition and consequent degradation of the downstream signaling ERK1/2, p38, and JNK, leading to the protective effect of H_2 [173]. In addition, rats are protected by anti-oxidants and anti-inflammatory activities, such as high-dose ISO-induced acute myocardial infarctions [173]. H_2-rich saline spontaneously attenuates left ventricular hypertrophy in hypertensive rats by suppressing the inflammatory mechanisms, minimizing oxidative stress, maintaining mitochondrial production, and locally inhibiting Ang II in the left ventricle [174].

14. Conclusions

H_2 is readily available because it has minimal harmful effects and is highly effective against nearly all pathogenic states related to oxidative stress and inflammation. H_2 has great potential for protective applications in many diseases, owing to its efficacy. Additionally, H_2 gas has proven to be safe in numerous studies, which is crucial for clinical experiments. H_2 controls aging primarily through anti-inflammatory and anti-oxidative properties. The treatment of numerous age-related diseases is possible with H_2 as promising therapeutic and protective options in the future. In addition, H_2-based therapies are anticipated to be novel and revolutionary methods for the prevention of age-related diseases, thereby promoting helpful longevity.

Author Contributions: Conceptualization, K.-J.L.; software, M.H.R.; validation, M.H.R.; writing—original draft preparation, M.H.R., E.-S.J., H.S.Y. and C.-S.K.; writing—review and editing, E.-S.J.; preparation of tables and figures, M.H.R.; visualization, C.-S.K. and H.S.Y.; supervision, K.-J.L. and C.-S.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

8-OHdG	8-hydroxy-desoxyguanosine
AD	Alzheimer's disease
ATP	Adenosine triphosphate
Aβ	Amyloid beta
BUN	Blood urea nitrogen
DNA	Deoxyribonucleic acid
ET-1	Endothelin-1
GHSR1-α	Growth hormone secretagogue receptor
GSC	Glioma stem-like cell
GSH	Glutathione
H_2	Molecular Hydrogen
HRW	Hydrogen rich water
H_2S	Hydrogen sulfide
HMGB-1	High-mobility group box 1
HO-1	Heme oxygenase-1
IL	Interleukin
JNK	c-Jun N-terminal kinase
LRP1	Low-density lipoprotein receptor 1
MDA	Malondialdehyde
MMP3	Matrix metalloproteinase 3
MS	Metabolic syndrome
NO	Nitric oxide
Nrf2	Nuclear factor erythroid 2–related factor 2
PD	Parkinson's disease
ROS	Reactive oxygen species
SOD	Superoxide dismutase
T2D	Type 2 diabetes
TNF-α	Tumor necrosis factor-α

References

1. Calder, P.C.; Carding, S.R.; Christopher, G.; Kuh, D.; Langley-Evans, S.C.; McNulty, H. A Holistic Approach to Healthy Ageing: How Can People Live Longer, Healthier Lives? *J. Hum. Nutr. Diet.* **2018**, *31*, 439–450. [CrossRef]
2. Ozawa, H.; Miyazawa, T.; Miyazawa, T. Effects of Dietary Food Components on Cognitive Functions in Older Adults. *Nutrients* **2021**, *13*, 2804. [CrossRef] [PubMed]
3. Vidaček, N.Š.; Nanić, L.; Ravlić, S.; Sopta, M.; Gerić, M.; Gajski, G.; Garaj-Vrhovac, V.; Rubelj, I. Telomeres, Nutrition, and Longevity: Can We Really Navigate Our Aging? *J. Gerontol.-Ser. A Biol. Sci. Med. Sci.* **2018**, *73*, 39–47. [CrossRef]
4. Sim, M.; Kim, C.S.; Shon, W.J.; Lee, Y.K.; Choi, E.Y.; Shin, D.M. Hydrogen-Rich Water Reduces Inflammatory Responses and Prevents Apoptosis of Peripheral Blood Cells in Healthy Adults: A Randomized, Double-Blind, Controlled Trial. *Sci. Rep.* **2020**, *10*, 12130. [CrossRef] [PubMed]
5. Taniguchi-Fukatsu, A.; Yamanaka-Okumura, H.; Naniwa-Kuroki, Y.; Nishida, Y.; Yamamoto, H.; Taketani, Y.; Takeda, E. Natto and Viscous Vegetables in a Japanese-Style Breakfast Improved Insulin Sensitivity, Lipid Metabolism and Oxidative Stress in Overweight Subjects with Impaired Glucose Tolerance. *Br. J. Nutr.* **2012**, *107*, 1184–1191. [CrossRef] [PubMed]
6. Mizuno, K.; Sasaki, A.; Ebisu, K.; Tajima, K.; Kajimoto, O.; Nojima, J.; Kuratsune, H.; Hori, H.; Watanabe, Y. Hydrogen-Rich Water for Improvements of Mood, Anxiety, and Autonomic Nerve Function in Daily Life. *Med. Gas Res.* **2017**, *7*, 247–255.
7. Hehemann, J.H.; Correc, G.; Barbeyron, T.; Helbert, W.; Czjzek, M.; Michel, G. Transfer of Carbohydrate-Active Enzymes from Marine Bacteria to Japanese Gut Microbiota. *Nature* **2010**, *464*, 908–912. [CrossRef]
8. Aoki, Y. Antioxidant Bioactivity of Molecular Hydrogen Gas Produced by Intestinal Bacteria with Undigested Carbohydrates. *Acta Sci. Nutr. Health* **2018**, *2*, 23–25.

9. Zanini, D.; Todorovic, N.; Korovljev, D.; Stajer, V.; Ostojic, J.; Purac, J.; Kojic, D.; Vukasinovic, E.; Djordjievski, S.; Sopic, M.; et al. The Effects of 6-Month Hydrogen-Rich Water Intake on Molecular and Phenotypic Biomarkers of Aging in Older Adults Aged 70 Years and over: A Randomized Controlled Pilot Trial. *Exp. Gerontol.* **2021**, *155*, 111574. [CrossRef]
10. Turnbaugh, P.J.; Hamady, M.; Yatsunenko, T.; Cantarel, B.L.; Duncan, A.; Ley, R.E.; Sogin, M.L.; Jones, W.J.; Roe, B.A.; Affourtit, J.P.; et al. A Core Gut Microbiome in Obese and Lean Twins. *Nature* **2009**, *457*, 480–484. [CrossRef] [PubMed]
11. Tehrani, A.B.; Nezami, B.G.; Gewirtz, A.; Srinivasan, S. Obesity and Its Associated Disease: A Role for Microbiota? *Neurogastroenterol. Motil.* **2012**, *24*, 305–311. [CrossRef]
12. Ichihara, M.; Sobue, S.; Ito, M.; Ito, M.; Hirayama, M.; Ohno, K. Beneficial Biological Effects and the Underlying Mechanisms of Molecular Hydrogen—Comprehensive Review of 321 Original Articles. *Med. Gas Res.* **2015**, *5*, 12. [CrossRef] [PubMed]
13. Itoh, T.; Hamada, N.; Terazawa, R.; Ito, M.; Ohno, K.; Ichihara, M.; Nozawa, Y.; Ito, M. Molecular Hydrogen Inhibits Lipopolysaccharide/Interferon γ-Induced Nitric Oxide Production through Modulation of Signal Transduction in Macrophages. *Biochem. Biophys. Res. Commun.* **2011**, *411*, 143–149. [CrossRef]
14. Song, G.; Zong, C.; Zhang, Z.; Yu, Y.; Yao, S.; Jiao, P.; Tian, H.; Zhai, L.; Zhao, H.; Tian, S.; et al. Molecular Hydrogen Stabilizes Atherosclerotic Plaque in Low-Density Lipoprotein Receptor-Knockout Mice. *Free Radic. Biol. Med.* **2015**, *87*, 58–68. [CrossRef] [PubMed]
15. Li, Y.; Xie, K.; Chen, H.; Wang, G.; Yu, Y. Hydrogen Gas Inhibits High-Mobility Group Box 1 Release in Septic Mice by Upregulation of Heme Oxygenase 1. *J. Surg. Res.* **2015**, *196*, 136–148. [CrossRef]
16. Stohs, S.J. The Role of Free Radicals in Toxicity and Disease. *J. Basic Clin. Physiol. Pharm.* **1995**, *6*, 205–228. [CrossRef] [PubMed]
17. Kawamura, T.; Wakabayashi, N.; Shigemura, N.; Huang, C.S.; Masutani, K.; Tanaka, Y.; Noda, K.; Peng, X.; Takahashi, T.; Billiar, T.R.; et al. Hydrogen Gas Reduces Hyperoxic Lung Injury via the Nrf2 Pathway in Vivo. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2013**, *304*, L646–L656. [CrossRef]
18. Matsumoto, A.; Yamafuji, M.; Tachibana, T.; Nakabeppu, Y.; Noda, M.; Nakaya, H. Oral "hydrogen Water" Induces Neuroprotective Ghrelin Secretion in Mice. *Sci. Rep.* **2013**, *3*, 3273. [CrossRef]
19. Sbodio, J.I.; Snyder, S.H.; Paul, B.D. Redox Mechanisms in Neurodegeneration: From Disease Outcomes to Therapeutic Opportunities. *Antioxid. Redox Signal.* **2019**, *30*, 1450–1499. [CrossRef]
20. Ohsawa, I.; Ishikawa, M.; Takahashi, K.; Watanabe, M.; Nishimaki, K.; Yamagata, K.; Katsura, K.I.; Katayama, Y.; Asoh, S.; Ohta, S. Hydrogen Acts as a Therapeutic Antioxidant by Selectively Reducing Cytotoxic Oxygen Radicals. *Nat. Med.* **2007**, *13*, 688–694. [CrossRef]
21. Qian, L.; Shen, J.; Chuai, Y.; Cai, J. Hydrogen as a New Class of Radioprotective Agent. *Int. J. Biol. Sci.* **2013**, *9*, 887–894. [CrossRef] [PubMed]
22. Fujita, K.; Seike, T.; Yutsudo, N.; Ohno, M.; Yamada, H.; Yamaguchi, H.; Sakumi, K.; Yamakawa, Y.; Kido, M.A.; Takaki, A.; et al. Hydrogen in Drinking Water Reduces Dopaminergic Neuronal Loss in the 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine Mouse Model of Parkinson's Disease. *PLoS ONE* **2009**, *4*, e7247. [CrossRef]
23. Liu, B.; Xie, Y.; Chen, J.; Xue, J.; Zhang, X.; Zhao, M.; Jia, X.; Wang, Y.; Qin, S. Protective Effect of Molecular Hydrogen Following Different Routes of Administration on D-Galactose-Induced Aging Mice. *J. Inflamm. Res.* **2021**, *14*, 5541–5550. [CrossRef] [PubMed]
24. Dixon, B.J.; Tang, J.; Zhang, J.H. The Evolution of Molecular Hydrogen: A Noteworthy Potential Therapy with Clinical Significance. *Med. Gas Res.* **2013**, *3*, 10. [CrossRef]
25. Ge, L.; Yang, M.; Yang, N.N.; Yin, X.X.; Song, W.G. Molecular Hydrogen: A Preventive and Therapeutic Medical Gas for Various Diseases. *Oncotarget* **2017**, *8*, 102653. [CrossRef]
26. Di Mascio, P.; Martinez, G.R.; Miyamoto, S.; Ronsein, G.E.; Medeiros, M.H.G.; Cadet, J. Singlet Molecular Oxygen Reactions with Nucleic Acids, Lipids, and Proteins. *Chem. Rev.* **2019**, *119*, 2043–2086. [CrossRef]
27. Okamoto, A.; Kohama, K.; Aoyama-Ishikawa, M.; Yamashita, H.; Fujisaki, N.; Yamada, T.; Yumoto, T.; Nosaka, N.; Naito, H.; Tsukahara, K.; et al. Intraperitoneally Administered, Hydrogen-Rich Physiologic Solution Protects against Postoperative Ileus and Is Associated with Reduced Nitric Oxide Production. *Surgery* **2016**, *160*, 623–631. [CrossRef]
28. Muramatsu, Y.; Ito, M.; Oshima, T.; Kojima, S.; Ohno, K. Hydrogen-Rich Water Ameliorates Bronchopulmonary Dysplasia (BPD) in Newborn Rats. *Pediatr. Pulmonol.* **2016**, *51*, 928–935. [CrossRef]
29. Diao, M.; Zhang, S.; Wu, L.; Huan, L.; Huang, F.; Cui, Y.; Lin, Z. Hydrogen Gas Inhalation Attenuates Seawater Instillation-Induced Acute Lung Injury via the Nrf2 Pathway in Rabbits. *Inflammation* **2016**, *39*, 2029–2039. [CrossRef] [PubMed]
30. Yang, M.; Dong, Y.; He, Q.; Zhu, P.; Zhuang, Q.; Shen, J.; Zhang, X.; Zhao, M. Hydrogen: A Novel Option in Human Disease Treatment. *Oxid. Med. Cell. Longev.* **2020**, *7*, 35. [CrossRef]
31. Ren, A.; Liu, R.; Miao, Z.G.; Zhang, X.; Cao, P.F.; Chen, T.X.; Li, C.Y.; Shi, L.; Jiang, A.L.; Zhao, M.W. Hydrogen-Rich Water Regulates Effects of ROS Balance on Morphology, Growth and Secondary Metabolism via Glutathione Peroxidase in Ganoderma Lucidum. *Env. Microbiol.* **2017**, *19*, 566–583. [CrossRef] [PubMed]
32. Abraini, J.H.; Gardette-Chauffour, M.C.; Martinez, E.; Rostain, J.C.; Lemaire, C. Psychophysiological Reactions in Humans during an Open Sea Dive to 500 m with a Hydrogen-Helium-Oxygen Mixture. *J. Appl. Physiol.* **1994**, *76*, 1113–1118. [CrossRef]
33. Fontanari, P.; Badier, M.; Guillot, C.; Tomei, C.; Burnet, H.; Gardette, B.; Jammes, Y. Changes in Maximal Performance of Inspiratory and Skeletal Muscles during and after the 7.1-MPa Hydra 10 Record Human Dive. *Eur. J. Appl. Physiol.* **2000**, *81*, 325–328. [CrossRef] [PubMed]

34. Nagata, K.; Nakashima-Kamimura, N.; Mikami, T.; Ohsawa, I.; Ohta, S. Consumption of Molecular Hydrogen Prevents the Stress-Induced Impairments in Hippocampus-Dependent Learning Tasks during Chronic Physical Restraint in Mice. *Neuropsychopharmacology* **2009**, *34*, 501–508. [CrossRef] [PubMed]
35. Fu, Y.; Ito, M.; Fujita, Y.; Ito, M.; Ichihara, M.; Masuda, A.; Suzuki, Y.; Maesawa, S.; Kajita, Y.; Hirayama, M.; et al. Molecular Hydrogen Is Protective against 6-Hydroxydopamine-Induced Nigrostriatal Degeneration in a Rat Model of Parkinson's Disease. *Neurosci. Lett.* **2009**, *453*, 81–85. [CrossRef]
36. Sun, H.; Chen, L.; Zhou, W.; Hu, L.; Li, L.; Tu, Q.; Chang, Y.; Liu, Q.; Sun, X.; Wu, M.; et al. The Protective Role of Hydrogen-Rich Saline in Experimental Liver Injury in Mice. *J. Hepatol.* **2011**, *54*, 471–480. [CrossRef]
37. Lu, W.; Li, D.; Hu, J.; Mei, H.; Shu, J.; Long, Z.; Yuan, L.; Li, D.; Guan, R.; Li, Y.; et al. Hydrogen Gas Inhalation Protects against Cigarette Smokeinduced COPD Development in Mice. *J. Thorac. Dis.* **2018**, *10*, 3232–3243. [CrossRef]
38. Xu, X.F.; Zhang, J. Saturated Hydrogen Saline Attenuates Endotoxin-Induced Acute Liver Dysfunction in Rats. *Physiol. Res.* **2013**, *62*, 395–403. [CrossRef]
39. Gharib, B.; Hanna, S.; Abdallahi, O.M.S.; Lepidi, H.; Gardette, B.; De Reggi, M. Anti-Inflammatory Properties of Molecular Hydrogen: Investigation on Parasite-Induced Liver Inflammation. *Comptes Rendus L'academie Sci.-Ser. III-Sci. Vie* **2001**, *324*, 719–724. [CrossRef]
40. Chen, H.; Sun, Y.P.; Li, Y.; Liu, W.W.; Xiang, H.G.; Fan, L.Y.; Sun, Q.; Xu, X.Y.; Cai, J.M.; Ruan, C.P.; et al. Hydrogen-Rich Saline Ameliorates the Severity of l-Arginine-Induced Acute Pancreatitis in Rats. *Biochem. Biophys. Res. Commun.* **2010**, *393*, 308–313. [CrossRef]
41. Shao, A.; Wu, H.; Hong, Y.; Tu, S.; Sun, X.; Wu, Q.; Zhao, Q.; Zhang, J.; Sheng, J. Hydrogen-Rich Saline Attenuated Subarachnoid Hemorrhage-Induced Early Brain Injury in Rats by Suppressing Inflammatory Response: Possible Involvement of NF-KB Pathway and NLRP3 Inflammasome. *Mol. Neurobiol.* **2016**, *53*, 3462–3476. [CrossRef] [PubMed]
42. Tan, Y.C.; Xie, F.; Zhang, H.L.; Zhu, Y.L.; Chen, K.; Tan, H.M.; Hu, B.S.; Yang, J.M.; Tan, J.W. Hydrogen-Rich Saline Attenuates Postoperative Liver Failure after Major Hepatectomy in Rats. *Clin. Res. Hepatol. Gastroenterol.* **2014**, *38*, 337–345. [CrossRef] [PubMed]
43. Xu, F.; Yu, S.; Qin, M.; Mao, Y.; Jin, L.; Che, N.; Liu, S.; Ge, R. Hydrogen-Rich Saline Ameliorates Allergic Rhinitis by Reversing the Imbalance of Th1/Th2 and Up-Regulation of CD4+CD25+Foxp3+Regulatory T Cells, Interleukin-10, and Membrane-Bound Transforming Growth Factor-β in Guinea Pigs. *Inflammation* **2018**, *41*, 81–92. [CrossRef]
44. Li, K.; Yin, H.; Duan, Y.; Lai, P.; Cai, Y.; Wei, Y. Pre-Inhalation of Hydrogen-Rich Gases Protect against Caerulein-Induced Mouse Acute Pancreatitis While Enhance the Pancreatic Hsp60 Protein Expression. *BMC Gastroenterol.* **2021**, *21*, 178. [CrossRef] [PubMed]
45. Tao, H.; Liu, S.; Liu, K.; Sun, Q.; Liu, W.; Xu, W.; Denoble, P.; Sun, X. Consumption of Hydrogen Water Reduces Paraquat-Induced Acute Lung Injury in Rats. *J. Biomed. Biotechnol.* **2011**, *7*, 35. [CrossRef]
46. Hirayama, M.; Ito, M.; Minato, T.; Yoritaka, A.; Lebaron, T.; Ohno, K. Inhalation of Hydrogen Gas Elevates Urinary 8-Hydroxy-2′-Deoxyguanine in Parkinson's Disease. *Med. Gas Res.* **2018**, *8*, 144–149. [CrossRef]
47. Bi, Y.; Zhu, Y.; Zhang, M.; Zhang, K.; Hua, X.; Fang, Z.; Zhou, J.; Dai, W.; Cui, Y.; Li, J.; et al. Effect of Shikonin on Spinal Cord Injury in Rats Via Regulation of HMGB1/TLR4/NF-KB Signaling Pathway. *Cell. Physiol. Biochem.* **2017**, *43*, 481–491. [CrossRef]
48. Kellogg, E.W.; Fridovich, I. Liposome Oxidation and Erythrocyte Lysis by Enzymically Generated Superoxide and Hydrogen Peroxide. *J. Biol. Chem.* **1977**, *252*, 6721–6728. [CrossRef]
49. Stibich, M. *The Wear and Tear Theory of Aging*; Verywell Health: New York, NY, USA, 2019.
50. HARMAN, D. Aging: A Theory Based on Free Radical and Radiation Chemistry. *J. Gerontol.* **1956**, *11*, 298–300. [CrossRef]
51. Sohal, R.S.; Weindruch, R. Oxidative Stress, Caloric Restriction, and Aging. *Science* **1996**, *273*, 59–63. [CrossRef]
52. Stadtman, E.R. Protein Oxidation and Aging. *Free Radic. Res.* **2006**, *40*, 1250–1258. [CrossRef] [PubMed]
53. Kirkwood, T.B.L.; Kowald, A. The Free-Radical Theory of Ageing—Older, Wiser and Still Alive: Modelling Positional Effects of the Primary Targets of ROS Reveals New Support. *BioEssays* **2012**, *34*, 692–700. [CrossRef] [PubMed]
54. Iuchi, K.; Nishimaki, K.; Kamimura, N.; Ohta, S. Molecular Hydrogen Suppresses Free-Radical-Induced Cell Death by Mitigating Fatty Acid Peroxidation and Mitochondrial Dysfunction. *Can. J. Physiol. Pharm.* **2019**, *97*, 999–1005. [CrossRef] [PubMed]
55. Ishibashi, T. Therapeutic Efficacy of Molecular Hydrogen: A New Mechanistic Insight. *Curr. Pharm. Des.* **2019**, *25*, 946–955. [CrossRef]
56. Tan, B.L.; Norhaizan, M.E.; Liew, W.P.P.; Rahman, H.S. Antioxidant and Oxidative Stress: A Mutual Interplay in Age-Related Diseases. *Front. Pharm.* **2018**, *9*, 1162. [CrossRef]
57. Ghezzi, P.; Jaquet, V.; Marcucci, F.; Schmidt, H.H.H.W. The Oxidative Stress Theory of Disease: Levels of Evidence and Epistemological Aspects. *Br. J. Pharm.* **2017**, *174*, 1784–1796. [CrossRef] [PubMed]
58. Uddin, M.S.; Kabir, M.T.; Rahman, M.H.; Alim, M.A.; Rahman, M.M.; Khatkar, A.; Al Mamun, A.; Rauf, A.; Mathew, B.; Ashraf, G.Md. Exploring the Multifunctional Neuroprotective Promise of Rasagiline Derivatives for Multi-Dysfunctional Alzheimer's Disease. *Curr. Pharm. Des.* **2020**, *26*, 4690–4698. [CrossRef]
59. Rahman, M.H.; Bajgai, J.; Fadriquela, A.; Sharma, S.; Thi, T.T.; Akter, R.; Goh, S.H.; Kim, C.S.; Lee, K.J. Redox Effects of Molecular Hydrogen and Its Therapeutic Efficacy in the Treatment of Neurodegenerative Diseases. *Processes* **2021**, *9*, 308. [CrossRef]
60. Ito, M.; Ibi, T.; Sahashi, K.; Ichihara, M.; Ito, M.; Ohno, K. Open-Label Trial and Randomized, Double-Blind, Placebo-Controlled, Crossover Trial of Hydrogen-Enriched Water for Mitochondrial and Inflammatory Myopathies. *Med. Gas Res.* **2011**, *1*, 24. [CrossRef]

61. Nakayama, M.; Nakano, H.; Hamada, H.; Itami, N.; Nakazawa, R.; Ito, S. A Novel Bioactive Haemodialysis System Using Dissolved Dihydrogen (H2) Produced by Water Electrolysis: A Clinical Trial. *Nephrol. Dial. Transplant.* **2010**, *25*, 3026–3033. [CrossRef]
62. Martins, A.D.; Sá, R.; Monteiro, M.P.; Barros, A.; Sousa, M.; Carvalho, R.A.; Silva, B.M.; Oliveira, P.F.; Alves, M.G. Ghrelin Acts as Energy Status Sensor of Male Reproduction by Modulating Sertoli Cells Glycolytic Metabolism and Mitochondrial Bioenergetics. *Mol. Cell. Endocrinol.* **2016**, *434*, 199–209. [CrossRef]
63. Nicolson, G.L. Mitochondrial Dysfunction and Chronic Disease: Treatment with Natural Supplements. *Integr. Med. (Boulder)* **2014**, *13*, 35.
64. Chung, H.Y.; Cesari, M.; Anton, S.; Marzetti, E.; Giovannini, S.; Seo, A.Y.; Carter, C.; Yu, B.P.; Leeuwenburgh, C. Molecular Inflammation: Underpinnings of Aging and Age-Related Diseases. *Ageing Res. Rev.* **2009**, *8*, 18–30. [CrossRef]
65. Lennicke, C.; Rahn, J.; Lichtenfels, R.; Wessjohann, L.A.; Seliger, B. Hydrogen Peroxide—Production, Fate and Role in Redox Signaling of Tumor Cells. *Cell Commun. Signal.* **2015**, *13*, 39. [CrossRef] [PubMed]
66. Mailloux, R.J. Mitochondrial Antioxidants and the Maintenance of Cellular Hydrogen Peroxide Levels. *Oxid. Med. Cell. Longev.* **2018**, *2018*. [CrossRef]
67. Viola, J.; Soehnlein, O. Atherosclerosis—A Matter of Unresolved Inflammation. *Semin. Immunol.* **2015**, *27*, 184–193. [CrossRef] [PubMed]
68. Santos, A.L.; Lindner, A.B. Protein Posttranslational Modifications: Roles in Aging and Age-Related Disease. *Oxid. Med. Cell. Longev.* **2017**, *2017*. [CrossRef]
69. Woods, J.A.; Vieira, V.J.; Keylock, K.T. Exercise, Inflammation, and Innate Immunity. *Immunol. Allergy Clin. N. Am.* **2009**, *29*, 381–393. [CrossRef]
70. Waldmann, T.A.; Miljkovic, M.D.; Conlon, K.C. Interleukin-15 (Dys)Regulation of Lymphoid Homeostasis: Implications for Therapy of Autoimmunity and Cancer. *J. Exp. Med.* **2020**, *217*, e20191062. [CrossRef]
71. Liu, K.Y.P.; Lu, X.J.D.; Zhu, Y.S.; Le, N.; Kim, H.; Poh, C.F. Plasma-Derived Inflammatory Proteins Predict Oral Squamous Cell Carcinoma. *Front. Oncol.* **2018**, *8*, 585. [CrossRef]
72. Leonardi, G.C.; Accardi, G.; Monastero, R.; Nicoletti, F.; Libra, M. Ageing: From Inflammation to Cancer. *Immun. Ageing* **2018**, *15*, 1. [CrossRef]
73. Li, S.; Liao, R.; Sheng, X.; Luo, X.; Zhang, X.; Wen, X.; Zhou, J.; Peng, K. Hydrogen Gas in Cancer Treatment. *Front. Oncol.* **2019**, *9*, 696. [CrossRef]
74. Wardill, H.R.; Mander, K.A.; Van Sebille, Y.Z.A.; Gibson, R.J.; Logan, R.M.; Bowen, J.M.; Sonis, S.T. Cytokine-Mediated Blood Brain Barrier Disruption as a Conduit for Cancer/Chemotherapy-Associated Neurotoxicity and Cognitive Dysfunction. *Int. J. Cancer* **2016**, *139*, 2635–2645. [CrossRef] [PubMed]
75. Demaria, M.; O'Leary, M.N.; Chang, J.; Shao, L.; Liu, S.; Alimirah, F.; Koenig, K.; Le, C.; Mitin, N.; Deal, A.M.; et al. Cellular Senescence Promotes Adverse Effects of Chemotherapy and Cancer Relapse. *Cancer Discov.* **2017**, *7*, 165–176. [CrossRef] [PubMed]
76. Padoan, A.; Plebani, M.; Basso, D. Inflammation and Pancreatic Cancer: Focus on Metabolism, Cytokines, and Immunity. *Int. J. Mol. Sci.* **2019**, *20*, 676. [CrossRef] [PubMed]
77. Wang, F.H.; Shen, L.; Li, J.; Zhou, Z.W.; Liang, H.; Zhang, X.T.; Tang, L.; Xin, Y.; Jin, J.; Zhang, Y.J.; et al. The Chinese Society of Clinical Oncology (CSCO): Clinical Guidelines for the Diagnosis and Treatment of Gastric Cancer. *Cancer Commun.* **2019**, *39*, 10. [CrossRef]
78. Lazzari, C.; Karachaliou, N.; Bulotta, A.; Viganó, M.; Mirabile, A.; Brioschi, E.; Santarpia, M.; Gianni, L.; Rosell, R.; Gregorc, V. Combination of Immunotherapy with Chemotherapy and Radiotherapy in Lung Cancer: Is This the Beginning of the End for Cancer? *Adv. Med. Oncol.* **2018**, *10*, 1–12. [CrossRef] [PubMed]
79. Susanne, K.; Michael, F.; Thomas, S.; Peter, E.; Andreas, H. Predictors of Fatigue in Cancer Patients: A Longitudinal Study. *Support. Care Cancer* **2019**, *27*, 3463–3471. [CrossRef]
80. Razzaghdoust, A.; Mofid, B.; Peyghambarlou, P. Predictors of Chemotherapy-Induced Severe Anemia in Cancer Patients Receiving Chemotherapy. *Support. Care Cancer* **2020**, *28*, 155–161. [CrossRef]
81. Cui, Q.; Wang, J.Q.; Assaraf, Y.G.; Ren, L.; Gupta, P.; Wei, L.; Ashby, C.R.; Yang, D.H.; Chen, Z.S. Modulating ROS to Overcome Multidrug Resistance in Cancer. *Drug Resist. Updat.* **2018**, *41*, 1–25. [CrossRef]
82. Shen, B.-Y.; Chen, C.; Xu, Y.-F.; Shen, J.-J.; Guo, H.-M.; Li, H.-F.; Li, X.-N.; Kang, D.; Shao, Y.-H.; Zhu, Z.-P.; et al. Is the Combinational Administration of Doxorubicin and Glutathione a Reasonable Proposal? *Acta Pharm. Sin* **2019**, *40*, 699–709. [CrossRef]
83. Luo, W.; Wen, G.; Yang, L.; Tang, J.; Wang, J.; Wang, J.; Zhang, S.; Zhang, L.; Ma, F.; Xiao, L.; et al. Dual-Targeted and PH-Sensitive Doxorubicin Prodrug-Microbubble Complex with Ultrasound for Tumor Treatment. *Theranostics* **2017**, *7*, 452–465. [CrossRef] [PubMed]
84. Kitamura, A.; Kobayashi, S.; Matsushita, T.; Fujinawa, H.; Murase, K. Experimental Verification of Protective Effect of Hydrogen-Rich Water against Cisplatin-Induced Nephrotoxicity in Rats Using Dynamic Contrast-Enhanced CT. *Br. J. Radiol.* **2010**, *83*, 509–514. [CrossRef]
85. Matsushita, T.; Kusakabe, Y.; Kitamura, A.; Okada, S.; Murase, K. Investigation of Protective Effect of Hydrogen-Rich Water against Cisplatininduced Nephrotoxicity in Rats Using Blood Oxygenation Level-Dependent Magnetic Resonance Imaging. *Jpn. J. Radiol.* **2011**, *29*, 503–512. [CrossRef]

86. Meng, X.; Chen, H.; Wang, G.; Yu, Y.; Xie, K. Hydrogen-Rich Saline Attenuates Chemotherapy-Induced Ovarian Injury via Regulation of Oxidative Stress. *Exp. Med.* **2015**, *10*, 2277–2282. [CrossRef] [PubMed]
87. Kang, K.M.; Kang, Y.N.; Choi, I.B.; Gu, Y.; Kawamura, T.; Toyoda, Y.; Nakao, A. Effects of Drinking Hydrogen-Rich Water on the Quality of Life of Patients Treated with Radiotherapy for Liver Tumors. *Med. Gas Res.* **2011**, *1*, 11. [CrossRef]
88. Gao, Y.; Yang, H.; Fan, Y.; Li, L.; Fang, J.; Yang, W. Hydrogen-Rich Saline Attenuates Cardiac and Hepatic Injury in Doxorubicin Rat Model by Inhibiting Inflammation and Apoptosis. *Mediat. Inflamm.* **2016**, *2016*. [CrossRef] [PubMed]
89. Zhao, P.; Jin, Z.; Chen, Q.; Yang, T.; Chen, D.; Meng, J.; Lu, X.; Gu, Z.; He, Q. Local Generation of Hydrogen for Enhanced Photothermal Therapy. *Nat. Commun.* **2018**, *9*, 4241. [CrossRef]
90. Liu, M.Y.; Xie, F.; Zhang, Y.; Wang, T.T.; Ma, S.N.; Zhao, P.X.; Zhang, X.; Lebaron, T.W.; Yan, X.L.; Ma, X.M. Molecular Hydrogen Suppresses Glioblastoma Growth via Inducing the Glioma Stem-like Cell Differentiation. *Stem. Cell Res.* **2019**, *10*, 145. [CrossRef]
91. Nakashima-Kamimura, N.; Mori, T.; Ohsawa, I.; Asoh, S.; Ohta, S. Molecular Hydrogen Alleviates Nephrotoxicity Induced by an Anti-Cancer Drug Cisplatin without Compromising Anti-Tumor Activity in Mice. *Cancer Chemother. Pharm.* **2009**, *64*, 753–761. [CrossRef] [PubMed]
92. Shang, L.; Xie, F.; Li, J.; Zhang, Y.; Liu, M.; Zhao, P.; Ma, X.; Lebaron, T.W. Therapeutic Potential of Molecular Hydrogen in Ovarian Cancer. *Transl. Cancer Res.* **2018**, *7*, 988–995. [CrossRef]
93. Yang, Q.; Ji, G.; Pan, R.; Zhao, Y.; Yan, P. Protective Effect of Hydrogen-Rich Water on Liver Function of Colorectal Cancer Patients Treated with MFOLFOX6 Chemotherapy. *Mol. Clin. Oncol.* **2017**, *7*, 891–896. [CrossRef] [PubMed]
94. Zhou, P.; Lin, B.; Wang, P.; Pan, T.; Wang, S.; Chen, W.; Cheng, S.; Liu, S. The Healing Effect of Hydrogen-Rich Water on Acute Radiation-Induced Skin Injury in Rats. *J. Radiat. Res.* **2019**, *60*, 17–22. [CrossRef]
95. Terasaki, Y.; Suzuki, T.; Tonaki, K.; Terasaki, M.; Kuwahara, N.; Ohsiro, J.; Iketani, M.; Takahashi, M.; Hamanoue, M.; Kajimoto, Y.; et al. Molecular Hydrogen Attenuates Gefitinib-Induced Exacerbation of Naphthalene-Evoked Acute Lung Injury through a Reduction in Oxidative Stress and Inflammation. *Lab. Investig.* **2019**, *99*, 793–806. [CrossRef]
96. Kawai, D.; Takaki, A.; Nakatsuka, A.; Wada, J.; Tamaki, N.; Yasunaka, T.; Koike, K.; Tsuzaki, R.; Matsumoto, K.; Miyake, Y.; et al. Hydrogen-Rich Water Prevents Progression of Nonalcoholic Steatohepatitis and Accompanying Hepatocarcinogenesis in Mice. *Hepatology* **2012**, *56*, 912–921. [CrossRef]
97. Provasi, S.; Cattaneo, A.; Cattane, N.; Galluzzi, S.; Lopizzo, N.; Plazzotta, G.; Boccardi, M.; Frisoni, G. Association of Brain Amyloidosis with Pro-Inflammatory Gut Bacterial Strains and Peripheral Inflammation Markers in Cognitively Impaired Elderly. *Eur. Neuropsychopharmacol.* **2016**, *26*, S649–S650. [CrossRef]
98. Simrén, M.; Öhman, L.; Olsson, J.; Svensson, U.; Ohlson, K.; Posserud, I.; Strid, H. Clinical Trial: The Effects of a Fermented Milk Containing Three Probiotic Bacteria in Patients with Irritable Bowel Syndrome—A Randomized, Double-Blind, Controlled Study. *Aliment. Pharm.* **2010**, *31*, 218–227. [CrossRef]
99. Takakura, W.; Pimentel, M. Small Intestinal Bacterial Overgrowth and Irritable Bowel Syndrome—An Update. *Front. Psychiatry* **2020**, *11*, 664. [CrossRef]
100. Marthinsen, D.; Fleming, S.E. Excretion of Breath and Flatus Gases by Humans Consuming High-Fiber Diets. *J. Nutr.* **1982**, *112*, 1133–1143. [CrossRef]
101. Lebaron, T.W.; Singh, R.B.; Fatima, G.; Kartikey, K.; Sharma, J.P.; Ostojic, S.M.; Gvozdjakova, A.; Kura, B.; Noda, M.; Mojto, V.; et al. The Effects of 24-Week, High-Concentration Hydrogen-Rich Water on Body Composition, Blood Lipid Profiles and Inflammation Biomarkers in Men and Women with Metabolic Syndrome: A Randomized Controlled Trial. *Diabetes Metab. Syndr. Obes.* **2020**, *13*, 889–896. [CrossRef]
102. Guinane, C.M.; Cotter, P.D. Role of the Gut Microbiota in Health and Chronic Gastrointestinal Disease: Understanding a Hidden Metabolic Organ. *Ther. Adv. Gastroenterol.* **2013**, *6*, 295–308. [CrossRef] [PubMed]
103. Xiao, H.W.; Li, Y.; Luo, D.; Dong, J.L.; Zhou, L.X.; Zhao, S.Y.; Zheng, Q.S.; Wang, H.C.; Cui, M.; Fan, S.J. Hydrogen-Water Ameliorates Radiation-Induced Gastrointestinal Toxicity via Myd88′s Effects on the Gut Microbiota. *Exp. Mol. Med.* **2018**, *50*, e433. [CrossRef] [PubMed]
104. Zheng, W.; Ji, X.; Zhang, Q.; Yao, W. Intestinal Microbiota Ecological Response to Oral Administrations of Hydrogen-Rich Water and Lactulose in Female Piglets Fed a Fusarium Toxin-Contaminated Diet. *Toxins* **2018**, *10*, 246. [CrossRef]
105. Sha, J.-B.; Zhang, S.S.; Lu, Y.M.; Gong, W.J.; Jiang, X.P.; Wang, J.J.; Qiao, T.L.; Zhang, H.H.; Zhao, M.Q.; Wang, D.P.; et al. Effects of the Long-Term Consumption of Hydrogen-Rich Water on the Antioxidant Activity and the Gut Flora in Female Juvenile Soccer Players from Suzhou, China. *Med. Gas Res.* **2018**, *8*, 135–143. [CrossRef]
106. Shen, N.Y.; Bi, J.B.; Zhang, J.Y.; Zhang, S.M.; Gu, J.X.; Qu, K.; Liu, C. Hydrogen-Rich Water Protects against Inflammatory Bowel Disease in Mice by Inhibiting Endoplasmic Reticulum Stress and Promoting Heme Oxygenase-1 Expression. *World J. Gastroenterol.* **2017**, *23*, 1375–1386. [CrossRef]
107. Ji, X.; Zhang, Q.; Zheng, W.; Yao, W. Morphological and Molecular Response of Small Intestine to Lactulose and Hydrogen-Rich Water in Female Piglets Fed Fusarium Mycotoxins Contaminated Diet. *J. Anim. Sci. Biotechnol.* **2019**, *10*, 9. [CrossRef] [PubMed]
108. Kamimura, N.; Nishimaki, K.; Ohsawa, I.; Ohta, S. Molecular Hydrogen Improves Obesity and Diabetes by Inducing Hepatic FGF21 and Stimulating Energy Metabolism in Db/Db Mice. *Obesity* **2011**, *19*, 1396–1403. [CrossRef]
109. Tanaka, Y.; Kiuchi, M.; Higashimura, Y.; Naito, Y.; Koyama, K. The Effects of Ingestion of Hydrogen-Dissolved Alkaline Electrolyzed Water on Stool Consistency and Gut Microbiota: A Double-Blind Randomized Trial. *Med. Gas Res.* **2021**, *11*, 138–144. [CrossRef]

110. Jin, Z.; Sun, Y.; Yang, T.; Tan, L.; Lv, P.; Xu, Q.; Tao, G.; Qin, S.; Lu, X.; He, Q. Nanocapsule-Mediated Sustained H2 Release in the Gut Ameliorates Metabolic Dysfunction-Associated Fatty Liver Disease. *Biomaterials* **2021**, *276*, 121030. [CrossRef]
111. Qiu, X.; Ye, Q.; Sun, M.; Wang, L.; Tan, Y.; Wu, G. Saturated Hydrogen Improves Lipid Metabolism Disorders and Dysbacteriosis Induced by a High-Fat Diet. *Exp. Biol. Med.* **2020**, *245*, 512–521. [CrossRef]
112. Ehrenpreis, E.D.; Swamy, R.S.; Zaitman, D.; Noth, I. Short Duration Exercise Increases Breath Hydrogen Excretion after Lactulose Ingestion: Description of a New Phenomenon. *Am. J. Gastroenterol.* **2002**, *97*, 2798–2802. [CrossRef] [PubMed]
113. Gaskell, S.K.; Taylor, B.; Muir, J.; Costa, R.J.S. Impact of 24-h High and Low Fermentable Oligo-, Di-, Monosaccharide, and Polyol Diets on Markers of Exercise-Induced Gastrointestinal Syndrome in Response to Exertional Heat Stress. *Appl. Physiol. Nutr. Metab.* **2020**, *45*, 569–580. [CrossRef] [PubMed]
114. Lin, S.; Ye, F.; Rong, W.; Song, Y.; Wu, F.; Liu, Y.; Zheng, Y.; Siqin, T.; Zhang, K.; Wang, L.; et al. Nomogram to Assist in Surgical Plan for Hepatocellular Carcinoma: A Prediction Model for Microvascular Invasion. *J. Gastrointest. Surg.* **2019**, *23*, 2372–2382. [CrossRef] [PubMed]
115. Parsanathan, R.; Jain, S.K. Hydrogen Sulfide Regulates Circadian-Clock Genes in C2C12 Myotubes and the Muscle of High-Fat-Diet-Fed Mice. *Arch. Biochem. Biophys.* **2019**, *672*, 108054. [CrossRef]
116. Dong, B.M.; Abano, J.B.; Egan, T.M. Nitric Oxide Ventilation of Rat Lungs from Non-Heart-Beating Donors Improves Posttransplant Function. *Am. J. Transplant.* **2009**, *9*, 2707–2715. [CrossRef] [PubMed]
117. Ozaki, K.S.; Yoshida, J.; Ueki, S.; Pettigrew, G.L.; Ghonem, N.; Sico, R.M.; Lee, L.Y.; Shapiro, R.; Lakkis, F.G.; Pacheco-Silva, A.; et al. Carbon Monoxide Inhibits Apoptosis during Cold Storage and Protects Kidney Grafts Donated after Cardiac Death. *Transpl. Int.* **2012**, *25*, 107–117. [CrossRef]
118. LeBaron, T.W.; Kura, B.; Kalocayova, B.; Tribulova, N.; Slezak, J. A New Approach for the Prevention and Treatment of Cardiovascular Disorders. Molecular Hydrogen Significantly Reduces the Effects of Oxidative Stress. *Molecules* **2019**, *24*, 2076. [CrossRef]
119. Ohsawa, I.; Nishimaki, K.; Yamagata, K.; Ishikawa, M.; Ohta, S. Consumption of Hydrogen Water Prevents Atherosclerosis in Apolipoprotein E Knockout Mice. *Biochem. Biophys. Res. Commun.* **2008**, *377*, 1195–1198. [CrossRef]
120. Wu, D.; Wang, J.; Li, H.; Xue, M.; Ji, A.; Li, Y. Role of Hydrogen Sulfide in Ischemia-Reperfusion Injury. *Oxid. Med. Cell. Longev.* **2015**, *2015*. [CrossRef]
121. Iida, A.; Nosaka, N.; Yumoto, T.; Knaup, E.; Naito, H.; Nishiyama, C.; Yamakawa, Y.; Tsukahara, K.; Terado, M.; Sato, K.; et al. The Clinical Application of Hydrogen as a Medical Treatment. *Acta Med. Okayama* **2016**, *70*, 331–337.
122. Amilan Jose, D.; Sharma, N.; Sakla, R.; Kaushik, R.; Gadiyaram, S. Fluorescent Nanoprobes for the Sensing of Gasotransmitters Hydrogen Sulfide (H2S), Nitric Oxide (NO) and Carbon Monoxide (CO). *Methods* **2019**, *168*, 62–75. [CrossRef]
123. Qian, L.; Cao, F.; Cui, J.; Wang, Y.; Huang, Y.; Chuai, Y.; Zaho, L.; Jiang, H.; Cai, J. The Potential Cardioprotective Effects of Hydrogenin Irradiated Mice. *J. Radiat. Res.* **2010**, *51*, 741–747. [CrossRef] [PubMed]
124. Hayashida, K.; Sano, M.; Kamimura, N.; Yokota, T.; Suzuki, M.; Ohta, S.; Fukuda, K.; Hori, S. Hydrogen Inhalation during Normoxic Resuscitation Improves Neurological Outcome in a Rat Model of Cardiac Arrest Independently of Targeted Temperature Management. *Circulation* **2014**, *130*, 2173–2180. [CrossRef] [PubMed]
125. Nakao, A.; Toyoda, Y.; Sharma, P.; Evans, M.; Guthrie, N. Effectiveness of Hydrogen Rich Water on Antioxidant Status of Subjects with Potential Metabolic Syndrome—An Open Label Pilot Study. *J. Clin. Biochem. Nutr.* **2010**, *46*, 140–149. [CrossRef] [PubMed]
126. Ohta, S. Molecular Hydrogen as a Preventive and Therapeutic Medical Gas: Initiation, Development and Potential of Hydrogen Medicine. *Pharmacol. Ther.* **2014**, *144*, 1–11. [CrossRef] [PubMed]
127. Zhang, Y.; Tan, S.; Xu, J.; Wang, T. Hydrogen Therapy in Cardiovascular and Metabolic Diseases: From Bench to Bedside. *Cell. Physiol. Biochem.* **2018**, *47*, 1–10. [CrossRef]
128. Song, G.; Li, M.; Sang, H.; Zhang, L.; Li, X.; Yao, S.; Yu, Y.; Zong, C.; Xue, Y.; Qin, S. Hydrogen -Rich Water Decreases Serum LDL-Cholesterol Levels and Improves HDL Function in Patients with Potential Metabolic Syndrome. *J. Lipid Res.* **2013**, *54*, 1884–1893. [CrossRef]
129. Takahashi, H. Application of Hydrogen in Ophthalmology. *Curr. Pharm. Des.* **2020**, *27*, 592–594. [CrossRef]
130. Suzuki, Y.; Sano, M.; Hayashida, K.; Ohsawa, I.; Ohta, S.; Fukuda, K. Are the Effects of α-Glucosidase Inhibitors on Cardiovascular Events Related to Elevated Levels of Hydrogen Gas in the Gastrointestinal Tract? *FEBS Lett.* **2009**, *583*, 2157–2159. [CrossRef]
131. Sakai, T.; Sato, B.; Hara, K.; Hara, Y.; Naritomi, Y.; Koyanagi, S.; Hara, H.; Nagao, T.; Ishibashi, T. Consumption of Water Containing over 3.5 Mg of Dissolved Hydrogen Could Improve Vascular Endothelial Function. *Vasc. Health Risk Manag.* **2014**, *10*, 591–597. [CrossRef]
132. Ostojic, S.M.; Stojanovic, M.D. Hydrogen-Rich Water Affected Blood Alkalinity in Physically Active Men. *Res. Sports Med.* **2014**, *22*, 49–60. [CrossRef] [PubMed]
133. Kajiyama, S.; Hasegawa, G.; Asano, M.; Hosoda, H.; Fukui, M.; Nakamura, N.; Kitawaki, J.; Imai, S.; Nakano, K.; Ohta, M.; et al. Supplementation of Hydrogen-Rich Water Improves Lipid and Glucose Metabolism in Patients with Type 2 Diabetes or Impaired Glucose Tolerance. *Nutr. Res.* **2008**, *28*, 137–143. [CrossRef] [PubMed]
134. Yoritaka, A.; Takanashi, M.; Hirayama, M.; Nakahara, T.; Ohta, S.; Hattori, N. Pilot Study of H2 Therapy in Parkinson's Disease: A Randomized Double-Blind Placebo-Controlled Trial. *Mov. Disord.* **2013**, *28*, 836–839. [CrossRef] [PubMed]
135. Xia, C.; Liu, W.; Zeng, D.; Zhu, L.; Sun, X.; Sun, X. Effect of Hydrogen-Rich Water on Oxidative Stress, Liver Function, and Viral Load in Patients with Chronic Hepatitis B. *Clin. Transl. Sci.* **2013**, *6*, 372–375. [CrossRef]

136. Ishibashi, T.; Sato, B.; Rikitake, M.; Seo, T.; Kurokawa, R.; Hara, Y.; Naritomi, Y.; Hara, H.; Nagao, T. Consumption of Water Containing a High Concentration of Molecular Hydrogen Reduces Oxidative Stress and Disease Activity in Patients with Rheumatoid Arthritis: An Open-Label Pilot Study. *Med. Gas Res.* **2012**, *2*, 27. [CrossRef]
137. Aoki, K.; Nakao, A.; Adachi, T.; Matsui, Y.; Miyakawa, S. Pilot Study: Effects of Drinking Hydrogen-Rich Water on Muscle Fatigue Caused by Acute Exercise in Elite Athletes. *Med. Gas Res.* **2012**, *2*, 12. [CrossRef]
138. Nagatani, K.; Nawashiro, H.; Takeuchi, S.; Tomura, S.; Otani, N.; Osada, H.; Wada, K.; Katoh, H.; Tsuzuki, N.; Mori, K. Safety of Intravenous Administration of Hydrogen-Enriched Fluid in Patients with Acute Cerebral Ischemia: Initial Clinical Studies. *Med. Gas Res.* **2013**, *3*, 13. [CrossRef]
139. Li, Q.; Kato, S.; Matsuoka, D.; Tanaka, H.; Miwa, N. Hydrogen Water Intake via Tube-Feeding for Patients with Pressure Ulcer and Its Reconstructive Effects on Normal Human Skin Cells in Vitro. *Med. Gas Res.* **2013**, *3*, 20. [CrossRef]
140. Ostojic, S.M.; Vukomanovic, B.; Calleja-Gonzalez, J.; Hoffman, J.R. Effectiveness of Oral and Topical Hydrogen for Sports-Related Soft Tissue Injuries. *Postgrad. Med.* **2014**, *126*, 188–196. [CrossRef]
141. Sampson, T.R.; Debelius, J.W.; Thron, T.; Janssen, S.; Shastri, G.G.; Ilhan, Z.E.; Challis, C.; Schretter, C.E.; Rocha, S.; Gradinaru, V.; et al. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. *Cell* **2016**, *167*, 1469–1480. [CrossRef]
142. Ito, M.; Hirayama, M.; Yamai, K.; Goto, S.; Ito, M.; Ichihara, M.; Ohno, K. Drinking Hydrogen Water and Intermittent Hydrogen Gas Exposure, but Not Lactulose or Continuous Hydrogen Gas Exposure, Prevent 6-Hydorxydopamine-Induced Parkinson's Disease in Rats. *Med. Gas Res.* **2012**, *2*, 15. [CrossRef] [PubMed]
143. Dohi, K.; Satoh, K.; Miyamoto, K.; Momma, S.; Fukuda, K.; Higuchi, R.; Ohtaki, H.; Banks, W.A. Molecular Hydrogen in the Treatment of Acute and Chronic Neurological Conditions: Mechanisms of Protection and Routes of Administration. *J. Clin. Biochem. Nutr.* **2017**, *61*, 1–5. [CrossRef] [PubMed]
144. Yoritaka, A.; Abe, T.; Ohtsuka, C.; Maeda, T.; Hirayama, M.; Watanabe, H.; Saiki, H.; Oyama, G.; Fukae, J.; Shimo, Y.; et al. A Randomized Double-Blind Multi-Center Trial of Hydrogen Water for Parkinson's Disease: Protocol and Baseline Characteristics. *BMC Neurol.* **2016**, *16*, 66. [CrossRef] [PubMed]
145. Forsyth, C.B.; Shannon, K.M.; Kordower, J.H.; Voigt, R.M.; Shaikh, M.; Jaglin, J.A.; Estes, J.D.; Dodiya, H.B.; Keshavarzian, A. Increased Intestinal Permeability Correlates with Sigmoid Mucosa Alpha-Synuclein Staining and Endotoxin Exposure Markers in Early Parkinson's Disease. *PLoS ONE* **2011**, *6*, e28032. [CrossRef] [PubMed]
146. Suzuki, A.; Ito, M.; Hamaguchi, T.; Mori, H.; Takeda, Y.; Baba, R.; Watanabe, T.; Kurokawa, K.; Asakawa, S.; Hirayama, M.; et al. Quantification of Hydrogen Production by Intestinal Bacteria That Are Specifically Dysregulated in Parkinson's Disease. *PLoS ONE* **2018**, *13*, e0208313. [CrossRef]
147. Scheperjans, F.; Aho, V.; Pereira, P.A.B.; Koskinen, K.; Paulin, L.; Pekkonen, E.; Haapaniemi, E.; Kaakkola, S.; Eerola-Rautio, J.; Pohja, M.; et al. Gut Microbiota Are Related to Parkinson's Disease and Clinical Phenotype. *Mov. Disord.* **2015**, *30*, 350–358. [CrossRef]
148. Sonnenburg, J.L.; Sonnenburg, E.D. Vulnerability of the Industrialized Microbiota. *Science* **2019**, *366*, eaaw9255. [CrossRef]
149. Illiano, P.; Brambilla, R.; Parolini, C. The Mutual Interplay of Gut Microbiota, Diet and Human Disease. *FEBS J.* **2020**, *287*, 833–855. [CrossRef]
150. Kowalski, K.; Mulak, A. Brain-Gut-Microbiota Axis in Alzheimer's Disease. *J. Neurogastroenterol. Motil.* **2019**, *25*, 48–60. [CrossRef]
151. De-Paula, V.d.J.R.; Forlenza, A.S.; Forlenza, O.V. Relevance of Gutmicrobiota in Cognition, Behaviour and Alzheimer's Disease. *Pharm. Res* **2018**, *136*, 29–34. [CrossRef]
152. Kabir, M.T.; Rahman, M.H.; Shah, M.; Jamiruddin, M.R.; Basak, D.; Al-Harrasi, A.; Bhatia, S.; Ashraf, G.M.; Najda, A.; El-kott, A.F.; et al. Therapeutic Promise of Carotenoids as Antioxidants and Anti-Inflammatory Agents in Neurodegenerative Disorders. *Biomed. Pharmacother.* **2022**, *146*, 112610. [CrossRef] [PubMed]
153. Arya, A.; Chahal, R.; Rao, R.; Rahman, M.H.; Kaushik, D.; Akhtar, M.F.; Saleem, A.; Khalifa, S.M.A.; El-Seedi, H.R.; Kamel, M.; et al. Acetylcholinesterase Inhibitory Potential of Various Sesquiterpene Analogues for Alzheimer's Disease Therapy. *Biomolecules* **2021**, *11*, 350. [CrossRef]
154. Li, S.; Fujino, M.; Ichimaru, N.; Kurokawa, R.; Hirano, S.; Mou, L.; Takahara, S.; Takahara, T.; Li, X.K. Molecular Hydrogen Protects against Ischemia-Reperfusion Injury in a Mouse Fatty Liver Model via Regulating HO-1 and Sirt1 Expression. *Sci. Rep.* **2018**, *8*, 14019. [CrossRef] [PubMed]
155. Fan, Y.; Pedersen, O. Gut Microbiota in Human Metabolic Health and Disease. *Nat. Rev. Microbiol.* **2021**, *19*, 55–71. [CrossRef] [PubMed]
156. Ostojic, S.M. Hydrogen-Rich Water as a Modulator of Gut Microbiota? *J. Funct. Foods* **2021**, *78*, 104360. [CrossRef]
157. Chen, S.Y.; Gao, Y.; Sun, J.Y.; Meng, X.L.; Yang, D.; Fan, L.H.; Xiang, L.; Wang, P. Traditional Chinese Medicine: Role in Reducing β-Amyloid, Apoptosis, Autophagy, Neuroinflammation, Oxidative Stress, and Mitochondrial Dysfunction of Alzheimer's Disease. *Front. Pharm.* **2020**, *11*, 497. [CrossRef] [PubMed]
158. Islam, M.T. Oxidative Stress and Mitochondrial Dysfunction-Linked Neurodegenerative Disorders. *Neurol. Res.* **2017**, *39*, 73–82. [CrossRef]
159. Kuriakose, M.; Younger, D.; Ravula, A.R.; Alay, E.; Rama Rao, K.V.; Chandra, N. Synergistic Role of Oxidative Stress and Blood-Brain Barrier Permeability as Injury Mechanisms in the Acute Pathophysiology of Blast-Induced Neurotrauma. *Sci. Rep.* **2019**, *9*, 7717. [CrossRef]

160. Zhang, P.; Kishimoto, Y.; Grammatikakis, I.; Gottimukkala, K.; Cutler, R.G.; Zhang, S.; Abdelmohsen, K.; Bohr, V.A.; Misra Sen, J.; Gorospe, M.; et al. Senolytic Therapy Alleviates Aβ-Associated Oligodendrocyte Progenitor Cell Senescence and Cognitive Deficits in an Alzheimer's Disease Model. *Nat. Neurosci.* **2019**, *22*, 719–728. [CrossRef]
161. Erickson, M.A.; Dohi, K.; Banks, W.A. Neuroinflammation: A Common Pathway in CNS Diseases as Mediated at the Blood-Brain Barrier. *Neuroimmunomodulation* **2012**, *19*, 121–130. [CrossRef]
162. Wang, C.; Li, J.; Liu, Q.; Yang, R.; Zhang, J.H.; Cao, Y.P.; Sun, X.J. Hydrogen-Rich Saline Reduces Oxidative Stress and Inflammation by Inhibit of JNK and NF-KB Activation in a Rat Model of Amyloid-Beta-Induced Alzheimer's Disease. *Neurosci. Lett.* **2011**, *491*, 127–132. [CrossRef]
163. Li, J.; Wang, C.; Zhang, J.H.; Cai, J.M.; Cao, Y.P.; Sun, X.J. Hydrogen-Rich Saline Improves Memory Function in a Rat Model of Amyloid-Beta-Induced Alzheimer's Disease by Reduction of Oxidative Stress. *Brain Res.* **2010**, *1328*, 152–161. [CrossRef] [PubMed]
164. Gu, Y.; Huang, C.S.; Inoue, T.; Yamashita, T.; Ishida, T.; Kang, K.M.; Nakao, A. Drinking Hydrogen Water Ameliorated Cognitive Impairment in Senescence-Accelerated Mice. *J. Clin. Biochem. Nutr.* **2010**, *46*, 269–276. [CrossRef] [PubMed]
165. Nishimaki, K.; Asada, T.; Ohsawa, I.; Nakajima, E.; Ikejima, C.; Yokota, T.; Kamimura, N.; Ohta, S. Effects of Molecular Hydrogen Assessed by an Animal Model and a Randomized Clinical Study on Mild Cognitive Impairment. *Curr. Alzheimer Res.* **2018**, *15*, 482–492. [CrossRef]
166. Ohta, S. Recent Progress toward Hydrogen Medicine: Potential of Molecular Hydrogen for Preventive and Therapeutic Applications. *Curr. Pharm. Des.* **2011**, *17*, 2241–2252. [CrossRef]
167. Ohta, S. Molecular Hydrogen Is a Novel Antioxidant to Efficiently Reduce Oxidative Stress with Potential for the Improvement of Mitochondrial Diseases. *Biochim. Biophys. Acta Gen. Subj.* **2012**, *1820*, 586–594. [CrossRef] [PubMed]
168. Hayashida, K.; Sano, M.; Ohsawa, I.; Shinmura, K.; Tamaki, K.; Kimura, K.; Endo, J.; Katayama, T.; Kawamura, A.; Kohsaka, S.; et al. Inhalation of Hydrogen Gas Reduces Infarct Size in the Rat Model of Myocardial Ischemia-Reperfusion Injury. *Biochem. Biophys. Res. Commun.* **2008**, *373*, 30–35. [CrossRef] [PubMed]
169. Schirone, L.; Forte, M.; Palmerio, S.; Yee, D.; Nocella, C.; Angelini, F.; Pagano, F.; Schiavon, S.; Bordin, A.; Carrizzo, A.; et al. A Review of the Molecular Mechanisms Underlying the Development and Progression of Cardiac Remodeling. *Oxid. Med. Cell. Longev.* **2017**, *2017*, 3920195. [CrossRef] [PubMed]
170. Zhang, Y.; Zhang, X.-J.; Li, H. Targeting Interferon Regulatory Factor for Cardiometabolic Diseases: Opportunities and Challenges. *Curr. Drug Targets* **2017**, *18*, 1754–1778. [CrossRef]
171. Zhang, Y.; Sun, Q.; He, B.; Xiao, J.; Wang, Z.; Sun, X. Anti-Inflammatory Effect of Hydrogen-Rich Saline in a Rat Model of Regional Myocardial Ischemia and Reperfusion. *Int. J. Cardiol.* **2011**, *148*, 91–95. [CrossRef]
172. Zhang, Y.; Xu, J.; Long, Z.; Wang, C.; Wang, L.; Sun, P.; Li, P.; Wang, T. Hydrogen (H2) Inhibits Isoproterenol-Induced Cardiac Hypertrophy via Antioxidative Pathways. *Front. Pharm.* **2016**, *7*, 392. [CrossRef] [PubMed]
173. Zhang, Y.; Long, Z.; Xu, J.; Tan, S.; Zhang, N.; Li, A.; Wang, L.; Wang, T. Hydrogen Inhibits Isoproterenol-Induced Autophagy in Cardiomyocytes in Vitro and in Vivo. *Mol. Med. Rep.* **2017**, *16*, 8253–8258. [CrossRef] [PubMed]
174. Yu, Y.S.; Zheng, H. Chronic Hydrogen-Rich Saline Treatment Reduces Oxidative Stress and Attenuates Left Ventricular Hypertrophy in Spontaneous Hypertensive Rats. *Mol. Cell. Biochem.* **2012**, *365*, 233–242. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.