clean technologies

Review

Hydrogen Is Promising for Medical Applications

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Received: 24 November 2020; Accepted: 14 December 2020; Published: 16 December 2020

Abstract: Hydrogen (H_2) is promising as an energy source for the next generation. Medical applications using H_2 gas can be also considered as a clean and economical technology. Since the H_2 gas based on electrolysis of water production has potential to expand the medical applications, the technology has been developed in order to safely dilute it and to supply it to the living body by inhalation, respectively. H_2 is an inert molecule which can scavenge the highly active oxidants including hydroxyl radical (·OH) and peroxynitrite ($ONOO^-$), and which can convert them into water. H_2 is clean and causes no adverse effects in the body. The mechanism of H_2 is different from that of traditional drugs because it works on the root of many diseases. Since H_2 has extensive and various effects, it may be called a "wide spectrum molecule" on diseases. In this paper, we reviewed the current medical applications of H_2 including its initiation and development, and we also proposed its prospective medical applications. Due to its marked efficacy and no adverse effects, H_2 will be a next generation therapy candidate for medical applications.

Keywords: hydrogen; medical application; medical gas; oxidative stress; inflammation; clinical efficacy; clean technology

1. Introduction

Power generation systems include thermal, hydroelectric, and solar power. In recent years, however, hydrogen (H_2) power generation has been gaining attention around the world. H_2 is a clean energy source because it does not emit carbon dioxide (CO_2) when using it for generating electricity. H_2 can be converted from fuel to electric energy through fuel cells. On the other hand, medical applications using H_2 gas can also be considered as a clean and economical technology. Even H_2 gas produced using the electrolysis method of water has the risk of explosion without the safety mechanism. Therefore, we have developed the technology in order to safely dilute it and to supply it to the living body by inhalation [1,2]. H_2 is an inert molecule which can scavenge the highly active oxidants including hydroxyl radical (·OH) and peroxynitrite ($ONOO^-$), and which can convert them into water [3]. Many clinical studies have reported that H_2 has no safety issue [4–8]. Using H_2 is a clean technology in medical applications.

In 1975, Dole et al. first reported the therapeutic applications of H_2. He demonstrated that hyperbaric hydrogen has significant anti-tumor effects in mice with skin carcinoma [9]. However, the potential of H_2 in medical applications has not been widely reported except in a few studies. In 2007, Ohsawa et al. demonstrated that H_2 has selective scavenging effects by reducing the reactive oxygen species (ROS) including hydroxyl radical (·OH) and peroxynitrite ($ONOO^-$) [3]. Since then, many studies have explored therapeutic and preventive effects of H_2. In 2005, however, 2 years before Ohsawa's study, Yanagihara et al. showed that the oxidative stress induced by chemical oxidants was significantly reduced by the daily consumption of neutral H_2-rich water produced by electrolysis in rats, indicating that this is a pioneering report in H_2 medicine [10]. H_2 has become a novel antioxidant as a result of the antiapoptotic, antioxidant, anti-inflammatory and antiallergy effects. Moreover, H_2 has marked therapeutic and preventive effects on many diseases such as cancer [11], sepsis [12], cardiovascular disease [13], brain and neurological disorder [14], diabetes [15], and metabolic syndrome [16].

2. Oxidative Stress as a Root of Many Diseases

2.1. Hydrogen Can Eliminate the Hydroxyl Radical

The human adult consumes approximately 430 L of oxygen per day at rest. However, various reactive oxygen species (ROS) are formed by imbalance between free radical and reactive metabolic production. The excessive ROS are produced by imbalance, including smoking, atmospheric pollution, ultraviolet or irradiation ray exposure, intense exercise, and physical or psychological stress etc. The oxidative stress is induced by the excessive decrease in endogenous antioxidant capacity, and indiscriminate oxidation elicits harmful effects. ROS are products of oxygen-derived small molecules involved in cellular metabolism, including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and ·OH, etc. [3]. Among the ROS, the ·OH has about 100 times greater oxidation power than O_2^- and oxidizes intranuclear DNA, while O_2^- and H_2O_2 do not have sufficient oxidation power to oxidize the DNA directly [17]. In addition, since the mitochondria produce large amounts of ROS, they are always affected by ·OH especially, and it causes DNA damage and cellular apoptosis. [3].

Since biologic membranes are quite permeable to H_2, H_2 is distributed into the cytosol, mitochondria, and nucleus [3]. H_2 is an inactive molecule that has no metabolic system in mammalian cells and does not interact with biological substances, but it is a molecule that reacts with ·OH, which occurs inside mitochondria [3]. In addition, because H_2 itself is an inert substance and the reaction product of H_2 and ·OH is a water molecule, and the production of H_2 in the intestine, adverse effects caused by H_2 has not been observed in many clinical studies [4–8]. In a recent paper, we proposed that H_2 is the only molecule that enters the mitochondria and undergoes a hydrogen withdrawal reaction from the ·OH [18]. Thus, H_2 is a molecule entering the mitochondria that can protect cells from cytotoxicity caused by ·OH. It is considered that ideal antioxidant could be H_2 because it selectively eliminates ·OH but does not have the chemical reaction with O_2^-, H_2O_2, and nitric oxide (NO·) that have physiological roles [3].

2.2. Chronic Inflammation as a Root of Many Disease

Chronic inflammation is at the root of many diseases. It is no exaggeration to say that "chronic inflammation is the source of all diseases" since the chronic inflammation is involved in many diseases. Modern medical treatment can control the acute inflammatory disease, but it cannot control chronic inflammatory disease. Many parts of inflammation are induced by releasing inflammatory cytokines produced by macrophages and neutrophils. Minor but prolonged inflammation can damage the living body and induce the chronic inflammation. Recent studies have shown that mitochondria play an important role in producing the cytokines. It has also been reported that mitochondria-related ROS activate the nucleotide-binding and oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, and its stimulation triggers producing inflammatory cytokines [19–28]. It has been shown by some studies that H_2 in the various animal models of inflammation could be based on the mechanisms by inhibitions of mitochondrial oxidation and NLRP3 inflammasome activation [29–37]. Therefore, the mitochondrial selective ·OH scavenger such as H_2 can block the cascade leading to the activation of the NLRP3 inflammasome.

3. Methods of Hydrogen Ingestion

3.1. Hydrogen Gas Inhalation

H_2 is a gas that exhibits tasteless and odorless characteristics. Inhalation of H_2 gas is one of the most straightforward therapeutic methods and provides the largest amount of H_2 gas in a time-dependent manner compared to other ingestion methods, because the maximum tissue and blood concentrations (Cmax) in H_2 gas inhalation are low, while their area under the curve (AUC) is extremely high compared to other administration routes [38,39]. It has been considered that H_2 gas will burn in air at the concentrations between 4% and 75% by volume. However, in our recent study, we investigated the safe concentrations of H_2 gas from a literature survey and explosion experiments, and we reported that H_2 gas does not explode when the concentration is less than 10% [2]. Therefore, we developed the safe H_2 gas supply system as follows [1,2].

As shown in Figure 1a,b, this H_2 gas inhaler consists of a purified water tank, cathode, anode, diaphragm, and blasting pump. The H_2 gas produced by the electrolysis of water on the surface of the cathode is immediately diluted with air to a safe concentration, and the H_2 concentration was maintained at about 5.0–6.0%. In addition, since the electrolysis is designed to stop when the blasting pump is inactive, the lower explosive limit concentration of H_2 gas will not be exceeded. Patients can inhale the H_2 gas through a nasal cannula or mask connected to a H_2 gas outlet for a long time.

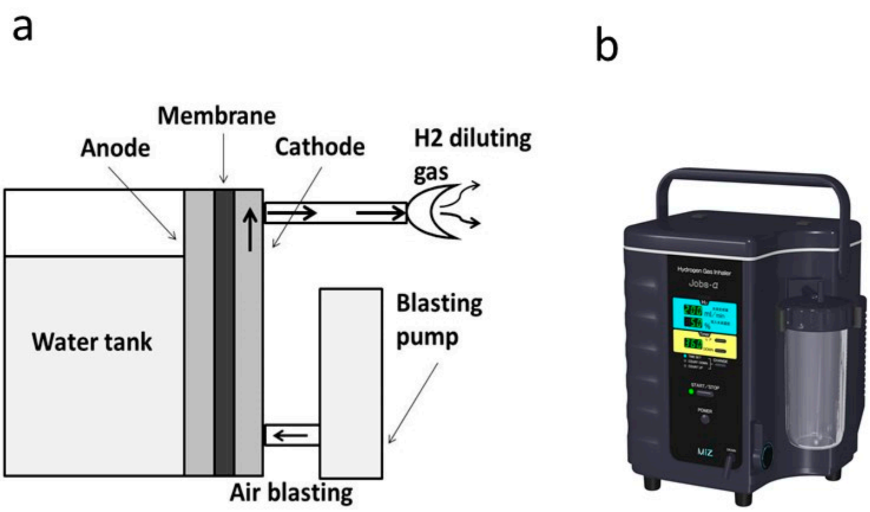

Figure 1. Schematic diagram (**a**) and photograph (**b**) of a hydrogen gas inhaler. The H_2 gas produced by the electrolysis of water on the surface of the cathode is immediately diluted with air to a safe concentration, and the H_2 concentration was maintained at about 5.0–6.0%.

3.2. Oral Ingestion by Drinking Hydrogen Water

The solubility of H_2 gas under normal temperature and pressure conditions is 1.6 ppm (1.6 mg/L; 0.8 mM). As the pressure increases, however, H_2 can be dissolved in water in a pressure-dependent manner (Henry's Law). Therefore, we developed super-saturated H_2 water (10 ppm-water) for drinking using H_2-generating agent with chemical reaction as follows [1]:

$$2\ Al + Ca(OH)_2 + 6\ H_2O \rightarrow Ca[Al(OH)_4]_2 + 3\ H_2$$

As shown in Figure 2a,b, in a pressure-resistant 500 mL polyethylene terephthalate (PET) bottle (e.g., Coke bottle), a non-woven fabric containing a water-wetted H_2-generating agent was first inserted into an acrylic resin tube, and the PET bottle was sealed tightly. In about 5 min at room temperature, the H_2 gas generated in the tube was released into the bottle through a check valve. After 24 h, the bottle was shaken for about 30 s to dissolve the H_2 gas and obtain 10 ppm water. We have demonstrated the important fact in the previous paper that if the bottle is not opened, the concentration of 10 ppm can be maintained for about a week (Figure 2c) [1]. This "supersaturated H_2 water" would be convenient because it is portable, easy to administer, and provides a safe way to ingest H_2.

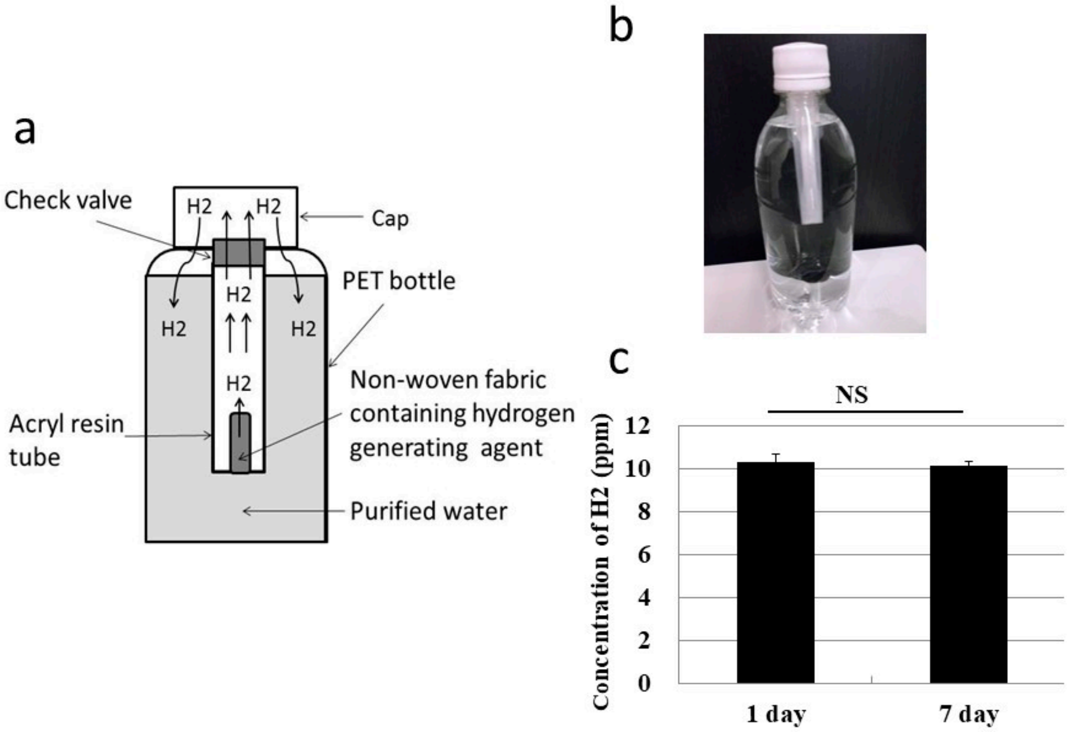

Figure 2. (**a**,**b**) Device for super-saturated hydrogen (H_2) water. In a pressure-resistant polyethylene terephthalate (PET) bottle, a non-woven fabric containing a water-wetted H_2-generating agent was inserted into an acrylic resin tube. In about 5 min at room temperature, the H_2 gas generated in the tube was released into the bottle. After 24 h, the PET bottle was shaken for about 30 s and 10 ppm water was obtained. (**c**) The concentration of 10 ppm water can be maintained for about a week. Data are shown as mean ± standard deviation (SD) for 3 or 5 experiments.

3.3. Injection of Hydrogen-Dissolved Saline

H_2 can be dissolved in saline and administered intravenously or intraperitoneally. We developed a device for injectable H_2-dissolved saline [1]. As shown in Figure 3a–c, non-woven fabric containing a H_2-generating agent was moistened with a small amount of water, and both the drip infusion bag and the non-woven fabric were wrapped in aluminum foil and vacuumed. The H_2-generating agent in the non-woven fabric reacted with water to produce H_2, and the H_2 gas permeated the polyethylene film inside the bag and dissolved aseptically into the saline. The concentration of H_2 in the infusion bag depends on its thickness and the contents of the solution. However, about 1.3 ppm of H_2 can be dissolved in normal saline solution and the H_2 concentrations in the bags can be maintained at least for 12 months without opening the aluminum foil. We named this method of dissolving H_2-saline using the device as the "non-destructive hydrogen adding method".

Cold reservation of organ grafts such as lung, heart, kidney, and liver in H_2-rich solution baths has been reported to improve organ damage due to ischemia and reperfusion [40,41]. Such a method of saturating organs with H_2 during cold preservation may ameliorate the damage during organ transplantation in humans. In addition, the H_2-rich saline is used as a rinse solution to protect corneal endothelial cells from injury during cataract surgery [42,43]. These H_2-rich solutions can be also produced by the "non-destructive hydrogen adding method".

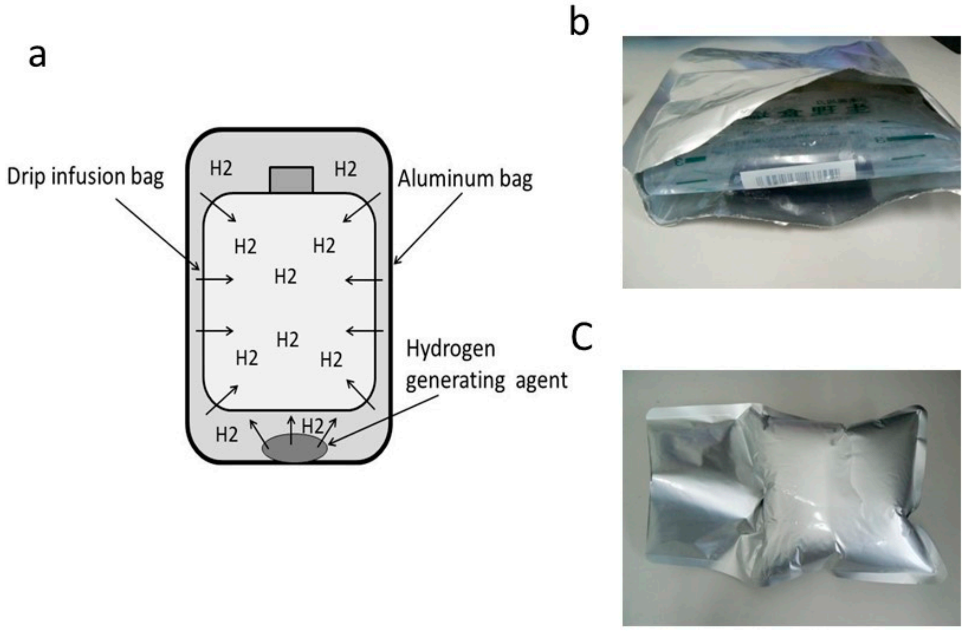

Figure 3. (**a**–**c**) Device for hydrogen (H_2)-rich saline. (**a**,**b**) Non-woven fabric containing H_2-generating agent was moistened with a small amount of water, and both the drip infusion bag and the non-woven fabric were wrapped in aluminum foil and vacuumed. (**c**) The H_2-generating agent in the non-woven fabric reacted with water to produce H_2, and the H_2 gas permeated the polyethylene film inside the bag and dissolved aseptically into the saline.

4. Effects of Hydrogen on Clinical Examinations

4.1. Effects on Brain and Neurological Disorders

Effects of H_2 on acute cerebral infarction were examined by Ono et al. [44]. The patients were intravenously treated with Edaravone (a ROS scavenger) alone (26 patients) or in a combination treatment with Edaravone and H_2-rich saline (1.6 ppm: eight patients) in a pilot study. The protective effects were significantly observed in the Edaravone and H_2-rich saline group compared to the Edaravone only group. Moreover, Ono et al. showed the effects of H_2 gas inhalation in patients with acute cerebral infarction [5]. The patients were treated with 3% H_2 gas inhalation or conventional medications (25 patients each) in a randomized controlled clinical study. He showed that H_2 gas treatment was effective with no adverse effects in patients with acute cerebral infarction.

Nishimaki et al. showed the effects of H_2-rich water on mild cognitive impairment (MCI) [8]. The subjects with MCI were orally treated with H_2-rich water (1.2 ppm; 35 subjects) or placebo water (38 subjects) for 1 year in a randomized clinical study. Although the significant difference was not observed between the H_2-group and control group, carriers of the apolipoprotein E4 (APOE4) genotype in the H_2-group (seven subjects) were improved significantly compared to the placebo water group (six subjects), suggesting that H_2-water has a potential for suppressing MCI in APOE4 carriers. Ono et al. evaluated the effects of H_2 gas inhalation in the patient with Alzheimer's disease [45]. The patients inhaled 3% H_2 gas and received oral Li_2CO_3 for 4–7 months (11 patients) in a pilot study. The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) was significantly improved in the H_2 gas inhalation group in comparison with that in the control group (five patients). Yoritaka et al. reported the effects H_2-rich water on Parkinson's disease in a randomized controlled clinical study [4]. The patients with Parkinson's disease drank H_2-water (1.6 ppm; nine patients) or placebo water (eight patients) for 48 weeks. The authors showed that drinking H_2-water significantly improved the Parkinson's disease.

Effects of H_2 water were evaluated in newborns with hypoxic-ischemia encephalopathy (HIE) by Yang et al. [46]. In the retrospective study, 40 newborns with neonatal HIE were treated with 1.2 ppm H_2 water in addition to conventional treatment or conventional treatment only (20 patients each) for 10 days after birth. The H_2 water group significantly decreased the levels of serum neuron-specific enolase (NSE), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) in comparison with the conventional group, suggesting that H_2 water has a protective effect on neonatal HIE.

4.2. Effects on Cardiovascular Disease

Tamura et al. demonstrated the effects of H_2 gas inhalation in patients with post-cardiac arrest syndrome [47]. Five patients with post-cardiac arrest syndrome (PCAS) received 2% H_2 gas inhalation and target temperature management (TTM) for 18 h in a pilot study. H_2 gas inhalation showed no undesirable effects and four patients survived 90 days with a favorable neurological outcome. In another pilot study by Tamura et al., five patients were also treated with 2% H_2 gas inhalation with TTM for 18 h [48]. In four cardiogenic patients, the oxidative stress was reduced but cytokine levels were unchanged. However, in a septic cardiac arrest patient, the cytokine levels were diminished but oxidative stress was unchanged.

Katsumata et al. reported the effects of H_2 gas inhalation in patients with adverse left ventricular remodeling after percutaneous coronary intervention for ST-elevated myocardial infarction [13]. The patients were assigned to either a treated 1.3% H_2 gas inhalation group or a control group in a pilot study. In some of the outcomes at 6-month follow-up, H_2 gas inhalation group (six patients) showed a greater numerical improvement from day 7 than control group did (5 patients), suggesting that H_2 inhalation is safe and promotes left ventricular reverse remodeling.

4.3. Effects on Thoracic Disease

As of December 16, 2020, more than 73.4 million cases of infection and 1.63 million deaths have been reported worldwide for coronavirus disease 2019 (COVID-19). Guan et al. reported the improvements of H_2-O_2 mixed gas inhalation in patients with COVID-19 [49]. In an open-label multicenter clinical trial in China, the patients with COVID-19 were divided into treatment group and control group. The patients in treatment group (44 patients) inhaled H_2-O_2 mixed gas (67% H_2: 33% O_2) daily until discharge, and the patients in control group (46 patients) received only the conventional standard-of-care (with O_2 gas therapy each day) until discharge. He showed that the improvements in disease severity, dyspnea, cough, chest distress, chest pain, and oxygen saturation were significantly greater in H_2-O_2 treatment group than those in control group. The authors suggested that H_2 gas inhalation with O_2 gas may be useful to patients with dyspnea or those in facilities without sufficient oxygen supplies.

Effects of H_2 on the lung injury of sanitation workers exposed to haze were examined by Gong et al. [50]. The clinical examination was conducted by a randomized controlled clinical trial. The patients in the treatment group inhaled H_2-O_2 mixed gas (67% H_2: 33% O_2) for 30 days, and control group inhaled N_2-O_2 mixed gas for 30 days (48 patients each). Inhalation of H_2 gas significantly could alleviate airway inflammation and oxidative stress of the sanitation workers. On the other hand, effects of H_2 gas inhalation on asthma and chronic obstructive pulmonary disease (COPD) were reported by Wang et al. [51]. An amount of 2.4% H_2 containing steam mixed gas was inhaled once for 45 min in 10 patients with asthma and 10 patients with COPD. A single inhalation of H_2 for 45 min attenuated inflammatory status in airways in patient with asthma and COPD. Moreover, Zhou et al. reported the effects of H_2-O_2 mixed gas (67% H_2: 33% O_2) in patients with severe acute tracheal stenosis [52]. Thirty-five patients were inhaled with air, oxygen, and H_2-O_2 mixed gas in that order in a prospective self-control study. A single inhalation of H_2-O_2 mixed gas for 120 min reduced the inspiratory effort in patients with acute severe tracheal stenosis in comparison with other air or oxygen treatment.

4.4. Effects on Diabetes, Liver Disease and Metabolic Syndrome

Effects of H_2-rich water on lipid and glucose metabolism in patients with either type 2 diabetes mellitus (T2DM) or impaired glucose tolerance (IGT) were examined by Kajiyama et al. [53]. The study was performed as a randomized controlled crossover study in 30 patients with T2DM and 6 patients with IGT. The patients consumed either 1.2 ppm H_2-rich water or placebo water for 8 weeks, with a 12-week washout period. The authors demonstrated that sufficient supply of H_2-rich water prevents or delays the development and progression of T2DM and insulin resistance by providing protection against oxidative stress.

Effects of H_2-rich water on oxidative stress, liver function and hepatitis B virus (HBV) were investigated in patients with chronic hepatitis B (CHB) by Xia et al. [54]. The patients were assigned into routine treatment group in which patients received routine treatment alone or additional oral 1.2 ppm H_2-rich water (30 patients each), respectively, for 6 weeks. Although H_2-rich water did not affect liver function and HBV DNA level, it significantly attenuated oxidative stress in CHB patients.

Effects of H_2-rich water were investigated by Song et al. in patients with potential metabolic syndrome in a randomized controlled study [55]. The patients were allocated to either drinking H_2-rich water (1.0–1.2 ppm) or placebo water for 10 weeks (34 patients each). H_2-rich water decreased plasma low-density lipoprotein (LDL) cholesterol levels and improved high-density lipoprotein (HDL) function. The authors also examined the effects of supplementation with H_2-rich water (0.4–0.5 ppm) on the content, composition, and biological activities of serum lipoproteins on 20 patients with potential metabolic syndrome for 10 weeks [56]. H_2-rich water decreased the serum LDL cholesterol and apolipoprotein B (apo B) levels, and improved HDL function in patients with potential metabolic syndrome. Moreover, effects of H_2-rich water (1.1–1.3 ppm) on antioxidant status of subjects with potential metabolic syndrome were also investigated by Nakao et al. [16]; twenty patients received H_2-rich water for 8 weeks in an open label pilot study. The consumption of H_2-rich water resulted in an increase in antioxidant enzyme superoxide dismutase (SOD) and a decrease in thiobarbituric acid reactive substances (TBARS). Further, subjects demonstrated an increase in HDL cholesterol and a decrease in LDL cholesterol.

Effects of H_2-rich water were investigated by Korovljev et al. in patients with non-alcoholic fatty liver disease (NAFLD) in a randomized controlled trial [57]. Twelve patients with NAFLD were allocated to receive 1.2 ppm H_2-rich water or placebo water for 28 days. Although H_2-rich water did not affect the weight and body composition, it significantly reduced liver fat accumulation and liver enzyme profiles in comparison with placebo water.

4.5. Effects on Cancer and Side Effects by Cancer Therapies

Effects of H_2 gas inhalation on 82 advanced cancer patients with stage III and IV were investigated by Chen et al. in a prospective follow-up study [58]. The H_2 inhalation (67% H_2: 33% O_2) was continued for >3 h per day for at least 3 consecutive months. After 3–46 months of follow-up, 12 patients died in stage IV. The patients reported significant improvements in fatigue, insomnia, anorexia and pain after 4 weeks of H_2 inhalation. In addition, 42.5% of patients had improved physical status. Of the 80 cases with a tumor visible in imaging, the total disease control rate was 57.5%, and it was significantly higher in stage III patients than in stage IV patients (83.0% and 47.7%). In a case study, he also showed the efficacy of H_2 therapy (67% H_2: 33% O_2) in a patient with metastatic gallbladder cancer [59], and a patient with brain metastases in non-small cell lung cancer [60], respectively. The antitumor mechanism of H_2 gas was investigated by Akagi et al. in 55 patients with stage IV colorectal cancer, and it was showed that H_2 gas (67% H_2: 33% O_2) may have restored the exhausted $CD8^+$ T cells in the patients with advanced colorectal cancer to improve prognosis [11].

Effects of drinking H_2-rich water on the quality of life (QOL) of patients treated with radiotherapy for liver tumors were examined by Kang et al. in a randomized controlled study [61]. The patients received H_2-rich water (1.1–1.3 ppm: 25 patients) or placebo water (24 patients) for 6 weeks. The H_2-rich water reduced reactive oxygen metabolites and maintained blood oxidation potential. QOL scores were significantly improved in patients treated with H_2-rich water compared to that with placebo water, suggesting that H_2-rich water reduces the blood reaction to radiation-induced oxidative stress without compromising anti-tumor effects.

Moreover, we recently examined the protective effects of H_2 gas inhalation on radiation-induced bone marrow damage in cancer patients in a retrospective observational study [62]. The patients with stage IV cancer received intensity-modulated radiation therapy (IMRT) once per day for 1 to 4 weeks. After each IMRT, the patients in the control group (seven patients) were placed in health care chamber (HCC, mild hyperbaric oxygen chamber) for 30 min; the patients in the H_2 group (16 patients) were also placed in the HCC and received 5% H_2 gas inhalation for 30 min once a day. The total number of radiation times and total exposure doses of radiation were similar between the control and H_2 groups. White blood cells (WBC) and platelets (PLT) were significantly decreased by IMRT, while red blood cells (RBC), hemoglobin (HGB), and hematocrit (HT) were unchanged. In contrast, the decrease in WBC and PLT observed in the control group was significantly improved in H_2 group. Tumor responses to IMRT were similar between the two groups.

5. Future Possibilities of Hydrogen Medicine

5.1. Problems in Modern Medicine

Modern medicine is believed to have originated from Hippocrates, who represented ancient Greece in the 5th–4th century. Hippocrates is called the "Father of Medicine". Modern medicine views the human body as an aggregation of organs and conducts microscopic analysis of organs as objects. It subdivides the object of study from organ to cell, then to molecule, and finally to gene to identify the factors that most affect diseases. Drugs are designed to act on a single factor (e.g., enzymes, receptors, genes) in order to ameliorate the diseases. These methods of modern medicine are called the "elemental reductionist approach". In modern medicine, it is also said that there is a "one-to-one relationship" between the cause of a disease and its treatment. However, many diseases are not caused by a single factor alone, but by multiple factors and a wide variety of mechanisms. In some cases, these factors are not yet understood by modern medicine.

Based on the World Health Organization's (WHO) Statistical Classification and Related Health Problems (ICD), the number of diseases should be from 30,000 to 40,000 [63]. However, pharmacopeia illustrates approximately 20,000 drugs registered [64,65]. The registered drugs with a variety of dosages are duplicated so that only several thousand drugs exist in our society. Most of the drugs used in modern medicine are symptomatic treatments and are far from being a cure for the diseases. In addition, the adverse effects are unavoidable in the use of drugs. It was reported in the Lancet in 2017 that global health care costs are increasing every year, from USD 9.21 trillion per year in 2014 to USD 24.21 trillion by 2040 [66]. As such, health care using modern medicine is approaching its limits and needs fundamental reform.

5.2. Prospective Medical Application of Hydrogen

In this paper, we demonstrated that the root of many diseases is caused by ·OH-induced oxidative stress in the mitochondria, and at the same time, the root of chronic inflammation may be also attributed to the ·OH; we have also showed that H_2 is a new and easily applicable medical therapy that can be replaced by modern medicine. Indeed, the clinical effects of H_2 were positive in patients with various diseases, and more than 70 clinical papers have been published. In traditional Chinese medicine, there is a concept called "pre-symptomatic disease" ("mibyou"), which is defined as a state without boundaries between health and illness. Even if a person is apparently healthy, the "seeds of disease" exist, but H_2 is thought to have the potential to improve the "mibyou" as well. Since the H_2 alleviates the root of disease and can treat many diseases at the same time, H_2 has potential for preventive and therapeutic applications in many diseases due to its marked efficacy with no adverse effects (Figure 4).

Since H_2 is arguably a molecule essential for the survival of life, we proposed in the recent paper that H_2 is a "philosophical molecule" [18].

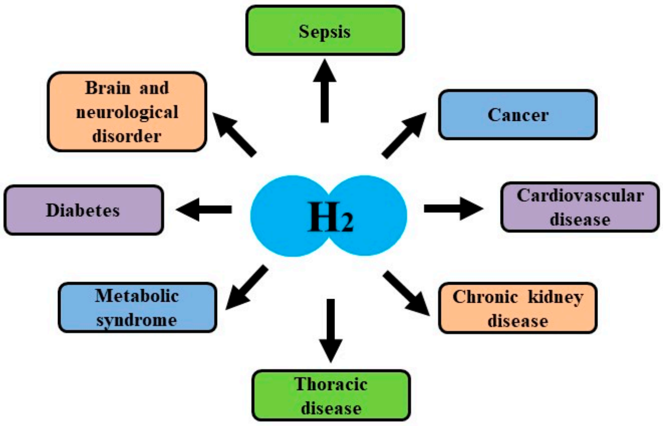

Figure 4. Therapeutic effects of hydrogen (H_2) on various diseases. The H_2 can treat many oxidative stress-related diseases without causing adverse effects.

There are many drugs that can alleviate oxidative stress. However, very few ROS scavengers have been clinically applied and they are not as effective as H_2. For example, Edaravone, which is used for acute cerebral infarction, and Amifostine, which is used as a radioprotective agent, are less effective than H_2 and have adverse effects [44,67]. In addition, non-steroidal anti-inflammatory drugs (NSAIDs), steroids, and biological products such as anti-IL-6 monoclonal antibody and anti-TNF-α monoclonal antibody have been applied clinically as anti-inflammatory drugs. However, these drugs have less effects and adverse effects. Therefore, H_2 is an ideal antioxidant with potent anti-inflammatory effects and without adverse effects.

In the recent pre-clinical studies, hydrogen nanomedicine to address the issues of H_2 medicine by using functional/nanomaterials for augmented H_2 therapy has been reported [68–71]. Zhao et al. demonstrated that local generation of H_2 for enhanced photothermal therapy has a cancer-selective effects on synergistic cancer [69]. Yu et al. also demonstrated that hydrogen-releasing Pd hydride (PdH) nanoparticles exhibits antibacterial and wound-healing effects [70]. Moreover, Zhang et al. also showed that PdH nanoparticles have ameliorating effects on the cognitive impairment in Alzheimer's disease model mice [71].

In Japan, H_2 gas has been approved by the Ministry of Health, Labor and Welfare as an advanced medical treatment B and is under clinical study as a treatment for post-cardiac arrest syndrome [72]. Following this clinical study, the pharmaceutical approval of H_2 gas as a medical gas is planned. Apart from this clinical study, we are also trying to develop a H_2 gas inhaler as a medical device. The day will come when H_2 gas or H_2 gas inhalers will be used in the market as a medical gas or a medical device in the near future.

6. Conclusions

This article reported the progress and perspective of hydrogen medicine including its initiation and clinical applications. H_2 is easily applicable because it has no adverse effects and shows marked efficacy for many diseases, including oxidative stress-related diseases and chronic inflammatory diseases. More than 70 papers reported the clinical effects of H_2 on various diseases. Although most traditional drugs specifically act on each target, H_2 works on the root of many diseases. It is different from the traditional drugs from the viewpoint of efficacy and adverse effects. Since H_2 has extensive and various effects, it may be called a "wide spectrum molecule" on diseases. Moreover, due to its marked efficacy with no adverse effects, H_2 has promising potential for clinical applications on many diseases. H_2 will be a next generation therapy candidate with clean and economical medical technology.

Author Contributions: Conceptualization, S.-i.H. and Y.T.; methodology, S.-i.H., B.S. and F.S.; investigation, S.-i.H. and Y.I.; writing—original draft preparation, S.-i.H., writing—review and editing, S.-i.H., Y.I., B.S., F.S. and Y.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: The authors are grateful to Yoko Satoh and Yoshihiro Mitekura (MiZ Company Limited) for their excellent advice on writing this manuscript.

Conflicts of Interest: S.-i.H., Y.I., B.S. and F.S. are employees of MiZ Company Limited. For Y.T., a resource was provided by MiZ Company Limited, which manufactures and markets hydrogen-ingesting machine and device.

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