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A comprehensive review of molecular hydrogen as a novel nutrition therapy in relieving oxidative stress and diseases: Mechanisms and perspectives

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ABSTRACT

Oxidative stress is responsible for the pathogenesis of many diseases, and antioxidants are commonly included in their treatment protocols. Over the past two decades, numerous biomedical reports have revealed the therapeutic benefits of molecular hydrogen (H_2) in relieving oxidation-related diseases. H_2 has been found to have selective antioxidant properties against the most dangerous oxidants (hydroxyl radicals and peroxynitrite). H_2 demonstrates numerous biologically therapeutic properties, including anti-inflammatory, antioxidant, anti-cancer, anti-stress, anti-apoptotic, anti-allergic effects, signaling molecule functions, regulation of redox balance, modulation of antioxidant enzyme gene expression, improvement of blood vessel function, down-regulation of pro-inflammatory cytokines, stimulation of energy metabolism, and protection of the nervous system. Experimental and clinical studies have shown the potential use of hydrogen nutrition therapy for ameliorating various diseases, including cardiovascular, respiratory, and metabolic disorders, as well as obesity, gastrointestinal disorders, and brain and nervous system disorders. The administration methods of hydrogen include inhalation, hydrogen-rich water, hydrogen-rich saline, hydrogen-rich eye drops, and hydrogen-rich bathing. Hydrogen nutritional therapy can be applied to different diseases, and it offers a natural alternative to chemical and radiation therapies. This review covers the different administration methods and the latest experimental and clinical research on the potential applications of H_2 in nutritional therapy for different diseases.

1. Introduction

The human body generates free radicals during various physiological processes, such as respiration and inflammation. Free radicals, which include reactive oxygen species (ROS) and reactive nitrogen species (RNS), have important roles in various physiological functions. However, when these levels become excessive, they can lead to oxidative stress-related diseases and disorders of the cardiovascular, gastrointestinal, metabolic, neurodegenerative, liver, and respiratory systems [1]. The body has a natural defense system against free radicals that includes both enzymatic and non-enzymatic antioxidants. Enzymatic antioxidants consist of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX), while non-enzymatic antioxidants include glutathione and thioredoxin. However, during inflammation and illness, these endogenous antioxidant defense systems may become overwhelmed and unable to effectively neutralize the excessive free radicals. In such cases, the use of external antioxidants becomes necessary to restore balance [2,3].

Although H_2 is chemically stable due to the strong covalent bond of its atoms and the high dissociation energy of 107 kcal/mol [4], the discovery of its selective antioxidant properties against hydroxyl radical ($^{\bullet}OH$) and peroxynitrite ($ONOO^-$) by Ohsawa et al., in 2007 surprised the research community. This is because cells contain more abundant compounds with lower dissociation energy, and thus higher antioxidant activity than H_2 [5]. Another attractive property of H_2 is its ability to easily cross the blood-brain barrier and penetrate biomembranes, diffusing throughout the different tissues and organs. The above-cited properties led some researchers to refer to it as a "miracle" molecule

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[6]. H_2 has been the subject of hundreds of studies investigating its potential health benefits [7]. Studies have shown that H_2 positively affects weight control, inflammation, metabolic markers, and diseases (Fig. 1) [8–15]. Although several reviews have been published on the use of molecular hydrogen in medicine [8,16–19], none have specifically addressed its potential as a nutritional therapy for preventing and treating diseases related to oxidative stress. This review examines recent findings on hydrogen's role in managing oxidative stress-related diseases from a dietician's perspective.

2. Properties of molecular hydrogen

H_2 is the smallest known molecule, with a gas property at standard pressure and temperature conditions and a density of 0.089 g/L [20]. H_2 refers to hydrogen gas, which is a colorless, odorless, tasteless, non-toxic, and non-metallic gas. It has a relatively low solubility in water, with a concentration of 0.8 mmol per liter (1.6 mg/L or 1.6 parts per million by weight) under standard conditions. It has a high diffusion rate, conductivity, and specific heat [21]. H_2 can combust at concentrations between 4 and 75 % in air and cause an explosion between 18.3 and 59 % (v/v). Diluting H_2 with nitrogen (N_2) can lower these levels [22–24]. Regarding biological properties, H_2 is a selective antioxidant. It can reduce hydroxyl radicals and, to a lesser extent, peroxynitrite, protecting the cells against oxidative reactions [7]. Studies indicate that H_2 reduces oxidative stress and improves the cellular antioxidant system [25]. Moreover, it enhances the activity and expression of cellular antioxidant enzymes [26,27]. It can also regulate apoptosis-related factors, reducing apoptosis and neural damage and reducing the amount of inflammatory cytokines and immunocyte stimulation [28,29].

Regarding the biosafety of hydrogen, numerous reports, including those from the US government and the EU, have indicated that hydrogen is safe for biological systems, showing no acute or chronic toxicity under normal pressure [30]. Furthermore, the human large intestine often produces approximately 70–140 mL of hydrogen daily through the action of coliform bacteria such as *Escherichia coli* under typical environmental conditions. This production can increase with the intake of dietary fibers and sugars to over 10 L/day. Internally produced hydrogen has been shown to have several beneficial health effects, including cardioprotective properties, improved liver function, reduced oxidative stress, and prevention of Parkinson's disease [30]. However, external hydrogen intake (drinking hydrogen-rich water or inhaling hydrogen gas) has shown more potent biological activities, as the intermittent administration of hydrogen may have a more powerful effect than a continuous one [31].

3. Hydrogen administration methods

There are various methods for administering H_2, including inhalation, drinking hydrogen-rich water (HRW), injecting hydrogen-rich saline (HRS), taking a hydrogen-rich bath, and using hydrogen-rich eye drops (Fig. 2) [32].

3.1. Inhalation of hydrogen gas

Inhalation of H_2 can be easily administered through a face mask or nasal cannula [33]. The method is accomplished via electrolysis and can involve combining hydrogen with oxygen gas in a 2:1 ratio or as separated gases where pure H_2 gas is inhaled along with the outside air. These methods can be an effective treatment against acute oxidative stress, particularly those associated with the respiratory system. The encouraging aspect of this is that H_2 inhalation does not affect blood pressure and does not present any side effects or danger to patients [7,34]. The inhalation of hydrogen is considered safe at concentrations of up to ≈80 %, as to ensure sufficient O_2 concentrations [30].

3.2. Hydrogen-rich water (HRW)

The use of HRW is arguably more practical than inhalation because of its ease of transport and application. Inhalation of hydrogen may not be practical during outdoor activities [35,36]. H_2 dissolves in water by approximately 0.8 mM (1.6 mg/L) at standard ambient temperature and pressure conditions without changing the pH value [37]. HRW can be obtained in several ways, including electrolysis of water, bubbling H_2 into water, and mixing metallic non-ionic magnesium (Mg) or its hydride form (MgH_2) with water [27,33].

3.3. Hydrogen-rich saline (HRS)

Although drinking HRW is safe, controlling the amount of dissolved hydrogen can be challenging as it escapes over time, and some is lost during absorption in the body's organs and tissues via exhalation [38]. To prevent this loss, H_2 can be administered intraperitoneally or intravenously by injecting HRS [27]. By administering H_2 through an injectable HRS method, a more precise amount of H_2 can be delivered. This method can relieve symptoms such as pain and fever in patients

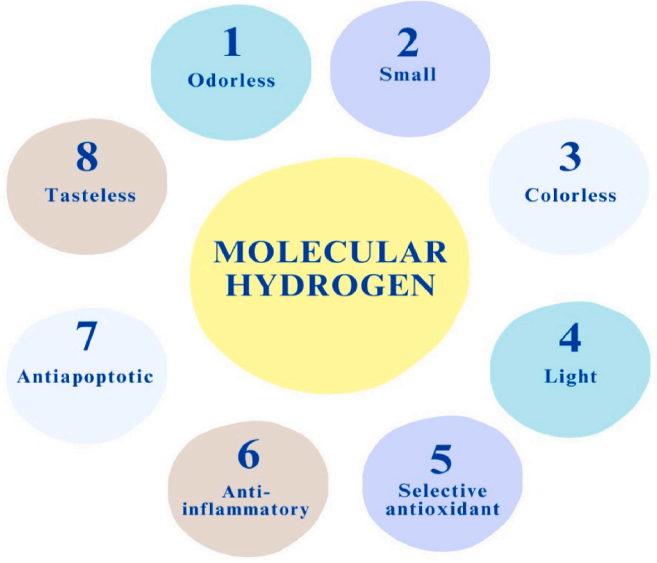

Fig. 1. Properties of molecular hydrogen.

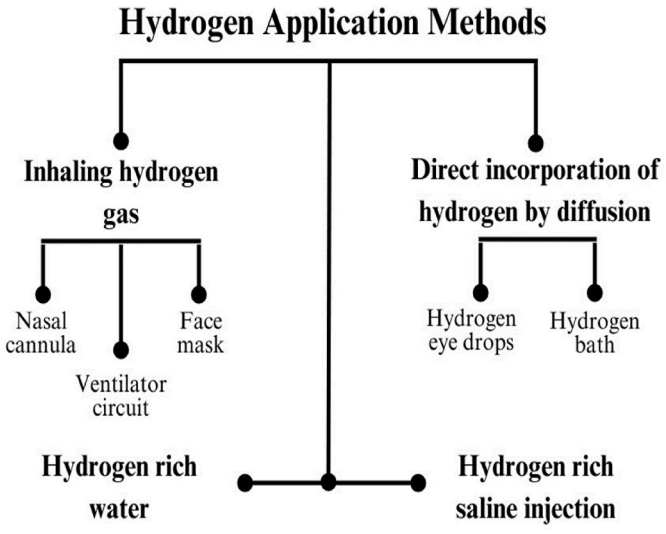

Fig. 2. Hydrogen administration methods.

with acute erythematous skin conditions [39]. It can also be used in the treatment of patients with viral infections, hypertension, liver damage, diabetes, and various other diseases [6,32,40,41].

3.4. Hydrogen administration by diffusion: hydrogen eye drops and a hydrogen bath

Hydrogen-rich eye drops are created by infusing H_2 into a saline solution and can be applied directly onto the surface of the eye. Several studies have reported an improvement of approximately 70 % on the ocular surface as a result of the continuous application of H_2-rich eye drops [42,43].

Regarding the H_2-rich bath, H_2 in warm HRW can quickly penetrate skin and tissues, diffusing throughout the body by blood flow [32]. This can reduce the appearance of spots on the body, lighten dark spots, and improve lipid metabolic markers and visceral fat area [44].

4. Effect of H_2 on nutrients

In addition to impacting human health, hydrogen also affects plant growth and the nutritional value of crops [45]. Moreover, applying hydrogen to postharvest crops and foods can extend their shelf life and preserve their quality properties [46–53].

The ability of molecular hydrogen to facilitate the separation of phytochemicals from its source of plant material through the extraction process has been recently demonstrated [54]. Many recent reports have revealed that molecular hydrogen's specific physical, chemical, and biological properties make it highly effective in the extraction of phenolics and antioxidants [55]. For example, the use of HRW as a solvent has been shown to improve the extraction of many phytochemicals, such as anthocyanins, flavonoids, and phenolic acids, from various crop and fruit parts [55–59]. This novel extraction technique led to a several-fold increase in phenolic substances like gallic acid, *p*-coumaric acid, epicatechin, and rutin [60]. It is possible that consuming HRW together with plant-based meals may improve the separation of bioactive compounds during digestion, leading to improved bioavailability [61]. However, this hypothesis requires further research studies to confirm its validity.

5. H_2 administration in the nutritional therapy of different diseases

Hydrogen nutritional therapy is an emerging field with promising potential as a natural and eco-friendly treatment alternative to chemical and radiation therapies. Administration of H_2 can help prevent and alleviate a variety of diseases, including cardiovascular, respiratory, and metabolic disorders, obesity, gastrointestinal issues, and brain and nervous system disorders (Fig. 3).

Regarding the dose and the administration protocol of hydrogen, up to now there is no defined or standard dosage or protocol. Researchers used different dosages and protocols in their studies. However, Nakao and co-workers outlined the following protocol for administering hydrogen-rich water (HRW) in their study on the potential preventive and therapeutic effects of HRW for individuals at risk of metabolic syndrome [62].

- 300–400 mL 1 h before breakfast
- 300–400 mL 1 h before lunch
- 300–400 mL 2 h after lunch
- 300–400 mL 1 h before dinner
- 300–400 mL 30 min before bedtime

In total, individuals should consume 300–400 mL five times a day, which is 1.5–2 L of HRW per day, corresponding to a dosage of 1.65–2.6 mg H_2/day (Table 1).

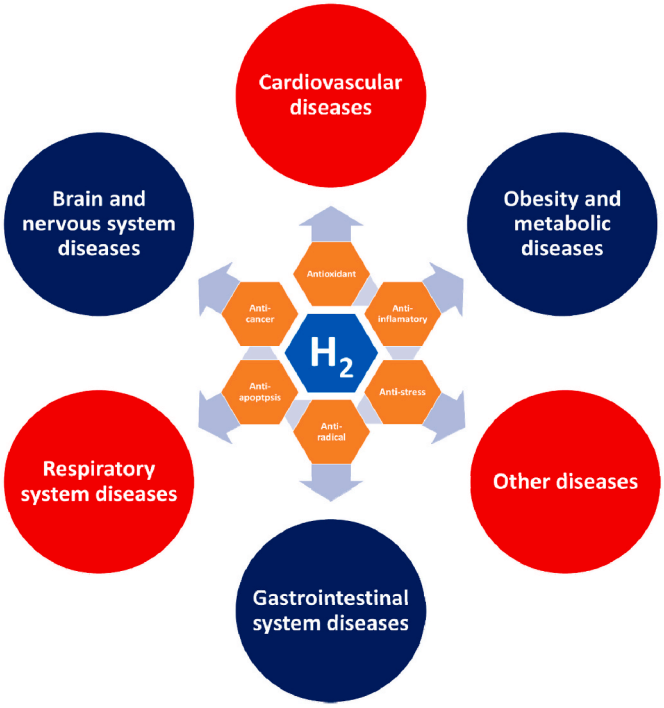

Fig. 3. Diseases for which hydrogen nutritional therapy is applicable.

5.1. Hydrogen nutrition therapy application in cardiovascular diseases

The excessive production of free radicals leads to the oxidation of LDL and cell membrane affecting Endothelin-1, leading to vasoconstriction [1]. Additionally, the excessive production of ROS leads to the activation of various hypertrophic signaling kinases and transcription factors, which promote myocardial growth, matrix reorganization, and cellular dysfunction [3].

Nutrition plays a crucial role in preventing and managing cardiovascular diseases. These conditions include high levels of triglycerides, high levels of LDL-cholesterol, low HDL-cholesterol, damage to the structure and function of the heart and blood vessels, high blood pressure, accumulation of fat tissue, and chronic inflammation [63–65].

Studies have shown that a well-balanced and nutritious diet, with a low meat and sugar intake and high consumption of fruits, vegetables, legumes, and grains, can considerably reduce the risk factors for cardiovascular disease. Furthermore, dietary approaches such as Mediterranean and DASH diets have been found to be effective in reducing risk factors associated with cardiovascular diseases [65,66].

Hydrogen nutritional therapy can be a useful preventive tool for cardiovascular disease (Fig. 4). A research study explored the potential cardiovascular benefits of HRW consumption in mice with high-fat diet-induced obesity (DIO). The study results revealed that the two-week consumption of HRW did not lead to an increase in blood glucose or body weight. However, it resulted in various positive effects, such as reduced heart weight, improved cardiac hypertrophy, narrowed cardiomyocyte width, dilated capillaries, and arterioles. Furthermore, HRW consumption restored left ventricular function to baseline levels. The study also revealed that HRW activated the expansion, differentiation, and mobilization of EPCs, which maintained vascular homeostasis. As a result, it was revealed that HRW administration can exert cardiovascular protective impacts in DIO mice [67].

In a study by Song et al. (2013), the effects of HRW consumption on the structure, presence, and biological potency of serum lipoproteins were evaluated in 20 patients with metabolic syndrome. The study found that consuming 0.9–1.0 L of HRW per day for 10 weeks reduced serum total cholesterol and LDL cholesterol levels, as well as

Table 1
Effect of molecular hydrogen administration on obesity, diabetes, and metabolic syndrome.

Disease	Model System	H_2 Application Method	H_2 Concentration	Dosage	Treatment Duration	Outcomes	Reference
Metabolic syndrome	10 men 10 women	1.5–2.0 L/day drinking HRW orally	0.55–0.65 mM	1.65–2.6 mg H_2/day	8 weeks	SOD: ↑ TRABS: ↓ HDL: ↑ Total cholesterol/HDL: ↓ Glucose level:=	[62]
Obesity and Diabetes	Leprdb/db mice, HFD-induced obesity mice	Orally *ad libitum* drinking HRW	0.8 mmol/L	15 mg H_2/Kg	3 months	Hepatic oxidative stress and lipid accumulation: ↓ Body weight, serum FBG, TG, insulin: TC, LDL, HDL: NSC	[37]
Obesity	high-fat diet-induced obesity mice	0.5 mL of saline intragastrically once a day	>0.6 mmol/L.	0.0006 mg/day	42 days	Body weight, total cholesterol, total glyceride, low-density lipoprotein: ↓ high-density lipoprotein: ↑	[101]
Obesity	2 men 2 women	10-min hydrogen bath once daily	300–310 μg/L	–	1–6 months	Visceral fat, LDL in two women: ↓	[44]
Obesity	10 women	Oral intake of H_2 generating minerals	~6 ppm	–	4 weeks	Body fat, arm fat index, TG, insulin: ↓ Ghrelin: ↑, Lactate: ↓ BW, FBG, other lipid parameters: NSC	[74]
Metabolic syndrome	30 men 30 women	Orally drinking HRW	>5.5 mmol H_2/day	11 mg H_2/day	6 months	BMI, WHC, TG, TC, LDL, HDL, FBG, HbA1c: ↓ TNF-α, IL-6, CRP: ↓ MDA: ↓, TBARS: NSC Vitamin E, Vitamin C: ↑	[77]
Metabolic syndrome	12 men 8 women	Orally drinking 0.9–1.0 L HRW	0.2–0.25 mM	0.4–0.5 mg H_2/day	10 weeks	TC, LDL, apoB100, apoE: ↓ TG, HDL, FBG: NSC MDA: ↓, SOD: ↑ TNF-α, IL-6: NSC	[68]
Metabolic syndrome	10 men 10 women	Orally drinking HRW	0.55–0.65 mM	1.65–1.95 mg H_2/day	8 weeks	SOD: ↑ TBARS: ↓ HDL: ↑ (4. weeks)LDL, TC/HDL: ↓ TC, TG, FBG: NSC	[78]
T2DM/IGT	18 men 18 women	Orally drinking HRW	~1.2 mg/L	1.08 mg H_2/day	8 weeks	sdLDL, emLDL, u-IsoP: ↓, ox-LDL: ↑ Glucose tolerance: ↑ TG, TC, LDL, HDL, FBG, HbA1C, insulin: NSC	[76]
Type 2 DM	HFD and low-dose STZ-induced DM rat	Orally drinking HRW	1.2 ppm	1.08 mg H_2/day	3 weeks	FBG, TG, TC, LDL-c, HDL-c, IL-1β, hepatic fat, renal and spleen tissue damage: ↓ GHb: NSC	[75]
Type 2 DM	HFD and STZ-induced DM mice	Subcutaneous injection of H_2 gas at 1 mL/mouse/week	100 %	1 mL H_2/mouse/week	4 weeks	AKŞ, insulin, TG, LDL-c: ↓ HDL-c: ↑ Glucose tolerance and insulin sensitivity: ↑ Diabetic renal injury: ↓	[102]
Type 2 DM	HGHFD-induced insulin resistance rat model, high glucose and HFD and low-dose STZ-induced DM rat	Oral gavage of HRS	–	10 mL HRS/kg	2 months	IR: FBG, insulin, TG, TC, LDL-c: ↓ Insulin sensitivity: ↑ DM: FBG, TG, TC, LDL-c: ↓	[103]
Type 2 DM	HFD and low-dose STZ-induced DM rat	Orally 3 mL *ad libitum* drinking HRW	1.0 ppm	0.003 mg H_2/day	14 days	Insulin: ↑ IRs expression in adipose and skeletal muscle tissues: ↑	[104]
Type 2 DM	HFD and low-dose STZ-induced DM rat	Intragastric injection of 500 μl HRS	>0.6 mmol/L	0.0006 mg H_2/day	80 days	FBG, TG, TC, LDL-c: ↓ HDL-c: ↑ Insulin resistance, pancreatic islets and glomeruli damage: ↓ Insulin: NSC	[105]
Type 2 DM	Lepr *db/db* mice	Orally *ad libitum* drinking HRW	0.8 mM	0.024 mg H_2/day	3 months	FBG, insulin, TG, hepatic fat: ↓	[37]
Type 2 DM	Lepr *db/db* mice	Orally drinking ERW	0.3–0.6 mg/L	–	6 weeks	FBG: ↓ insulin: ↑; glucose tolerance: NSC	[106]
Type 1 DM	STZ-induced T1DM mice	Orally drinking ERW	0.3–0.6 mg/L	–	6 weeks	FBG: ↓ Insulin: NSC Glucose tolerance: ↑	[106]

Abbreviations WAT, white adipose tissue; PON-1, paraoxonase-1; BAT, brown adipose tissue; HR, heart rate; FFA, free fatty acids; 4-HNE, 4-hydroxy-2-nonenal; PGPC, 1-palmitoyl-2-glutaroyl-sn-glycero-3-phosphatidylcholine; PONPC, 1-palmitoyl-2-(9-oxo-nonanoyl)-sn-glycero-3-phosphatidylcholine; PAzPC, 1-palmitoyl-2-azelaoyl-sn-glycero-3-phosphatidylcholine; Lp-PLA2, lipoprotein-associated phospholipase A2; LCAT, lecithin:cholesterol acyltransferase; HFD, high-fat diet; STZ,

streptozotocin; FBG, fast blood sugar; TG, total triglyceride; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; IL-1β, interleukin-1 beta; GHb, glycated hemoglobin; HGHFD, high glucose and high fat diet; IR, insulin resistance; IRs, insulin receptors; Lepr db/db, db/db with leptin receptor deficiency; HRW, hydrogen rich water; HRS, hydrogen rich saline; ERW, electrolyzed reduced water; IGT, impaired glucose tolerance; sdLDL, small dense LDL; emLDL, electronegative charge of modified LDL; u-IsoP, urinary 8-isoprostanes; oxLDL, oxidized LDL; HbA1C, hemoglobin A1c; TBARS, thiobarbituric acid reactive substances; apoB100, apolipoprotein B100; apoE, apolipoprotein E; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; BMI, body mass index; WHC, waist-hip circumference; CRP, C-reactive protein; MDA, malondialdehyde; ALP, alkaline phosphatase; BA, brachial artery; ⇓, insignificant decrease; ⇑, insignificant increase; NSC, no significant change; No, not available [107].

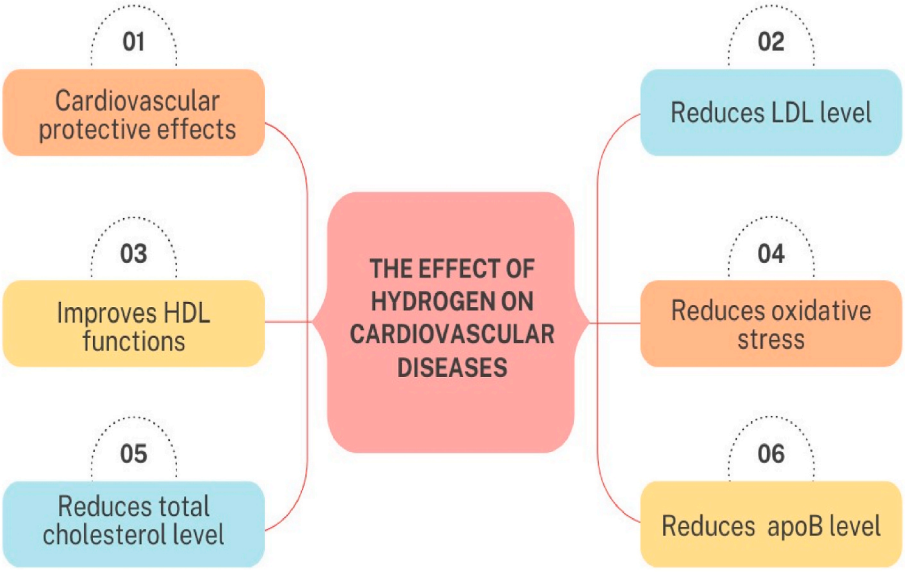

Fig. 4. The effect of hydrogen nutrition therapy on cardiovascular disease.

apolipoprotein (apo) B100 and apoE. Furthermore, the study concluded that HRW significantly improved HDL functionality by protecting endothelial cells from tumor necrosis factor alpha (TNF α)-induced apoptosis, inhibiting TNF-α-induced monocyte adhesion to endothelial cells, stimulating cholesterol efflux from macrophage foam cells, and protecting against LDL oxidation. The study also found a decrease in reactive substances of thiobarbituric acid reactive substances in whole serum and LDL. At the same time, HRW intake increased the level of the antioxidant enzyme, i.e., superoxide dismutase. The study proposed HRW intake as a helpful tool to prevent possible metabolic syndrome by reducing serum LDL cholesterol levels and apoB grades, reducing oxidative stress, and improving HDL functions damaged by dyslipidemia [68].

Another recent study examined the impact of drinking 0.9 L per day of HRW versus regular water for 10 weeks in 68 patients with high cholesterol levels. Although there was no difference in HDL-cholesterol levels in the blood, the pre-β-HDL levels increased. Furthermore, HRW intake improved various HDL functions, such as protecting against LDL oxidation, inhibiting oxidized LDL-excited inflammation, and protecting endothelial cells from oxidized LDL-excited apoptosis. The study also showed that drinking HRW decreased LDL cholesterol levels (47.06 % vs. 23.53 %) and total cholesterol (47.06 % vs. 17.65 %) in the blood. Furthermore, HRW treatment significantly reduced some inflammatory and oxidative stress markers in both the full plasma and HDL corpuscles. The study findings suggest that H_2 can potentially reduce hypercholesterolemia and atherosclerosis [69].

5.2. Hydrogen nutrition therapy application in obesity and metabolic disorders

The excessive production of free radicals can induce discontinuation of the gastrointestinal tract barrier, thereby causing the inflammation and the loss of redox homeostasis observed in some gastrointestinal diseases and implicated in the pathogenesis of several gastrointestinal disorders [2].

Individuals diagnosed with metabolic syndrome (MetS), impaired glucose tolerance, diabetes, and obesity tend to have higher fasting plasma glucose levels (above 110 mg/dl), triglyceride levels (above 150 mg/dl), and lower levels of HDL cholesterol (below 50 mg/dl in women and 40 mg/dl in men). Other conditions such as hypertension, high CRP, and abdominal obesity have also been linked to metabolic diseases [70,71].

By adhering to a healthy lifestyle and eating habits, positive improvements in diseases can be achieved. When discussing the nutritional model that can help with these diseases, it is important to mention reducing the intake of saturated fats and increasing the intake of unsaturated fats. The Mediterranean diet is a good example, as it recommends increasing the consumption of fruits, vegetables, nuts, legumes, whole grains, fish, and fiber, while also incorporating complex carbohydrate-rich foods, as well as foods rich in sterols and stanols [72]. In addition to the Mediterranean diet, other nutritional styles that have positive effects on obesity and metabolic diseases include vegan, vegetarian, Korean, Paleolithic, ketogenic, and DASH diets [65,73].

Recent studies have shown that H_2 has the potential to effectively treat diseases related to oxidative stress, such as obesity, diabetes, and metabolic syndrome (Fig. 5). This can be done through various administration methods, such as hydrogen saline injection, hydrogen gas inhalation, and HRW intake [37] (Table 1).

In a double-blind, placebo-controlled crossover pilot study, Korovljev and co-workers (2018) investigated the effects of molecular hydrogen on hormonal status, body composition, and mitochondrial function in 10 middle-aged obese women. During the study, participants received a mineral tablet providing approximately 1.6 mg of H_2 or a placebo capsule every day orally for four weeks. Although there were no significant differences between the treatment and control groups in weight changes, body mass index, and body circumference, hydrogen

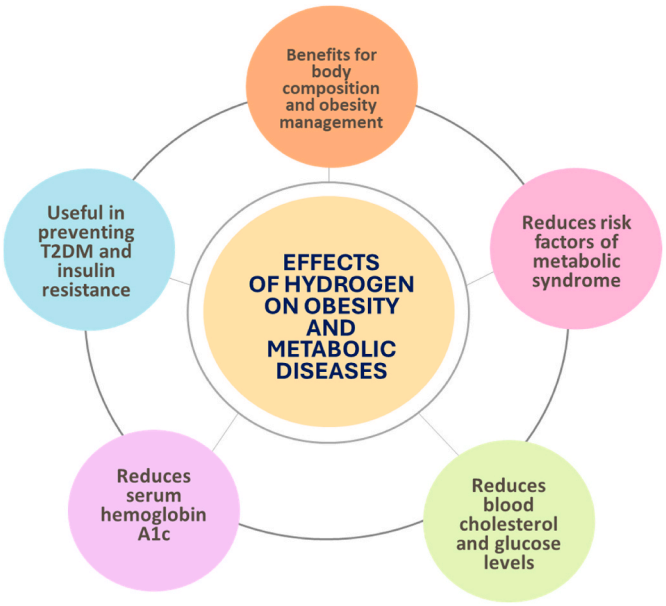

Fig. 5. Effects of hydrogen nutrition therapy on obesity and metabolic diseases.

treatment significantly reduced arm fat index (from 9.7 % to 6.0 %) and body weight percentage (from 3.2 % to 0.9 %) compared to the placebo group. Furthermore, there was a notable decrease in serum triglycerides after the H_2 intervention (21.3 % vs. 6.5 %), while other blood lipids did not change during the study. Fasting serum insulin level decreased by 5.4 % after hydrogen intervention, while it increased by 29.3 % in the placebo group. The study suggests that orally administered hydrogen, as a combination of hydrogen-producing minerals, may be a helpful tool for controlling body composition and insulin resistance in overweight individuals [74].

A recent study investigated the potential benefits of HRW consumption on glucose and lipid metabolism, inflammation, and oxidative stress in mice with type 2 diabetes mellitus (DM2). The study used well-modeled T2DM mice in two groups. The first group was fed a high-fat diet and consumed purified water or HRW at 1.0 mg/L. The control group included normal mice who followed a regular diet and consumed purified water. After three weeks of treatment, multiple biomarkers were evaluated to assess glucose and lipid metabolism, inflammation, oxidative stress, and other factors. The results showed that the consumption of HRW can help alleviate the increase in glucose, total cholesterol, oxidative stress, and inflammation. Furthermore, HRW can also improve the liver, kidney, and spleen dysfunction caused by hyperglycemia. The study concluded that daily consumption of HRW by patients with Type 2 diabetes can potentially improve their condition [75].

Another clinical study investigated the effects of drinking HRW on patients with lipid metabolism, glucose metabolism, and DM2 or impaired glucose tolerance (IGT). The study comprised 30 patients with Type 2 DM who underwent diet therapy and exercise and 6 patients with IGT. Patients were randomly divided into two groups: one group received 900 mL of HRW daily for 8 weeks with a 12-week washout period, and the other group received 900 mL of placebo pure water. The study showed that drinking HRW was associated with a significant decrease (15.5 %) in modified low-density lipoprotein cholesterol (LDL), and urinary 8-isoprostane levels. HRW intake also led to a tendency to decrease serum concentrations of oxidized LDL and free fatty acids and an increase in plasma levels of adiponectin and extracellular superoxide dismutase. Drinking HRW normalized the oral glucose tolerance test in 4 out of 6 patients with IGT. These findings suggest that HRW drinking could play a beneficial role in preventing Type 2 DM and insulin resistance [76].

A study investigated the effects of HRW drinking on type 2 diabetes in obese db/db mice lacking functional leptin receptors. The results revealed that HRW consumption significantly reduced oxidative stress in the liver and fatty liver induced by a high-fat diet. In addition, long-term consumption of HRW significantly controlled body weight and fat without increasing diet or water intake. Furthermore, HRW was found to reduce plasma glucose, insulin, and triglyceride levels, increase the expression of FGF21, a hormone that enhances the consumption of glucose and fatty acids, and stimulate energy metabolism. These findings indicate that HRW intake has potential benefits to improve obesity, diabetes, and metabolic syndrome [37].

A randomized, double-blind, placebo-controlled trial was conducted on 60 individuals diagnosed with metabolic syndrome. The trial included an initial one-week observation period to record baseline clinical data. This was followed by a 24-week treatment phase in which participants were randomly assigned to receive a placebo or highly concentrated HRW (>5.5 mmol H_2 per day) through randomization. The study concluded that the administration of high-concentration HRW could significantly lower blood cholesterol and glucose levels, mitigate serum hemoglobin A1c, and improve inflammation and redox homeostasis biomarkers compared to the placebo group. Furthermore, HRW slightly affected body mass index and waist-hip ratio reduction. Based on these findings, the report suggested that high-concentration HRW may have the potential as a therapeutic approach to mitigate the risk factors associated with metabolic syndrome [77].

Another study was conducted in 20 people at risk of metabolic syndrome. Participants were asked to consume HRW for two months. The study found that this consumption of HRW increased the antioxidant enzyme, that is, superoxide dismutase (SOD), in urine by 39 % and decreased reactive substances of thiobarbituric acid (TBARS) by 43 %. Furthermore, participants experienced a 13 % decrease in total cholesterol/HDL cholesterol from baseline to week 4, and an 8 % increase in HDL cholesterol was observed. The study concluded that HRW drinking may be a preventive and therapeutic method for metabolic syndrome [78].

Another study explored the effects of HRW bathing on internal organ fat and weight loss. Participants were immersed in a warm hydrogen water bath for 10 min daily for one month. They did not make any changes to their diet or exercise regimen. The results showed that the abdominal circumference of two individuals decreased significantly after one month. The abdominal circumference of one person reduced from 91 to 82 cm, and the other individual decreased from 79 to 74 cm. The wrinkles in their abdomen disappeared, and their abdomen became tighter. After three months, the internal fat area of these individuals also decreased significantly. The internal fat area of one person decreased from 99 cm^2 to 76 cm^2, and the other decreased from 47 cm^2 to 36 cm^2. The study suggests that a hydrogen bath can effectively penetrate the skin and reach the internal organs of the body, thereby improving the visceral fat area and lipid metabolic markers [44].

Ulcerative colitis (UC) is a common disease that affects the rectum and the colon mucosa, causing severe abdominal pain, bloating, weakness, and diarrhea. A high-energy, high-protein diet (15–20 % of daily energy) rich in vitamins and minerals and low in fat and fiber has been found to have therapeutic benefits for people with this disease. Studies have also revealed that medium-chain fatty acids and n-3 fatty acids have a positive impact on these patients [79].

A study was carried out in mice to investigate the impact and mechanism of H_2 in chronic ulcerative colitis. The mice were divided into three groups: the control (NC) group, the UC (Dextran Sulfate Sodium, DSS) group, and the (DSS + HRW) group treated with HRW (0.8 ppm) and DSS. At the end of the study, mice in the DSS group showed typical clinical signs of colitis. At the same time, HRW treatment partially alleviated colitis symptoms, improved histopathological changes, significantly increased glutathione (GSH) concentration, and reduced the level of TNF-α. HRW treatment also significantly inhibited *Clostridium perfringens*, *Enterococcus faecalis*, and *Bacteroides fragilis*

growth, bringing their levels close to those of the NC group. Microarray analysis showed significant alterations in 252 genes after HRW treatment compared to the DSS treatment alone group, with 17 genes associated with inflammation, including 9 interferon-stimulated genes (ISG). HRW was found to exhibit partial relief of inflammation, oxidative stress, and dysbiosis in the intestinal flora of mice with chronic ulcerative colitis (UC) induced by dextran sulfate sodium (DSS) [80].

In a research study exploring the effects of H_2 on UC, mice were injected with 10 or 20 mL/kg of hydrogen-rich saline every two days for two weeks. Treatment with HRS resulted in reduced weight loss, reduced diarrhea, and alleviated colonic mucosal damage in UC mice [81].

5.3. Hydrogen nutrition therapy application in liver diseases

The liver is one of the primary targets for free radical attack due to its direct involvement in metabolic processes. Free radicals damage hepatocyte membranes, which in turn causes the deposition of collagen in the hepatocyte and finally causes liver fibrosis and cirrhosis [1].

The liver plays a crucial role in nutritional metabolism, performing essential functions such as glycogen storage, detoxification, and protein synthesis. These functions are impaired in liver disease, resulting in various metabolic disorders. The degradation of the nutritional condition of these patients can lead to progression of the disease. Therefore, diet counseling and nutrition therapy can be helpful in the treatment of certain liver diseases [82].

Nonalcoholic fatty liver disease (NAFLD) is caused by excessive consumption of saturated fat, salt, and fructose in a person's diet, leading to conditions such as obesity, insulin resistance, and the accumulation of triglycerides in liver cells. Therefore, nutritional therapy is crucial in the treatment of NAFLD. There is no single diet program that can be applied to all patients with NAFLD. However, a balanced diet consisting of whole grains, fruits, vegetables, and fish, with a limited intake of saturated fat, salt, and fructose, has been found to have beneficial effects on the disease [82,83].

Hepatitis is a liver disease that can cause malnutrition in patients. To prevent this, a diet high in protein and energy is recommended, with carbohydrates making up approximately 55–60 % of daily energy, fats accounting for 25–40 %, and proteins contributing 2–3 g/kg/day. This diet should also be rich in vitamins. For those with chronic hepatitis C, medical nutrition therapy can increase the effectiveness of antiviral treatment. Consumption of n-3 polyunsaturated fatty acids (PUFA) has been shown to inhibit HCV replication, and a low-iron diet can help reduce liver damage. In liver cirrhosis, which is the most advanced stage of chronic hepatitis, nutritional problems can arise and complicate the patient's condition and prognosis. Therefore, nutritional therapy is crucial to preventing these complications.

A study in mice evaluated the effects of HRW and electrolyzed alkaline water (EAW) on NAFLD induced by a high-fat diet. The findings showed that HRW effectively reduced the accumulation of lipids in the liver, inflammation, and CD36 expression. However, neither EAW nor HRW with low hydrogen concentration had any beneficial effect on NAFLD. The study concluded that hydrogen (H_2) is the active therapeutic agent in EAW and can relieve HFD-induced NAFLD in mice [84]. An eight-week double-blinded, placebo-controlled randomized clinical study in 30 subjects with NAFLD found that HRW decreased body weight and BMI. It also tended to improve lipid profile and have divergent antioxidant and anti-inflammatory effects [85].

A study was conducted to investigate the effect of HRW on people with chronic hepatitis B (CHB). The study randomly assigned 60 patients diagnosed with chronic hepatitis B to the routine treatment group or the hydrogen therapy group. Patients in the control treatment group received standard care, while those in the hydrogen therapy group consumed HRW orally (1200–1800 mL/day, twice daily) for 6 weeks in addition to standard care. The study also included a control group of 30 healthy subjects for comparison purposes. After the experiment, the control group exhibited a nonsignificant change in oxidative stress, whereas the hydrogen treatment group showed a notable improvement. Liver function demonstrated a significant improvement, and there was a substantial reduction in DNA levels of the hepatitis B virus after treatment. Although a nonsignificant difference in oxidative stress was observed between the two groups, the control and hydrogen groups showed an improving trend in liver function and DNA levels of the hepatitis B virus. Consistent with these findings, HRW was reported to reduce oxidative stress in patients with chronic hepatitis B significantly. However, further studies with long-term treatment were recommended to confirm the impact of HRW on liver function and hepatitis B virus DNA levels [86].

5.4. Hydrogen nutrition therapy application in respiratory system diseases

The production of reactive oxygen species (ROS) can deplete lung antioxidants, such as glutathione, leading to various lung diseases [41]. These include asthma, chronic obstructive pulmonary disease (COPD), acute lung injury, pulmonary fibrosis, and lung cancer. Oxidative stress is a key factor in the inflammatory responses associated with lung diseases, as it triggers the upregulation of redox-sensitive transcription factors, which promote the expression of pro-inflammatory genes. Additionally, the inflammation itself can further contribute to oxidative stress in the lungs [10,41,87].

Several respiratory diseases can affect a person's health. These include occupational lung diseases, respiratory allergies, chronic obstructive pulmonary disease, sleep apnea syndrome, asthma, and pulmonary hypertension. These diseases can cause chronic inflammation, abnormal response to injury, shortness of breath, decreased exercise tolerance, premature aging, and loss of macrophages, T lymphocytes, and lung neutrophils. These conditions may also lead to excessive activation of fibroblasts, which can negatively affect the person's respiratory health [88]. Individuals with respiratory system diseases have increased energy requirements. Breathing difficulties arise due to the accumulation of carbon dioxide in the lungs. A high protein intake is necessary to protect and repair lung and muscle tissue, meeting 15–20 % of daily energy needs (1.2–1.7 g/kg). Fat should comprise 30–45 % of daily energy needs, and saturated fat should be avoided. Patients with respiratory diseases need vitamins and minerals such as vitamin C, magnesium, and calcium. Furthermore, vitamin D and K should be taken if there is a decrease in bone mineral density. The diet should restrict sodium and fluid intake for those with edema while increasing potassium. Personalized nutritional therapy positively impacts patients with respiratory system diseases [89].

A study was conducted to evaluate the positive effects of hydrogen gas on lung damage caused by exposure to cigarette smoke (CS) in mice. The study used a murine model of chronic obstructive pulmonary disease, where mice were exposed to CS for 8 weeks and HRW was administered. The results showed that HRW administration had a mitigating effect on CS-induced lung injury, as demonstrated by a reduction in the mean linear intercept and the destructive index of the lungs. Furthermore, HRW administration significantly improved static lung compliance in mice exposed to CS compared to their non-hydrogen-treated counterparts. Furthermore, HRW-treated mice exhibited decreased levels of markers associated with oxidative DNA damage, such as phosphorylated histone H2AX and 8-hydroxy-2′-deoxyguanosine, as well as markers indicative of aging, such as the cyclin-dependent kinase inhibitor 2A, 1, and β-galactosidase. These findings indicate that HRW can potentially alleviate CS-induced emphysema by reducing oxidative DNA damage and premature cellular aging in the lungs [90].

A study has suggested that H_2 may be able to reduce lung injury caused by cecal ligation and puncture (CLP) in rats. The study showed that the animals subjected to CLP experienced inflammation and gas exchange dysfunction in their lungs. However, hydrogen-rich saline treatment significantly improved lung injury by reducing lung water

content and neutrophil infiltration, improving gas exchange and histological alterations in the lungs. H_2 also reduced lipid peroxidation and DNA oxidation in lung tissue by reducing the nitrotyrosine content. Furthermore, H_2 acted as an antioxidant by maintaining superoxide dismutase activity in the presence of CLP. Treatment with HRS also inhibited the activation of p-p38 and NF-κB while suppressing the production of several pro-inflammatory mediators, which showed that peritoneal injection of HRS improved histological and functional evaluations in the rat model of CLP-induced acute lung injury [91].

5.5. Hydrogen nutrition therapy application in brain and nervous system diseases

The brain abundantly produces ROS, which can cause neurological disorders, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis [92].

Certain diseases are caused by neurons' gradual degeneration, leading to functional and structural loss. Some examples of such neurological conditions include Alzheimer's disease, Parkinson's disease, Schizophrenia, Multiple Sclerosis, and Depression. However, certain diets such as the Mediterranean diet, ketogenic diet, or DASH diet can have beneficial effects in treating these conditions [93–96]. A medical nutritional diet should consist mainly of fruits, vegetables, nuts, spices, and legumes. These foods contain anti-inflammatory elements, such as polyphenols, vitamins, essential minerals, omega-3 fatty acids, and probiotics. Consuming a lot of these products in the diet benefits brain health and reduces the risk of neurological diseases [93–95,97].

During a study that lasted seven months, HRW treated triple transgenic Alzheimer's disease in mice. The study showed that HRW intake prevented synaptic loss and neuronal death, inhibited the formation of senile plaques, and reduced hyperphosphorylated neurofibrillary tangles in the mice. Furthermore, HRW intake improved disorders in brain energy metabolism, addressed imbalances in the intestinal flora, and mitigated inflammatory reactions [98].

In a clinical study, 48 patients with Parkinson's disease were randomly divided into two groups. All patients had already undergone levodopa treatment. One group drank 1 L of HRW daily, while the other drank normal water. After 48 weeks, clinical evaluations were conducted using the Unified Parkinson's Disease Rating Scale (UPDRS) score, which assesses both motor and non-motor symptoms of Parkinson's patients. The results showed that the control group showed a deterioration in symptoms, while the HRW-consuming group showed a significant improvement in symptoms [99].

In a study, mice were exposed to mild and unpredictable stress for four weeks and fed HRW during this time. The study found that mice who consumed HRW showed fewer symptoms of depression than those who did not. HRW intake was also found to suppress inflammatory activation, which resulted in lower levels of protein IL-1β and ROS production [100].

6. Conclusions

The overproduction of free radicals from various intrinsic and extrinsic factors leads to oxidative stress, which can alter redox homeostasis and the structural composition of numerous cellular and organ components, resulting in various disorders and diseases.

Molecular hydrogen has anti-inflammatory, antiapoptotic, selective antioxidant, and easy diffusion and penetration properties. Studies have shown that molecular hydrogen has benefits for the control of body weight, inflammation, metabolic markers, and diseases without adverse side effects. Most studies on using molecular hydrogen to relieve diseases suggest that hydrogen may provide health benefits because of its specific biological properties. The use of molecular hydrogen in nutritional therapy for diseases has not yet been thoroughly investigated. However, the findings obtained from recent experimental and clinical studies suggest that H_2 may be a promising nutritional therapy for various diseases. However, longer-term studies must be conducted to administer molecular hydrogen in defined protocols.

CRediT authorship contribution statement

Fatmanur Yıldız: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tyler W. LeBaron:** Writing – review & editing, Investigation. **Duried Alwazeer:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable.

Data availability

Data will be made available on request.

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