Review

Hydrogenated Water: Extra Healthy or a Hoax?: A Systematic Review

Gagandeep Dhillon * , Venkata Buddhavarapu , Harpreet Grewal , Pranjal Sharma , Ram Kishun Verma , Ripudaman Munjal , Ramprakash Ramprakash Devadoss , Rahul Kashyap

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Systematic Review

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Abstract: Hydrogenated water has emerged as a novel approach in the field of health and wellness. It is believed to have potent antioxidant properties that can neutralize harmful free radicals in the human body. It has also been shown to be beneficial in mitigating oxidative stress-induced damage through its anti-inflammatory and anti-apoptotic pathways. We aim to conduct a systematic review to evaluate the potential benefits of hydrogenated water. The review protocol was uploaded on PROSPERO. After the initial search criteria, the articles were reviewed by two blinded investigators, and a total of 25 articles were included in the systematic review. The potential benefits of hydrogenated water on various aspects of health, including exercise capacity, physical endurance, liver function, cardiovascular disease, mental health, COVID-19, oxidative stress, and anti-aging research, are a subject of growing interest and ongoing research. Although preliminary results in clinical trials and studies are encouraging, further research with larger sample sizes and rigorous methodologies is needed to substantiate these findings. Current research needs to fully explain the mechanisms behind the potential benefits of hydrogenated water. Continued scientific exploration will provide valuable insights into the potential of hydrogenated water as an adjunctive therapeutic approach in the future.

Keywords: hydrogen water; hydrogenated water; hydrogen-rich water; antioxidant; anti-apoptotic; anti-inflammatory

1. Introduction

Hydrogenated water, also known as hydrogen-rich water or hydrogen water, is regular water that has molecular hydrogen gas (H2) added to it [1]. Water can be hydrogenated by dissolving molecular hydrogen gas into water under elevated pressure, resulting in a supersaturated solution. The hydrogen molecules are extremely small, so they can easily penetrate water and stay dissolved for a while [1]. Hydrogenated water has recently gained significant attention as a potential health-promoting beverage. Studies have been done on animals [2] and humans [3] in the last few decades using molecular hydrogen-enhanced water showing antioxidant [3], anti-inflammatory [3], and anti-apoptotic [3] effects. Although there has been some research into the benefits of hydrogen-rich water, there is still a long way to go.

Over the last few years, hydrogenated water has become the latest trend to target the global market in the health and wellness industry. Studies have been done to understand its potential

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benefits. A randomized, double-blind, controlled trial [3] showed that hydrogen-rich water could reduce inflammatory responses in adults, leading to increased antioxidant capacity in healthy adults. Healthy adults consumed either 1.5 liters/day of hydrogenated water or plain water. Flow cytometry testing of CD4+, CD8+, CD11+, CD 14+, CD 20+ yielded interesting results. In the hydrogenated water group, the CD14+ cell frequency was decreased [3]. The benefits of hydrogen use have been evaluated in conditions such as cardiac fibrosis, neuronal disease, hepatic injury, radiation-induced disease, diabetes, and many more conditions. [4]. Through this systematic review, we aim to summarize current research findings related to using molecular hydrogen-enhanced water and its anti-inflammatory, antioxidant, and anti-apoptotic impact.

2. Materials and Methods

The initial search terms included were "hydrogenated water," "hydrogen water," "hydrogen-rich water," antioxidant," "anti-inflammatory," "anti-apoptotic," "fatigue," and "cytoprotective." This PubMed search yielded a total of 590 articles. Duplicate articles and animal studies were removed. All articles with titles not related to the topic were eliminated. After reviewing the abstracts by two blinded investigators, 25 articles were retained for a final review (Figure 1).

Studies were exported from PubMed to Rayyan software. At least two authors screened titles and abstracts independently to select appropriate studies. Afterward, the authors assessed the full texts of the articles to determine final eligibility. Conflicts were discussed with a non-reviewing author and were resolved. The study was also registered on PROSPERO (CRD42023445460)

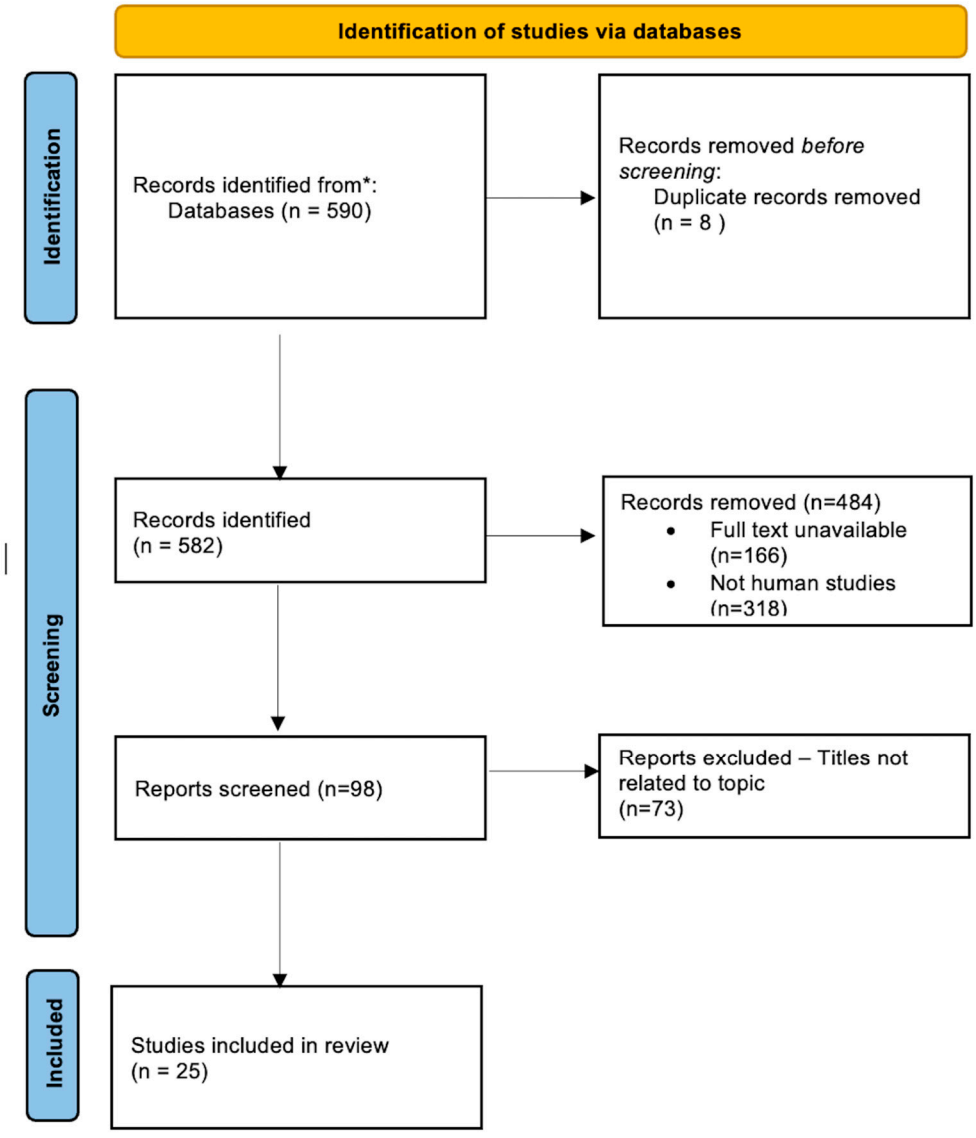

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Figure 1. Material and methods. Identification of studies via databases. PubMed search with 590 articles. Duplicate articles and animal studies were removed. All articles with titles not related to the topic were also removed. After a close review of the abstracts by two blinded investigators, 25 articles were retained for a final review.

3. Results

The final review was conducted with 25 articles, including 12 randomized controlled trials (RCTs), 8 reviews, 2 observational studies, 1 double-blinded crossover design, 1 experimental study, and 1 systemic review. (Figure 1)

One of the first documented human studies with hydrogen-rich water was conducted in 2008. An experimental drink was produced by dissolving hydrogen gas into water under high pressure. It was used for patients with type 2 diabetes or impaired glucose intolerance. Common medical disorders like hypertension, diabetes, and atherosclerosis are associated with oxidative stress. Although the sample size was small, drinking hydrogen-rich water did have some benefits in preventing type II diabetes mellitus [5]. Hydrogenated water can be consumed orally and can be produced in multiple ways, which include hydrogen-generating tablets, infusion machines, water generators, and ionizers. Effective delivery of hydrogen through inhalation might be difficult. An advantage of using hydrogenated water to deliver molecular hydrogen is that it can be easily administered and portable [6]. The beneficial effects can be seen even at low concentrations [6].

We have divided the summary of our findings into the following subheadings- (Figure 2)

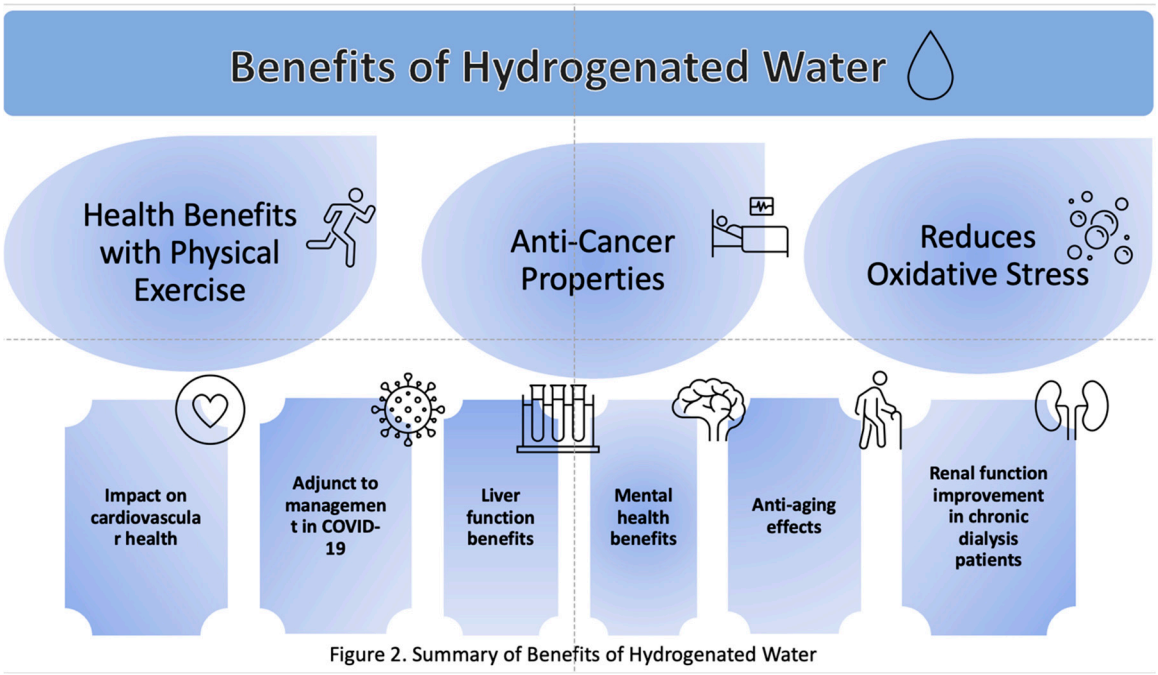

Figure 2. Summary of Benefits of Hydrogenated Water

Figure 2. Benefits of Hydrogenated Water on exercise capacity, physical endurance, liver function, cardiovascular disease, mental health, COVID-19, oxidative stress, anti-cancer activity, renal function and anti-aging research.

3.1. Health Benefits with Physical Exercise

Physical activity is good for several reasons, offering numerous mental, emotional, and physical benefits [7]. Studies have also been done to see the effect of physical activity on mental health [7]. Some advocates of hydrogenated water believe that it has the potential to provide multiple health benefits with physical exercise, like enhanced performance and recovery [8]. Although the data is still limited and inconclusive, studies have shown encouraging results, as discussed below.

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Physical exercise can result in increased reactive oxygen species, which can cause damage to tissue and fatigue. With most forms of exercise, sensations of fatigue and exhaustion occur after some time. Research has shown that drinking hydrogenated water before exercising can mitigate the effects of fatigue and build endurance [8]. A study done on cyclists showed that a seven-day consumption of nano-bubble hydrogen-rich water improved the anaerobic performance of trained cyclists compared to that of untrained ones [9]. There is a build-up of lactic acid in the muscles with exercise. Hydrogenated water administered pre-workout showed decreased blood lactic acid levels at a higher intensity and improved ventilatory efficiency [10]. Hydrogenated water pre-workout has also been gaining traction. Supplementation of hydrogenated water prior to exercise in other studies has been shown to reduce fatigue along with better endurance in the later stages of repeated sprints [11].

Not all have demonstrated encouraging results. A randomized, double-blind, placebo-controlled crossover design study by Botek et al. [12] showed unclear effects on fatigue. Study participants were placed in either placebo or hydrogenated water groups. Interestingly, hydrogenated water had an unclear effect on race time and minimal impact on heart rate. Endurance performance was improved by 1.3% in the slowest runners with prerace hydration with 1680 ml hydrogen-rich water, but the effect on the fastest runners was unclear as there was 0.8 % deterioration. Also, in the slowest runners, there was an improvement in race heart rate by 3.8%, along with an improvement in performance. However, in the fastest runners, the change was unclear (0.1%). Depending on the running ability of individuals, the effect of hydrogenated water on performance can vary [12].

Training and competition are part of athletes' lives. Oxidative stress has a vital role in the development of inflammation [3]. A study was done on female juvenile soccer players from Suzhou, China, with consumption of hydrogen-rich water for two months in the treatment group showed changes in serum malondialdehyde, interleukin-1, interleukin-6, tumor necrosis factor-α (TNF-α) levels with an increase in serum superoxide dismutase, total antioxidant capacity levels [13]. Post 8 weeks, serum malondialdehyde levels decreased from 13.80 ± 3.33 to 12.69 ± 1.94 μM in the hydrogenated water group and from 16.67 ± 4.19 to 15.79 ± 3.07 μM in the control group. In the same period, the interleukin-1 levels went up from 29.32 ± 7.09 μM to 34.47 ± 6.22 μM in the hydrogenated water group and from 32.56 ± 7.61 to 42.94 ± 6.24 μM in the control group [13]. The levels of interleukin-6 increased from .74 ± 2.57 to 12.37 ± 3.2 ng/L in the hydrogenated water group and from 10.53 ± 1.62 ng/L to 24.88 ± 6.11 ng/L in the hydrogenated water group after 8 weeks. The levels of serum TNF-α levels increased from 49.46 ± 11.59 to 107.00 ± 13.89 μM in the hydrogenated water group and from 60.57 ± 10.09 to 132.24 ± 10.46 μM in the other group. For superoxide dismutase, the levels decreased from 14.07 ± 1.91 to 13.69 ± 2.10 U/mL in the hydrogenated water group, while it decreased from 13.14 ± 2.18 to 13.01 ± 1.08 U/mL in the control group [13].

Studies have shown the antioxidant, anti-apoptotic, cytoprotective, and anti-inflammatory properties that hydrogen can exert on the cell. Hydrogenated water has the potential to be used for the treatment of many diseases, including cardiovascular and neurodegenerative, among others [14].

Hydrogenated water has the potential to be used for the treatment of many diseases, including cardiovascular and neurodegenerative, among others [14]. Hydrogen-rich water can improve acidosis due to exercise, energy levels, and enhanced muscular performance in athletes [15].

3.2. Impact on Oxidative Stress

Oxidative stress is known to be a common cause of lifestyle-related diseases, aging process, and even cancer [4]. Reactive oxygen species are generated internally as we breathe and consume oxygen [4]. Hydrogen is effective against oxidative stress and is also known for its anti-inflammatory [4] and anti-allergy [4] benefits. Another added advantage is that even at higher concentrations, hydrogen has no cytotoxicity [4]. Also, in deep diving gas mixed, hydrogen gas in high concentrations is used for inhalation to prevent arterial gas thrombi and to prevent decompression sickness [4].

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3.3. Impact on Cardiovascular Health-

The effects of molecular hydrogen on cardiovascular disease are interesting. It controls signal transduction and gene expression, suppressing pro-inflammatory cytokines and decreasing reactive oxygen species production. It also leads to the activation of nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant transcription factor. Even though hydrogen has antioxidant, anti-inflammatory, and anti-apoptotic effects, the exact mechanism of action is poorly understood. There is data to suggest that mild hormetic-like effects of hydrogen might be responsible for the benefits, but more research is still needed [1].

Hydrogenated water can potentially decrease LDL-C and apoB levels while improving HDL function. It may also have a role in the prevention of metabolic syndrome [16]. Furthermore, in unstable angina patients, consumption of hydrogenated water with conventional medications was shown to relieve symptoms associated with it (60% vs. 90%, $\chi^2 = 4.800$, $P < 0.05$) [17]. The hydrogenated water group was noted to have lower total cholesterol (35% vs. 15%), apoB (40% vs. 15%), and LDL-C (40% vs. 20%) levels compared to the control group [17]. Hydrogenated water can also improve the endothelial function of the arteries to improve cardiovascular health [18]. In evaluating vascular endothelial function and cardiovascular disease, reactive hyperemia index (RHI) using peripheral arterial tonometry (PAT) is useful. RHI improved by 25.4% ($p < 0.05$) after 2 weeks of hydrogenated water consumption [18] .

3.4. COVID-19 and Hydrogenated Water

COVID-19 pandemic has significantly impacted our lives in the last few years [19]. Although it is not a health emergency globally today, it is important to be vigilant as new variants have emerged in the last few years [19]. It is interesting to note that as hydrogen inhalation has anti-inflammatory, antioxidant, and anti-apoptotic action, it can aid in the management of COVID-19 [20]. Although hydrogen has shown potential in the last few years, it is still early to conclude its usefulness.

3.5. Hydrogenated Water and Dialysis

As we go forward, hydrogenated water has started to make an impact on various diseases and disorders. Oxidative stress plays an important role in chronic kidney disease pathology [21}. In chronic dialysis patients, a study showed that electrolyzed hydrogenated water (EHW) intake can improve blood urea nitrogen (BUN) and renal function. It can also decrease oxidative stress in patients with chronic dialysis during their hemodialysis sessions [21].

3.6. Effect on Cancer

As medical science continues to advance, molecular hydrogen has started to find its way into oncology. Colorectal cancer is a common cause of death due to cancer, and removal of tumor is still the mainstay of treatment [22]. Hydrogenated water did show anti-cancer properties in a study. With its antioxidant properties and ability to decrease oxidative stress, it can be a potential game changer in the future. A combination of hydrogenated water and 5-fluorouracil (5-FU) did show improvement in the size of the tumor, fibrosis, and content of collagen [22].

3.7. Mental Health Benefits

Mental health is another aspect of today's world that cannot be ignored. As we move on from the COVID pandemic, it is crucial to understand the effect it had on mental health. Higher rates of depression, anxiety, and stress were seen in the general population in many countries [23]. A study showed that subjects who drank hydrogenated water for 4 weeks had improved mood, anxiety, and overall mood [24]. Over the last few years, it has also been documented that LGBTQ individuals suffer from discrimination, which in turn affects their mental status [25]. Even in the healthcare system, they suffer a higher rate of disparities [26]. Another interesting study was done in women with panic disorder [27]. The control group was started on psychological treatment and a placebo, while the treatment group was placed on psychological treatment and 1500 ml of hydrogenated water

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daily for 3 months. Results showed no significant difference between the control and treatment groups. However, it should be noted that the treatment group did show a significant decrease in pro-inflammatory cytokines (IL-6, IL-1β, IL-12, and TNF-α) compared to the control group.

3.8. Liver Function Benefits

As hydrogenated water decreases oxidative stress, a study was done on patients with chronic hepatitis B. Hepatitis B is a global health problem and can be life-threatening. Subjects were administered hydrogenated water (1200-1800 mL/day, twice daily) with improved liver function and reduction in HBV DNA (28). Non-alcoholic fatty liver disease (NAFLD) affects 25% of the population. Liver dysfunction can be caused by inflammation, oxidative stress and aberrant cellular signaling. It has been shown that the administration of hydrogenated water can have beneficial effects in these patients [29]. 30 individuals with NAFLD were administered hydrogenated water in a randomized, double-blind, placebo-controlled study for eight weeks. Decreased body mass index and weight (≈1 kg) were observed in the group [29].

3.9. Effect on Aging

The risk factor for many cardiovascular diseases, neurodegenerative disorders, and even cancer is age [30]. With hydrogenated water making news in the last few years, a study was done to assess the effects of hydrogenated water in men and women above the age of 70 and if it had any effect on aging. It was found that drinking hydrogenated water for 6 months was harmless and also had a favorable effect on many of the factors associated with aging like pain, metabolic processes in the brain, strength of lower extremities, etc. [30]. Another study showed the hydrogen has anti-aging effects through the (Nrf2) pathway on the vascular endothelial cells. Therefore, it has the potential to increase longevity. This can even be seen after a temporary exposure to hydrogen [31].

4. Discussion

Hydrogenated water has gained worldwide attention over the last few years given its potential health benefits. Hydrogenated water's effect on exercise capacity and physical endurance is of particular interest to individuals with a fondness for physical activity. Additionally, the potential for a positive impact on cardiovascular function can reduce the risk of heart disease. Additionally, the possible effect of hydrogenated water on mental health is intriguing, with the initial results being encouraging. Also, its effect on anti-cancer properties holds promise in the field of oncology. Given its potential to positively impact liver function, anti-aging, and oxidative stress, hydrogenated water is a subject of ongoing research and growing interest. Hydrogenated water offers several potential strengths, including its antioxidant, anti-inflammatory, and anti-apoptotic properties. It can also help decrease oxidative stress. Some studies showed that it may also improve physical endurance, cognitive function, and overall well-being. Moreover, hydrogenated water is mostly considered safe, with minimal to no side effects. There is growing interest in hydrogen water benefits, and it may also have potential applications in medical therapies.

Hydrogenated water can help in the management of hyperlipidemia [16]. 20 patients (10 smokers and 10 nonsmokers) who received hydrogenated water for 10 weeks showed a drop in total cholesterol levels from 6.42mM to 5.47mM, whereas LDL levels dropped only from 3.96mM to 3.24mM. It is interesting to note that the beneficial effects were better in smokers than nonsmokers. Additionally, there was no effect on levels of HDL-C. The levels of serum triglyceride were decreased with hydrogenated water treatment in smokers from 2.93mM to 2.3mM, but the levels in nonsmokers went from 1.49mM to 1.67mM [16].

Comparison of hydrogenated water with other health supplements such as protein powder, herbal supplements, collagen, and vitamins is challenging yet essential, as they serve different purposes and can affect health and well-being.

Over the last few decades, protein powder has become popular among individuals with an interest in physical activity to support their fitness goals. There have been studies done to assess the

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impact of protein powders on physical endurance and fitness. In healthy individuals undergoing chronic endurance training, protein supplements were shown to increase aerobic capacity further, improve time trial performance, and lead to lean mass gain [32]. Another study showed that protein supplements and carbohydrate strategies in individuals undergoing endurance exercise can decrease muscle damage but did not improve endurance capacity [33]. Moreover, protein supplements may contain potential toxins that can/may affect renal or cardiac function. High protein intake for prolonged periods has been linked to various health concerns, including increased risk of renal disorders, calcium metabolism, progression of coronary artery disease, and even cancer [34]. There is not much data available specifically comparing protein powder and hydrogenated water strategies for individuals engaging in physical activity.

A separate study was done on 89 individuals to see the effect of protein powder (on whey or casein protein for 12 weeks of consumption) on cholesterol levels [35]. It caused decreased total cholesterol levels by 7% in the whey protein group compared to baseline and a 9% decrease in the whey protein group compared to the casein group. LDL levels were also decreased by 7% in the whey group compared to baseline. Protein powder and hydrogenated water can both be a part of a dietary regimen to support fitness goals. While hydrogenated water provides potential antioxidant and anti-inflammatory effects [15], protein supplementation is used for lean muscle gain and increased aerobic capacity. As medical science continues to evolve, we might better understand how these two strategies can be used synergistically or in certain scenarios.

Herbal supplements are commonly used in different parts of the world. A few studies were done to evaluate the impact of herbal supplements on COVID-19 patients. Zinc sulfate could decrease the duration of olfactory dysfunction. However, more well-designed studies are needed in the future given the low quality of included trials [36]. Also, there has been a debate on using herbal supplements to treat mood disorders. A few are effective in the management of depression, like Catha edulis, Tinospora cordifolia, Curcuma longa, Rhodio larosea, Crocus sativus, etc [37]. There has also been evidence for the use of Passiflora spp. (passionflower) and Piper methysticum (Kava) in anxiety; Crocus sativus (saffron) and Hypericum perforatum (St John's wort) for depression. In schizophrenia, Ginkgo biloba (ginkgo) has been used as adjunctive treatment [38]. EGb 761, a special extract of Gingko biloba stabilizes mood and improves cognitive functioning in elderly individuals with cognitive impairment [39]. In this study, 176 patients with generalized anxiety disorder or adjustment disorders with anxious mood were randomized to one of the 3 groups for 4 weeks: 480 mg EGb 761, 240 mg EGb 761, or placebo. The primary outcome measure used was the Hamilton rating scale for Anxiety (HAMA). In the high-dose EGb 761 group, the HAMA score decreased by – 14.3, by -12.1 in the low-dose EGb 761 group, and -7.8 in the placebo group [39].

In comparison, a few studies have been done to see the effect of hydrogenated water on mental health. In one of the studies done in women with panic disorder [27], the results were similar in control and hydrogenated water groups. However, it should be noted that this group did show a decrease in pro-inflammatory cytokines (IL-6, IL-1β, IL-12, and TNF-α) compared to the control group. In the treatment group, after treatment with hydrogenated water, IL-1β levels decreased from 94.1 to 65.5, IL-12 from 75.75 to 54.5, IL-6 from 72.3 to 51.67, and TNF- α from 74.5 to 49.25. This may have led to an improvement in physical health and body pain [27].

Going forward, there needs to be more focus on quality research to establish their efficacy and safety as it is not as well-established as psychotropic medications currently in use.

Collagen is associated with skin health and overall well-being. It constitutes approximately 80 percent of the dry weight of skin [40]. With aging, there is a decrease in the enzymes involved in its processing that, in turn, decreases the fibroblasts involved in the synthesis of collagen [40]. Topical and oral collagen can reduce skin aging [41]. The effects of vitamins and nutrients on aging are also shown [42]. Supplementation with zinc, carotenoids, selenium, and vitamins C and E could slow aging [42].

Hydrogenated water, protein powder, herbal supplements, vitamins, etc, are distinct dietary supplements and have different effects on the body. There is not much data available comparing hydrogenated water to protein powder, herbal supplements, collagen, and vitamins. As medical

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science continues to evolve, we might better understand how these strategies can be used synergistically or in certain scenarios.

One of the biggest concerns was the lack of consensus amongst the researchers: the concentration of hydrogen in water, methods of hydrogenation, best duration, etc. This, in turn, can lead to inconsistency in results. As the hydrogen concentration and quality can vary in studies, it can be challenging to compare results. Although the results of many studies reviewed have been encouraging, it should be noted that many were conducted in animals [2], and some used small sample sizes [42] in the study. This can have an impact on the statistical power of the research and the generalizability of findings. Research trials with a large sample size would be needed in the future. We also noticed that the studies on hydrogenated water primarily focused on short-term benefits [42] and did not consider the long-term effects. Some studies [16] did not have a placebo control group, so it is difficult to determine whether the results could be attributed to hydrogenated water.

Also, it should be noted that as some of the research studies might have been supported by organizations with an interest in hydrogenated water products, there could be commercial biases in publication. Due to this, there is also a concern that studies might have exaggerated health benefits, leading to misinformation. A proper conflict of interest analysis is required as we move forward. Last but not least, we still do not understand the mechanisms [1] by which hydrogenated water exerts its effects. This can impede the development of medical therapies in the future. Standardized manufacturing processes and strict quality control are needed. We should look forward to developing therapeutic protocols and validating the potential of hydrogen-rich water in a clinical setting.

5. Conclusions

Increased interest and continuous study are being directed toward the possible health advantages of hydrogenated water on a variety of topics, including physical endurance, exercise capacity, cardiovascular disease, liver function, COVID-19, mental health, anti-aging research, and oxidative stress. These potential consequences have aroused debate in the scientific and medical industries. Even though there is great potential in understanding the benefits of hydrogenated water, we still have to overcome the existing limitations. We need well-designed studies in humans, with large sample sizes and long-term trials, to ascertain the benefits.

6. Patents

Not Applicable

Supplementary Materials: Not Applicable.

Author Contributions:.Gagandeep Dhillon—Corresponding author, conceptualization, literature search, original draft. **V**enkata S Buddhavarapu—Visualisation, writing, review and editing, formal analysis. Harpreet Grewal—Study design, formal analysis, investigation Pranjal Sharma—Formal analysis, resources. Ram Kishun Verma— Literature search, validation, visualization. Resources, methodology. Ripudaman Munjal—Resources, methodology. Rahul Kashyap—Writing, review and editing, supervision.

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