



CLINICAL ADVANTAGES OF USING HYDROGEN WATER GENERATOR

Amir Nusrat Shadid^{*1}, Wei Hsiao², Chung-Hyun Lee³ and Sato Nagami⁴

¹Laboratory of Health and Medicine, Human Cardiovascular Disease Center, UAE.

²Laboratory of Molecular Sciences, Life Science and Research, China.

³Department of Biomaterial Research, Korean Laboratory of Geurmanc Inc., South Korea.

⁴Department of Molecular Science and Technology, Japan Water and Molecules Research Institute, Japan.

***Corresponding Author:** Amir Nusrat Shadid

Laboratory of Health and Medicine, Human Cardiovascular Disease Center, UAE.

Article Received on 01/09/2017

Article Revised on 22/09/2017

Article Accepted on 12/10/2017

ABSTRACT

Molecular hydrogen has been regarded as an inactive, nonfunctional molecule in our body. We overturned this concept and proposed the potential for preventive and therapeutic application by proving that H₂ reacts to strong oxidizers like hydroxyl radical. H₂ has many merits that show extensive effects. H₂ generated in the GEURMANC hydrogen water generator rapidly spreads to tissues and cells and does not have an impact, strong enough to disturb the oxidation-reduction reaction of metabolism or affect signal reactive oxygen species. Thus, there is little or no side effect of H₂. There are a few methods to absorb or digest H₂. In other words, H₂ gas inhalation, drinking water with dissolved H₂, injection of a saliferous substance with dissolved H₂, H₂ cleansing or dropping H₂-saliferous substance on the eyeball. The GEURMANC hydrogen water generator confines H₂ generated through electric injection in nano-pico hydrogen bubble and innovatively stimulates internal resorption. It turned out that H₂ absorbed like this directly reacts to strong oxidizers, indirectly controls various gene expressions and lowers oxidative stress. Moreover, by controlling gene expression, H₂ performs an anti-inflammatory function and anti-apoptosis and stimulates energy metabolism. The evidence obtained from animal model test increases and wide-range clinical surveys have been performed or are being performed. Since most drugs act specifically on the target, it seems that H₂ is different from the traditional prescription drugs. GEURMANC hydrogen water generator has a bright prospect for the potential of clinical use for various diseases because it has high efficacy and does not have any side effect.

KEYWORDS: Nano-pico hydrogen bubble and innovatively stimulates internal resorption.

INTRODUCTION

Molecular hydrogen has been known to act as an inactive gas at the body temperature in the cells of mammals.^[1] H₂ does not react to biological compounds, including oxidizing gas unless there is a catalyst at the body temperature.^[2] In contrast, in a few bacteria, H₂ is an energy source providing electrons, which is catabolized through enzymes or is a product of a few types of anaerobic metabolism.^[3] Such reactions, in general, are promoted by an enzyme containing iron or nickel, called hydrogenase.^[4] In opposition to this, mammals do not have a functional hydrogenase gene. For example, H₂ has been considered not to function in our cells.^[5]

We overturned the concept coming from a publication in 2007 that H₂ does therapeutic, preventive antioxidant actions by selectively reducing strong antioxidants such as hydroxyl radical (OH) and peroxynitrite (ONOO⁻) in the cells and that it has a cell protection effect for anti-oxidation stress.^[6] Later, several studies have explored the therapeutic, preventive effects of H₂. Articles

published like this deal with various biological effects on oxidation stress in almost all organisms. Moreover, it has been revealed that H₂ has more functions, including anti-inflammatory, anti-apoptosis and anti-allergy effects, and that it stimulates energy metabolism in the tissues of most animal models.^[7] Till 2013, the number of publications on the biologically, medically beneficial effects of H₂ has increased and it exceeded 300 articles. The existing review articles mostly introduced experiments on various cells and animals.^[8] In addition to publications on animal model experiments, more than 10 clinical studies have been published. In sum, this article will review the findings of the recent clinical studies aiming at the actual application.^[9] In addition, this review article reflects on the process of discovering the biological effects of H₂ generated from the GEURMANC hydrogen water generator and proposes a mechanism that can explain such effects of H₂.

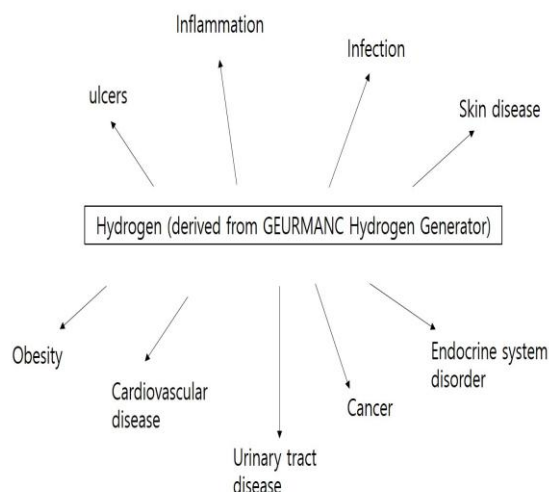


Fig 1. Various effects of hydrogen containing water.

Oxidation stress, the cause of diseases

Reactive oxygen species (ROS) is a by-product of energy metabolism by oxidative phosphorylation in all aerobic organisms, generated in the body all day long. According to circumstances, excess ROS is produced by smoking, air pollution, exposure to ultraviolet or infrared light, extreme exercise, physical or psychological stress.^[10] If ROS is produced excessively, or endogenous anti-oxidation capacity decreases, a harmful effect is caused by indiscriminate oxidation, which results in 'oxidation stress.' Acute oxidation stress occurs by various situations, in other words, inflammation, ischemic reperfusion in the state of myocardial infarction or cerebral infarction, coral transplant, and stopping of hemorrhage according to surgery, etc. Through new evidence, close correlations among wide-range cases have been found, including neurodegenerative diseases and aging process as well as chronic oxidation stress and malignant diseases, genuine diabetes, atheromatous arteriosclerosis and chronic inflammation process.^[11] Under the normal condition, ROS induced by the exercise that causes stress causes muscle fatigue.^[12]

Ideal oxidizer exploration

Anti-oxidizer treatment or prevention of various diseases attract attention because of the clinical importance of oxidative damage; however, the rate of the success of anti-oxidizer treatment is limited. It turned out that antioxidant supplements do not have any impact on cancer, myocardial infarction, atheromatous arteriosclerosis, but rather increase the death rate inversely. In sum, it is very important to pay attention to side effects in developing an anti-oxidizer, effective for the prevention of diseases related to oxidation stress.^[13]

In this situation, it is expected that an ideal anti-oxidizer molecule alleviates excessive oxidation stress, but does not disturb the homeostasis of oxidation-reduction. In other words, an ideal molecule should not reduce signal molecules like H_2O_2 , but effectively reduce strong oxidizers like OH. After the experiment, we reached the current conclusion that H_2 may be an ideal anti-oxidizer.

Ingestion by drinking hydrogen water

Intake of H_2 gas is neither suitable nor practical for continuous absorption for preventive use of H_2 in daily life. In contrast, the reasons why the dissolved H_2 is beneficial are that it is portable, easily administered and a safe method for the intake of H_2 . H_2 can be dissolved up to 0.8 mM (1.6 mg/L) at the room temperature under atmospheric pressure, while not changing pH. Drinking the water with saturated H_2 randomly was more effective than drinking the diluted water, but 80 μ M H_2 -water alone was effective to improve obesity.

H_2 -water can be produced by a few methods, such as injection of H_2 gas in water under high pressure, electric injection of water to produce H_2 and reaction of magnesium metal or hydride of metal to water. The methods can apply to other solvents in addition to water. The GEURMANC hydrogen water generator produces H_2 with the electric injection method of them and generates its original hydrogen bubble. The absorption, distribution, metabolism and excretion of the hydrogen molecules of this hydrogen bubble into the human body are done, optimized based on pharmacokinetic and pharmacodynamic studies. H_2 penetrates any glass containers and plastic bottles in a short time, while aluminum containers can store hydrogen water for a long time.^[14]

Observation of molecular hydrogen movement

H_2 has many merits as a potential anti-oxidant. H_2 has a good diffusion characteristic with its own physical abilities to penetrate biomembranes and spread to cell substrates. Nevertheless, GEURMANC developed its original delivery method through a joint study with Japan Molecular and Water Research Institute, and the hydrogen water generated in the GEURMANC hydrogen water delivers hydrogen through nano-pico hydrogen bubble so that it can be absorbed fast and delivered well in the body. H_2 arrives at the nucleus and mitochondria and protects DNA of the nucleus and mitochondria. Moreover, H_2 penetrates the blood-cerebral barrier. Most anti-oxidant compounds cannot penetrate, though.^[15]

H_2 in the blood can be observed by the following method. First, collect venous blood or arterial blood in a closed aluminum bag without any blind spot and add a limited amount of air in the bag. H_2 in an atmospheric stage, delivered from the blood can be measured by gas chromatography. The absorption of H_2 after one drinks GEURMANC hydrogen water substantially increased H_2 dissolved in arterial blood with a method dependent on the concentration of H_2 gas, and the H_2 level in the venous blood was lower than that in the arterial blood. The difference in the level between the arterial blood and the venous blood suggests the amount of H_2 included and absorbed in the tissues.

In addition, the GEURMANC hydrogen bubble moves according to the difference in hydrogen concentration, which has a strong anti-oxidant effect as hydrogen is

naturally distributed to a place with much active oxygen.

A clinical survey proved the difference in H_2 concentration between venous blood and arterial blood. With detection of a specific electrode, the diffusion of H_2 gas in various tissues can be observed. For example, H_2 concentration in the myocardium of a mouse has been observed. After coronary occlusion, to estimate the diffusion of H_2 to the ischemic myocardium, an electrode was inserted into a 'risky' region. In the state of the occlusion of the coronary artery, H_2 concentration increased by its spread.^[16]

In addition, we made tear with dissolved H_2 to administer H_2 in the retina directly and observed the time path of changes in H_2 level, using a needle-shaped hydrogen sensor electrode inserted into the vitreous body of a mouse through the sclera. H_2 could reach the vitreous body by administering H_2 in a normal saliferous substance so that H_2 would be saturated. When H_2 tear was administered consecutively, approximately 70% of H_2 were detected at the surface of the eye ball.

When the water saturated with H_2 was put in the stomach of a mouse H_2 , a few μM of H_2 were detected in the blood. In addition, with a needle-shaped hydrogen electrode, the H_2 in the liver was observed and after the oral administration of H_2 -water, glycogen in the liver maintained H_2 and this explains how various disease models could be improved efficiently with the absorption of a small amount of H_2 in a short duration.

When seven adult volunteers drank H_2 -water, the H_2 content in their breath exhaled was measured with a semiconductor and gas chromatography. With H_2 -water intake, the H_2 content increased to the maximum 10 minutes after inhalation, and later, in 60 minutes, it decreased to the level of the reference line. During the experiment procedures, the amount of H_2 lost from water was equivalent to less than 3% of H_2 . From the skin surface, H_2 discharge was estimated at approximately 0.1%. Based on the balance of H_2 substance remaining, approximately 40% of H_2 drunken were absorbed into the body. This report suggests that exogenous H_2 is trapped by oxygen radicals like OH at least partially.

Effect of GEURMANC hydrogen water and clinical study

Safety of molecular hydrogen to human beings

H_2 has a merit in terms of toxicity. H_2 does not have cytotoxicity even at high concentration. The reason why the safety criteria for H_2 at high concentration when inhaled has been established is that high-pressure H_2 gas is used in deep submergence gas compounds to prevent dysbarism and arterial gas thrombus. What is important in clinical use in terms of the safety of H_2 for human beings is that it is an interesting respiratory gas compound, consisting of 49% H_2 , 50% helium and 1% O_2 and during technical deep submergence and it is proven by the application of very high concentration of

H_2 gas in hydreliox, used to prevent dysbarism and nitrogen narcosis. To consider the fact that H_2 is an inactive gas and does not function in our body, the reason for its absence of toxic effect can easily be understood. As mentioned above, 1–4% H_2 gas inhalation can have a good effect.^[17]

Many reports have supported the fact that H_2 has a big effect in a wide-range disease model regardless of the method of H_2 inhalation as summarized in Fig. 4. This review article mainly focuses on a clinical study.

Effect on the protection of refusion damage

Ischemia/reperfusion induces severe oxidation stress, and its damage should be considered in various clinical treatments. H_2 gas inhalation improved ischemia/refusion damage in cerebral infarction and myocardial infarction. Hydrogen-saliferous substance protected the ischemia-refusion damage of the kidney. After cardiac arrest (CA), all clinical findings related to syndrome are considered to be caused by ischemia/refusion damage in various organs, including the brain and the heart. When a mouse model inhales H_2 gas, in the post-CA syndrome state, a considerable improvement of neuropathy score and survival score has been achieved.

H_2 also alleviated damage of transplantation of various organs by H_2 -gas, H_2 -water and H_2 -preservation solution.

Along with clinically approved radical scavenger Edaravone, the H_2 -saliferous substance was administered to eight patients with acute brainstem infarction via the vein, and then, the MRI indexes of 26 patients who were administered only with Edaravone were compared. When H_2 and Edaravone were injected together, relative diffusion-weighted images (rDWIs), local obvious diffusion coefficient (rADCs) and pseudo-normalization time of rDWI and rADC were all improved.

Effect on the prevention of neurodegeneration

Chronic oxidation stress is widely recognized as one of the causes for neurodegeneration, including dementia and Parkinson's disease (PD). Stress for a test in the brain can be induced by chronic physical restraint stress, and learning and memory can be damaged. In addition, neural proliferation in the dentate gyrus of the hippocampus is suppressed with restraint stress. By drinking H_2 -water, the increase in this oxidation stress was suppressed and this cognitive disorder was prevented. In addition, H_2 -water restored neural proliferation in the dentate gyrus of the hippocampus of this animal model. Since anti-depressant increases the generation of the adult's nerves, H_2 -water can be applied to improve depression and other mental disorders.^[18]

In the PD state, mitochondria dysfunction and the related oxidation stress are the main causes for the dopaminergic cell loss in the black substance. H_2 in drinking water was provided before and after stereotactic surgery on PD for the black substance corpus glandulosum atrophy induced

by 6-hydroxydopamine in a mouse model affected by PD. H₂-water prevented the occurrence and progress of the black substance corpus glandulosum in the mouse. Moreover, by drinking H₂-water, dopaminergic cell loss of another mouse model affected by PD, induced by MPTP, too, was suppressed.

In a placebo-controlled, randomized, double-blind, parallel group preliminary clinical study, the effect of H₂-water on the patients affected PD mediated by L-dopa was evaluated. The participants drank 1L H₂-water or pseudo water for 48 weeks. The UPDRS score improved in the H₂-water group (n=9) while that in the pseudo water group (n=8) deteriorated. The number of patients was small, and the experiment period was short, but this difference was a significant level ($P < .05$).

Effect on the prevention of metabolic syndrome

By H₂-water drinking, energy metabolism is stimulated. H₂-water significantly alleviated fatty liver of wild mouse induced by fat-diet as well as the fatty liver of db/db mouse, an obese mouse model with type 2 diabetes. Despite the diet and water intake of db/db mouse did not increase, long-term H₂-drinking significantly decreased fat and weight. Moreover, by H₂-water drinking, energy metabolism was stimulated to reduce the plasma, insulin, triglyceride levels.

In terms of the prevention of latent metabolic syndrome, H₂-water's beneficial roles have been reported by the following three independent clinical studies. With 30 patients with type 2 genuine diabetes and six patients with damaged glucose tolerance, a randomized, double-blind, placebo-controlled, cross-over study was conducted. The patients took 900mL H₂-water or placebo water for eight weeks and had a withdrawal period for 12 weeks. In the aspects of electronegative charge-transformed low-density lipoprotein (LDL)-cholesterol, low-density LDL, 8-isoprostanes improvement in urine, statistical significance was observed. The glucose tolerance test index of four persons out of the six patients with damaged glucose tolerance improved to the normal level by H₂.

With 20 research subjects with a latent metabolic syndrome, an open experiment was conducted. The participants drank H₂-water (1.5-2.0 L/day) for eight weeks and as a result, SOD of urine increased, TBARS in urine, that is, lipid peroxidation marker decreased, high-density lipoprotein (HDL)-cholesterol increased and Total cholesterol decreased.^[19]

The effects of H₂-water (0.9–1.0 L/day) on serum lipoprotein content, composition and biological action of 20 patients with the latent metabolic syndrome were characterized. Through serum analysis, by drinking H₂-water for 10 weeks, total cholesterol (TC) and LDL-cholesterol levels decreased. In addition, H₂-water improved the protection of endotheliocyte with i) the prevention of LDL oxidation, ii) the suppression of

monocyte attachment to endotheliocyte, induced by tumor necrosis factor- α (TNF- α), iii) the stimulation of discharge of cholesterol from macrophage foam cells and iv) apoptosis induced by TNF- α .

To sum up, these results strongly imply that drinking H₂-water is beneficial to patients with metabolic syndrome.

Effect on the suppression of inflammation

H₂ reduced inflammation in animal models for a test, induced by concanavalin A, dextran sodium sulfate, lipopolysaccharide (LPS), generalized inflammation derivative, zymosan and septicemia. H₂ gas, H₂-saliferous substance and H₂-water reduced the inflammation-friendly cytokinesis level and suppressed inflammation.^[20]

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by the destruction of the bone and cartilage. Ishibashi et al. Administered H₂-water containing 4–5 mg/L H₂ (High H₂-water) (0.5 L/day) to 20 patients with RA for four weeks. 8-hydroxy-deoxyguanine (8-OhdG) in urine significantly decreased by 14.3% on average ($P < 0.01$). During the same period, when DAS28 (C-responsive protein level) was used, the activity of the disease, too, decreased ($P < 0.01$). After the resting, both 8-OhdG in urine and the average DAS28 relatively decreased during the drinking period. During the second drinking period, the average DAS28 decreased ($P < 0.01$). In the early phase when there was no antibody for the cyclic citrullinated peptide (ACPA) (Period <12 months), all five patients with RA reached remission, and symptoms disappeared in four out of them at the end-point of the research. In sum, RA symptoms significantly improved by H₂-water.

Alleviation of side effects of tumor treatment

By H₂ gas inhalation and H₂-water drinking, the mortality and weight loss of mice improved with antibiotic, cisplatin treatment and nephrotoxicity was alleviated. In spite of the preventive effect of cisplatin-induced toxicity, H₂ did not affect the anti-tumor action of cisplatin on the mouse with a tumor in the body and extra-somatic cancer cells.

With 49 patients who had radiotherapy because of malignant hepatoma, a randomized placebo-controlled clinical study was conducted on H₂-water (0.55–0.65 mM, 1.5–2.0 L/day) for six weeks. H₂ suppressed the increase in the hydroperoxide level, maintained serum anti-oxidant dose and improved the QoL score. Especially, H₂-water efficiently prevented the loss of appetite. There was no difference in tumor reaction to radiotherapy between the two groups.^[21]

Impacts on dermatomyositis and mitochondria myopathic disorder

With 14 patients with muscular diseases, including muscular atrophy, polymyositis/dermatomyositis and mitochondria myopathic disorder, an open experiment

was conducted with H₂-water (1.0 L/day) for 12 weeks. In this open experiment, significant improvements were observed in lactate/pyruvate ratio, fasting blood glucose, serum matrix metalloproteinase-3 (MMP3) and triglyceride. Especially, a biomarker sensitive to the damaged mitochondria transmission system, lactate/pyruvate ratio decreased by 28% in the state of mitochondria myopathic disorder. MMP3 showing inflammatory action decreased by 27% in the state of dermatomyositis.

Later, they conducted a randomized, double-blind, placebo-controlled, cross-over experiment with H₂-water or placebo-dehydrogenized water (0.5 L/day) for eight weeks on 22 patients with dermatomyositis and mitochondria myopathic disorder. In this double-blind experiment, there was a statistically significant improvement of serum lactate only in the state of mitochondria myopathic disorder by the absorption of H₂-water, but it was observed that the lactate/pyruvate ratio in the state of mitochondria myopathic disorder and MMP3 in the state of dermatomyositis tended to decrease by H₂-water absorption.^[22]

Effect on the alleviation of hemodialysis

An open placebo-controlled cross-over experiment on 12 times of hemodialysis of eight patients and an open experiment on 78 times of hemodialysis of 21 patients were conducted. In the two studies, by continuous hemodialysis using H₂-dialysis solution, the systolic blood pressure declined before and after the dialysis. In a short-term study, plasma methylguanidine significantly decreased. In a long-term study, plasma monocyte chemoattractant protein 1 and myeloperoxidase significantly decreased.

Acute lupus skin disease

Four patients with an acute lupus skin disease accompanied by heat or pain were treated with the intravenous administration of 0.5L H₂-solution for 30 minutes for more than three days. The erythema and related symptoms of these four patients significantly improved after H₂ treatment. Consequently, After the administration of H₂-solution, acute lupus skin disease improved while not damaging the safety.

Impact on exercise

10 young male soccer players were selected to conduct an exercise test and collected their blood samples. Each subject was examined two times with a cross-over, double-blind method. For them, H₂-water or placebo water was provided at an interval of one week. After the subjects were asked to use a fixed bicycle at the maximum oxygen absorption (VO₂) of 75% for 30 minutes, the maximum torque and muscular activity were measured throughout the repetition of isokinetic knee extension 100 times. Through the emergency exercise, the blood lactate level of the research subjects provided with placebo water increased while the increase of the blood lactate was prevented during excessive

exercise when H₂-water was orally absorbed. The maximum torque in the placebo water group significantly decreased during the isokinetic knee exercise, which suggests muscle fatigue.^[23]

DISCUSSION

Hydrogen was proven powerful antioxidant. The strong antioxidant effect of hydrogen on active oxygen was published in *Nature Medicine*, a world-renowned international journal and there are numerous studies supporting it. GEURMANC Hydrogen Water has been scientifically proven to prevent or improve diseases owing to the antioxidative effect. For example, it is known to be effective in inhibiting ischemia, reperfusion, and oxidative stress, preventing metabolic syndrome, inflammation, relieving the side effects of cancer treatments, mitigating dermatomyositis and mitochondrial myopathic disorder, improving skin disease and enhancing mobility and these effects. Its effectiveness has been reported widely in many countries.

You can easily remove active oxygen, which causes various diseases and accelerates aging, easily and quickly by drinking GEURMANC Hydrogen Water. Active oxygen can cause various diseases such as skin disease, heart disease, obesity and aging. Active oxygen can be generated when people are exposed to fine dust, ultraviolet, germs, chemical substances and stress. It is also produced during exercising, even breathing. Active oxygen has a unique unstable and high energy level to easily oxidize other molecules. Consequently, it causes various diseases to people. GEURMANC hydrogen bubbles contained in GEURMANC Hydrogen Water diffuses into the human body quickly and effectively in a few minutes through the optimized ADME and eliminates active oxygen from your body quickly and effectively.^[24]

Hydrogen Water eliminates the active oxygen created every day. Therefore, it is getting super popular around the world. For example, the hydrogen water market of our neighborhood Japan has exceeded 300 billion and more than 10% of bottled water sales are hydrogen water. You can easily see how popular it is in Japan.

GEURMANC has secured an innovative novel nano-pico hydrogen bubble transfer system in the human body through the collaboration with Japan Water and Molecular Research Institute. Studies published in international journals have shown that its efficacy is twice of the existing water (Fig 2). If you drink 1L of GEURMANC Hydrogen Water per day, you will get the same antioxidant effect as taking 3g of vitamin C. How much is 3g of Vitamin C? It is equivalent to 3,000 bananas, 2,000 apples, 1,000 oranges, or 600 strawberries, You can easily ingest this vast amount of antioxidants through GEURMANC Hydrogen Water.

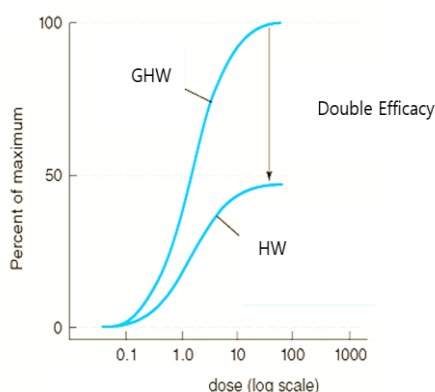


Fig 2. Geurmanc hydrogen water has shown double efficacy. (GHW: Geurmanc hydrogen water, HW, Hydrogen water).

Hydrogen tends to fly away as soon as it is produced. Therefore, it requires a high technology to produce effective hydrogen water. The cheap hydrogen water generator has a low probability to dissolve hydrogen in the water well and it may produce residual chlorine. GEURMANC Hydrogen Water introduces the latest 3rd generation electrolysis method and GEURMANC Hydrogen Bubble technology capture hydrogen in the water and does not let hydrogen go away. Consequently, it guarantees the maximum effects. GEURMANC Hydrogen bubbles are designed to diffuse into the human body rapidly based on pharmacokinetics and pharmacodynamics studies and it even increases the efficacy of it. In addition, when hydrogen is generated electrically, chlorine is formed as well. GEURMANC water adopts the expensive gas membrane isolation method to completely isolate and discharge chlorine.^[25]

The GEURMANC Hydrogen Water generator is produced based on the integration of these high technologies and that is why its efficacy could be published before. GEURMANC Hydrogen Water generator based on the advanced science of Japan Water and Molecular Research Institute.

CONCLUSION

This study reviewed the progress of hydrogen medicine after the first attempt till the clinical application and confirmed the strong antioxidant effect of the hydrogen water generated from the GEURMANC hydrogen water generator. The reasons why it is easy to apply GEURMANC H₂ are that it does not have any side effect and that it has a big effect on almost all cases related to oxidation stress and inflammation. In fact, the clinical effect of H₂ was positive for patients with more than 10 diseases. Since most medicines act particularly on the target, H₂ looks different from the traditional drugs as it has wide and diverse effects. There is a high potential for the preventive and therapeutic application of H₂ to

various diseases, thanks to its excellent efficacy and new concept.

ACKNOWLEDGEMENT

This research is supported by Lifescience and Health Research Institute of Germany.

REFERENCES

1. Zhai, X., Chen, X., Ohta, S. and Sun, X. (2014) Review and Prospect of the Biomedical Effects of Hydrogen. *Medical Gas Research*, 4, Article 19.
2. Christensen, H. and Sehested, K. (1983) Reaction of Hydroxyl Radicals with Hydrogen at Elevated Temperatures. *Journal of Physical Chemistry*, 87: 118-120.
3. Maise, K. (2015) New Insights for Oxidative Stress and Diabetes Mellitus. *Oxidative Medicine and Cellular Longevity*, 2015, Article ID: 875961.
4. Vendemiale, G., Grattagliano, I. and Altomare, E. (1999) An Update on the Role of Free Radicals and Antioxidant Defense in Human Disease. *International Journal of Clinical Laboratory Research*, 29: 49-55.
5. Miquel J., Economos, A.C., Fleming, J. and Johnson Jr., J.E. (1980) Mitochondrial Role in Cell Aging. *Experimental Gerontology*, 15: 575-591.
6. Carri, M.T., Valle, C., Bozzo, F. and Cozzolino, M. (2015) Oxidative Stress and Mitochondrial Damage: Importance in Non-SOD1 ALS. *Frontiers in Cellular Neuroscience*, 9, Article 41.
7. Reddy, P.H. (2008) Mitochondrial Medicine for Aging and Neurodegenerative Diseases. *Neuromolecular Medicine*, 10: 291-315.
8. Nicolson, G.L. (2014) Mitochondrial Dysfunction and Chronic Disease: Treatment with Natural Supplements. *Alternative Therapies for Health and Medicine*, 20: 18-25.
9. Maiese, K., Chong, Z.Z., Shang, Y.C. and Wang, S. (2012) Targeting Disease through Novel Pathways of Apoptosis and Autophagy. *Expert Opinions in Therapeutic Targets*, 16: 1203-1214.
10. Maiese, K., Chong, Z.Z., Shang, Y.C. and Wang, S. (2012) Targeting Disease through Novel Pathways of Apoptosis and Autophagy. *Expert Opinions in Therapeutic Targets*, 16: 1203-1214.
11. Suzen, S., Cihaner, S.S. and Coban, T. (2012) Synthesis and Comparison of Antioxidant Properties of Indole-Based Metatonin Analogue Indole Amino Acid Derivatives. *Chemical and Biological Drug Design*, 79: 76-83.
12. Collins, Y., Chouchani, E.T., James, A.M., Menger, K.E., Cocheme, H.M. and Murphy, M.P. (2012) Mitochondrial Redox Signaling at a Glance. *Journal of Cell Science*, 125: 801-816.
13. Liu, H., Colavitti, R., Rovira, I.I. and Finkel, T. (2005) Redox-Dependent Transcriptional Regulation. *Research*, 97: 967-974.
14. Dorweiler, B., Pruefer, D., Andrasi, T.B., Maksan, S.M., Schmiedt, W., Neufang, A. and Vahl, C.F. (2007) Ischemia Reperfusion Injury. *European*

- Journal of Trauma and Emergency Surgery*, 33: 600-612.
15. Di Lisa, F. and Bernardi, P. (2006) Mitochondria and Ischemia-Reperfusion Injury of the Heart: Fixing a Hole. *Cardiovascular Research*, 70: 191-199.
 16. Anaya-Prado, R., Toledo-Pereyra, L.H., Lentsch, A.B. and Ward, P.A. (2002) Ischemia/Reperfusion Injury. *The Journal of Surgical Research*, 105: 248-258.
 17. Kubler, W. and Haass, M. (1996) Cardioprotection: Definition, Classification and Fundamental Principles. *Heart*, 75: 330-333.
 18. Piot, C., Croisille, P., Staat, P., Thibault, H., Rioufol, G., et al. (2008) Effect of Cyclosporine on Reperfusion Injury in Acute Myocardial Infarction. *The New England Journal of Medicine*, 359: 473-481.
 19. Yoshida, A., Asanuma, H., Sasaki, H., Sanada, S., Yamazaki, S., et al. (2012) H₂ Mediates Cardioprotection via Involvements of K(ATP) Channels and Permeability Transition Pores of Mitochondria in Dogs. *Cardiovascular Drugs and Therapy*, 26: 217-226.
 20. Liu, H., Hua, N., Xie, K., Zhao, T. and Yu, Y. (2015) Hydrogen-Rich Saline Reduces Cell Death through Inhibition of DNA Oxidative Stress and Overactivation of Poly (ADP-Ribose) Polymerase-1 in Retinal Ischemia-Reperfusion Injury. *Molecular Medicine Reports*, 12: 2495-2502.
 21. Alberti, K.G., Zimmet, P. and Shaw, J., IDF Epidemiology Task Force Consensus Group (2005) The Metabolic Syndrome—A New Worldwide Definition. *Lancet*, 366: 1059-1062.
 22. Muller, M., Grobbee, D.E., den Tonkelaar, I., Lamberts, S.W. and van der Schouw, Y.T. (2005) Endogenous Sex Hormones and Metabolic Syndrome in Aging Men. *Journal of Clinical Endocrinology and Metabolism*, 90: 2618-2623.
 23. Iio, A., Ito, M., Itoh, T., Terazawa, R., Fujita, Y., Nozawa, Y., Ohsawa, I., Ohno, K. and Ito, M. (2013) Molecular Hydrogen Attenuates Fatty Acid Uptake and Lipid Accumulation through Downregulating CD36 Expression in HepG2 Cells. *Medical Gas Research*, 3, Article 6.
 24. Chen, Y., Jiang, J., Miao, H., Chen, X., Sun, X. and Li, Y. (2013) Hydrogen-Rich Saline Attenuates Vascular Smooth Muscle Cell Proliferation and Neointimal Hyperplasia by Inhibiting Reactive Oxygen Species Production and Inactivating the Ras-ERK1/2-MEK1/2 and Akt Pathways. *International Journal of Molecular Medicine*, 31: 597-606.
 25. Thompson, L.M. (2008) Neurodegeneration: A Question of Balance. *Nature*, 452: 707-708.