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## Hydrogen holds promise as a safe and effective antioxidant for alcohol

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**ABSTRACT** Alcohol consumption has been identified as a major risk factor for chronic disease and injury, imposing a considerable burden on sufferers, their families and society. Growing evidence suggests that increased oxidative stress caused by excessive use of alcohol is associated with many diseases. Nevertheless, there is no antioxidant that can protect all organs and tissues in the body from alcohol-mediated oxidative

damage. Notably, recent basic and clinical research has confirmed that molecular hydrogen can markedly decrease oxidative stress by selectively scavenging noxious reactive oxygen species (ROS), and protect cells and tissues against oxidative insults. Based on these data, it is hypothesized that hydrogen gas would be a favorable antioxidant additive for alcoholic beverages, namely hydrogen-rich alcohol. Molecular hydrogen may also be administered by alternative methods, involving direct inhalation, oral intake of hydrogen dissolved in water, and injection with hydrogen-saturated fluid, to ameliorate the oxidative damage derived from ethanol exposure, especially alcohol-induced liver disease.

**INTRODUCTION** Across cultural boundaries, alcohol has been consumed as a part of human life for thousands of years. Although moderate alcohol consumption

appears to be associated with favorable changes in several cardiovascular biomarkers of coronary heart disease and a reduced risk of multiple cardiovascular outcomes<sup>1,2</sup> the overall effect of alcohol use on health is overwhelmingly detrimental, even in regions in which the net cardiovascular outcome is beneficial<sup>3</sup>. Indeed, alcohol consumption has been identified as a major risk factor for chronic disease and injury<sup>3</sup>, imposing a considerable burden on sufferers, their families and society. In 2004, 3.8% of all global deaths and 4.6% of the global burden of disease and injury were attributable to alcohol<sup>3</sup>. Reactive oxygen species (ROS), a class of oxygen-containing free radicals, are generated in small amounts as a natural byproduct of the body's metabolic reactions and can react with and damage complex molecules in the cells, such as lipids, proteins,

and DNA<sup>4</sup>. It is well established that both acute and chronic alcohol exposure can increase ROS production, lower cellular antioxidant levels, and enhance oxidative stress in many tissues, including liver, heart, brain, and peripheral nerves. Alcohol-induced oxidative stress plays a dominant role in the development of alcoholic liver disease, which is one of major causes of preventable illness and death worldwide<sup>4,5</sup> and is also implicated in many other disorders that plague human beings, including fetal alcohol syndrome<sup>6</sup> alcohol use disorder<sup>7</sup> alcoholic pancreatitis<sup>8</sup> and hepatocellular carcinoma<sup>9</sup>.

Interestingly, beer, wine, and liquor all contain natural compounds with antioxidative properties. Resveratrol, a polyphenol that is abundant in wine, has been under intense study in a multitude of health conditions. This includes protec-

tion against mortality and liver lesions caused by alcohol in mice<sup>10</sup> attenuation of intestinal ischemia and reperfusion injury in rats<sup>11</sup> and significant improvement in cognitive deficits and brain damage in rats postnatally exposed to alcohol by blocking activation of nuclear factor kappa beta (NFκB) pathway and apoptotic signaling<sup>12</sup> Despite promising results, a convenient, effective, and safe approach that protects all organs from alcohol-mediated oxidative impairment is yet to be developed.

### RECENT ADVANCES IN HYDROGEN RESEARCH AS AN ANTIOXIDANT MEDICAL GAS

Hydrogen is the lightest and most abundant chemical element, constituting nearly 75% of the universe's elemental mass. As a highly combustible diatomic gas with the molecular formula H<sub>2</sub>, hydrogen is seldom regarded as a therapeutic gas. Interestingly, in 1975, a study

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reported that hyperbaric hydrogen therapy induced marked regression of tumors in hairless albino mice with squamous cell carcinoma<sup>13</sup>. This outcome may be partially due to hydroxyl radical ( $\bullet\text{OH}$ ) scavenging by hydrogen. A quarter of a century later, Gharib and colleagues found that animals infected percutaneously with *Schistosoma mansoni* and maintained in a hydrogen-supplemented hyperbaric chamber were significantly protected from schistosomiasis-induced liver injury, namely reduction of liver fibrosis, with increased activity of the hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) scavenging enzymes catalase and glutathione peroxidase, decreased lipid peroxide levels, and reduced circulating tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels<sup>14</sup>. Consistent with previous reports showing the antioxidant effect of hydrogen, it was found that  $\text{H}_2$  selectively reduced cellular  $\bullet\text{OH}$  and protected cultured cells, selectively reacted with and reduced cytotoxic oxygen radicals of  $\bullet\text{OH}$  and peroxynitrite ( $\text{ONOO}^-$ ) in cell-free systems, and significantly protected neurons against oxidative stress-induced cell death during *in vitro* ischemia and reperfusion<sup>15</sup>. In a focal ischemia rat model, inhalation of  $\text{H}_2$  not only resulted in a clear  $\text{H}_2$ -dependent decrease in infarct volume, with 2–4% of  $\text{H}_2$  providing the most substantial effect,

but also suppressed the progression of damage<sup>15</sup>. So far, there is growing basic and clinical evidence highlighting the potency of hydrogen as a promising antioxidant in preventive and therapeutic applications<sup>16,17</sup>. Several rodent studies indicate that oral intake of hydrogen water has the potential to prevent superoxide formation in brain slices of vitamin C-depleted SMP30/GNL knockout mice<sup>18</sup>, retard the development and progression of Parkinson's disease in a rat model<sup>19</sup>, prevent atherosclerosis in apolipoprotein E knockout mice<sup>20</sup>, alleviate cisplatin-induced nephrotoxicity without compromising anti-tumor activity<sup>21</sup>, and slow the progression of chronic allograft nephropathy in a model of kidney transplantation<sup>22</sup>. Meanwhile, other methods of hydrogen intake, for example, injection of hydrogen saline, direct absorption of hydrogen, and increasing the production of intestinal hydrogen, have also been successfully established<sup>17</sup>.

On the basis of encouraging data from previous studies, several groups have started clinical assessments of hydrogen-rich water. Patients with either type 2 diabetes mellitus or impaired glucose tolerance were treated with hydrogen dissolved in water (0.9 L/day) for 8 weeks. The results showed that intake of hydrogen-rich water had beneficial effects on

lipid and glucose metabolism by providing protection against oxidative stress<sup>23</sup>. In an open-label study, 20 subjects with potential metabolic syndrome, which is associated with elevated oxidative stress, were asked to regularly drink hydrogen-rich water (1.5–2 L/day) generated via a magnesium stick<sup>24</sup>. The consumption of hydrogen-rich water for 8 weeks led to a 39% increase in antioxidant enzyme superoxide dismutase and a 43% decrease in thiobarbituric acid reactive substances in urine, accompanied by an 8% increase in high density lipoprotein (HDL)-cholesterol and a 13% decrease in total cholesterol/HDL-cholesterol from baseline to week 4. Nakayama et al.<sup>25</sup> conducted a 6-month clinical study of hemodialysis using solutions with dissolved  $\text{H}_2$ . A significant decrease in systolic blood pressure (SBP) before and after dialysis was observed during the study, with no adverse effects, and a significant number of patients achieved SBP <140 mmHg after hemodialysis. Although changes in dialysis parameters were minimal, significant decreases in levels of the plasma inflammatory markers monocyte chemoattractant protein 1 and myeloperoxidase were observed. It is widely accepted that  $\bullet\text{OH}$  is highly destructive to tissues and aggravates cerebral infarction.

Recently, Ono and colleagues<sup>26</sup> reported improved magnetic resonance imaging (MRI) indices (relative Diffusion Weighted Image [rDWI] and relative Apparent Diffusion Coefficient [rADC]) against the natural course when the  $\bullet\text{OH}$  scavengers edaravone and hydrogen were given intravenously to patients with acute stage brainstem infarction. Compared with the edaravone only group, the favorable effects were more obvious and significant in the combined treatment group that received edaravone and hydrogen-enriched saline. Following observed improvements in several parameters, especially a decrease in the lactate-to-pyruvate ratio in mitochondrial myopathies (MM), in an open-label trial of drinking hydrogen water (1.0 L/day) for 12 weeks in 14 patients with muscle diseases, Ito et al.<sup>27</sup> carried out a randomized, double-blind, placebo-controlled, crossover trial of hydrogen-enriched water (0.5 L/day) for 8 weeks in 12 MM and 10 dermatomyositis (DM) cases. While no objective clinical effects were observed, a significant improvement was detected in lactate in MM. Moreover, lactate-to-pyruvate ratios in MM and serum matrix metalloproteinase-3 in DM also exhibited favorable responses, although this was not statistically significant. The results indicating

that hydrogen-enriched water is effective for mitochondrial dysfunction in MM have important implications for further expanding the possible medical uses of molecular hydrogen, because oxidative stress and mitochondrial dysfunction are central mechanisms underlying various pathological conditions, especially alcohol hepatotoxicity<sup>4</sup>.

**THE HYPOTHESIS** Alcohol is metabolized primarily in liver, and many processes and factors are involved in causing a state of oxidative stress in diverse tissues, with the production of different types of ROS, such as superoxide anion radical ( $\bullet\text{O}_2^-$ ), nitric oxide (NO),  $\text{H}_2\text{O}_2$ ,  $\bullet\text{OH}$ , and  $\text{ONOO}^-$ . Accumulated evidence has confirmed that  $\text{H}_2$  can markedly decrease oxidative stress by selectively scavenging the noxious ROS  $\bullet\text{OH}$  and  $\text{ONOO}^-$ , and protect cells and tissues against oxidative damage in a variety of disease models<sup>16,17</sup>.

These findings further support the presumption that hydrogen gas would be a favorable additive for alcoholic beverages, namely hydrogen-rich alcohol, to prevent healthy people, who either usually abstain from drinking alcohol or have a light to moderate alcohol consumption, from possible injury of liver or other organs and tissues, especially during occasional heavy drinking. In addition,

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hydrogen-rich alcohol may decrease the persistent oxidative insults in alcohol users resulting from chronic alcohol exposure. Molecular hydrogen may also be applied by different delivery methods, involving direct inhalation, oral intake of hydrogen dissolved in water, and injection with hydrogen-saturated fluid, as a separate treatment to ameliorate the oxidative damage in individuals with alcohol-induced disorders. In brief, this hypothesis underlines the potential of H<sub>2</sub>-based prophylactic or therapeutic approaches to deal with the injury in various organ systems of the body in which alcohol-related oxidative stress plays an important role. It must be strongly emphasized that the strategy provided here is not to encourage the consumption of alcohol, but to offer a novel cost-effective intervention for oxidative impairment brought about by excessive alcohol ingestion, especially alcohol-induced liver disease.

**DISCUSSION** Oxidative stress represents an imbalance between the activity of antioxidant defense systems and the production of ROS, and is now recognized as a major causative factor in the pathogenesis of alcoholic injury. Although a host of antioxidants have been found to possess the ability to attenuate alcohol-induced injury, there

is currently no antioxidant that protects all organs, tissues, and cells during all modes of exposure<sup>5</sup>. Increasing evidence has revealed that H<sub>2</sub> has a number of advantages as a potential antioxidant adjuvant for alcoholic beverages or a potentially novel drug with a significant clinical benefit to protect cells from oxidative insults engendered by alcohol exposure. Firstly, molecular hydrogen can increase antioxidant enzyme activity and levels<sup>14,24</sup>, selectively attenuate •OH as well as ONOO<sup>-</sup>, the strongest cytotoxic ROS, and does not interfere with the metabolism involved in oxidation-reduction reactions or the levels of essential ROS, such as •O<sub>2</sub><sup>-</sup>, H<sub>2</sub>O<sub>2</sub>, and NO, which are implicated in signal transduction<sup>15</sup>. This means that H<sub>2</sub> treatment is potentially mild enough not to produce serious side effects<sup>15</sup>. However, a systematic review and meta-analysis found that some conventional antioxidant supplements with strong reductive reactivity, including beta carotene, vitamin A, and vitamin E, increased all-cause mortality, possibly by disturbing essential defensive mechanisms<sup>28</sup>. Secondly, H<sub>2</sub> is highly diffusible and can readily permeate biological membranes and diffuse into the cytosol, mitochondria, and nucleus, which contributes to effectively reducing cytotoxic radicals<sup>15</sup>, while most known

antioxidants fail to successfully target organelles<sup>29</sup>. In fact, improvements in mitochondrial dysfunction in MM have been observed with administration of hydrogen-rich water<sup>29</sup>. Finally, hydrogen is a colorless, odorless, and tasteless gas, which ensures an inappreciable change in the alcoholic beverage after being mixed with H<sub>2</sub>, including in color, bouquet, and taste. In addition, the safety of hydrogen for humans is demonstrated by its application in Hydrex, a breathing gas mixture of 49% hydrogen, 50% helium, and 1% oxygen, used for very deep technical diving<sup>30</sup>. These favorable properties, together with recent progress in hydrogen medicine showing the therapeutic opportunities of hydrogen in a variety of disease models, suggest that hydrogen has the potential to not only serve as a safe and available additive for alcoholic beverages, but also act as a promising therapeutic agent for alcohol-induced disorders including alcoholic liver disease. Nevertheless, stringent animal and clinical investigations are required for roundly assessing the biological safety and effectiveness of this hypothesis. **H**

*The authors declare no conflicts of interest.*

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