

Advanced research on the health benefit of reduced water[☆]

Sanetaka Shirahata*,
Takeki Hamasaki and
Kiichiro Teruya

Department of Bioscience and Biotechnology,
Faculty of Agriculture, Kyushu University, 6-10-1
Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan
(Tel.: +81 92 642 3045; fax: +81 92 642 3052;
e-mail: sirahata@grt.kyushu-u.ac.jp)

In Japan, research on functional water, especially on reduced water, is developing at a rapid pace. Reduced water such as electrochemically reduced water and natural reduced water can scavenge reactive oxygen species in cultured cells. Reduced waters are expected to have preventive and positive effects on oxidative stress-related diseases such as diabetes, cancer, arteriosclerosis, neurodegenerative diseases, and side effects of hemodialysis. It has been suggested that the active agents in reduced water are hydrogen (atoms and molecules), mineral nanoparticles, and mineral nanoparticle hydrides.

Introduction: electrochemically reduced water is beneficial for health

In the field of food science and technology, water is an important ingredient influencing taste, rheology and preservation of foods. Research on functional foods is currently popular; however, it is not yet well known that drinking water also has physiological functions, and that there are some health-beneficial effects of water (Shirahata, 2002, 2004). In the past decade, the decrease in the quality of tap water because of pollution of the global environment over time has become a major social problem. Air pollution affects water in soils, rivers, and farm products by acid rain. Chemicals in polluted water are considered to generate

oxidative stress in the placenta of pregnant women, and this can cause various types of diseases in newborns (Obolenskaya *et al.*, 2010).

The human body is approximately 60–80% water. The function of water in the body is mainly classified as follows. (1) The water molecule itself: flowing water affects cellular function and both development and functions of organs (Hirokawa, Tanaka, Okada, & Takeda, 2006; Hove *et al.*, 2003), and hydration and Brownian movement of water are fundamentally important for protein function (Iwaki, Iwane, Shimokawa, Cooke, & Yanagida, 2009); (2) atoms and molecules derived from water molecules, such as protons (H^+), hydrogen atoms (active hydrogen [H]), hydrogen anions (H^-), hydrogen molecules (H_2), oxygen molecules (O_2), and reactive oxygen species (ROS); and (3) molecules dissolved in water, such as mineral ions, mineral nanoparticles, organic and inorganic compounds, and gases.

Functional water is activated water exhibiting specific functions. There are many activation methods such as electrolysis, treatment with a magnetic field, light irradiation, ultrasonication, bubbling with gases, strong water flow and collision, and treatment with some types of minerals or rocks. Functional water is defined by The Functional Water Association of Japan as water in which both treatment and function have been scientifically demonstrated or reproducible useful functions have been demonstrated among artificially treated waters. Among functional waters, electrolyzed water has been mostly investigated. Electrochemically reduced water (ERW) is produced near a cathode and electrochemically oxidized water (EOW) is produced near an anode. Potable ERW is a health-beneficial water as discussed here. EOW is also termed electrolyzed acidic water and is functional water exhibiting a sterilizing action, mainly due to hypochlorous acid, chlorine gas, and ozone (Bari, Sabina, Isobe, Uemura, & Isshiki, 2003) (Fig. 1A).

Potable ERW (pH 8–10) is popular as a health-beneficial water in Japan. ERW is also termed alkaline electrolyzed water, alkali-ionic water, alkaline cathodic water, and alkaline ionized water, based on its physicochemical and physiological aspects. ERW exhibits an alkaline pH, is hydrogen molecule-rich, and has a negative oxidation–reduction potential (ORP) and reactive oxygen species (ROS)-scavenging activity (Shirahata *et al.*, 2007). Studies on the functions of ERW were initiated in Japan in 1931, and its application to agriculture was first

[☆] This article was accepted as part of the Food Science in Japan special issue.

* Corresponding author.

1997). Electrolysis of water produces a strong reducing circumstance in the vicinity of a cathode, because most voltage is applied in the very narrow water layer nearby the cathode, forming very high electric field. Platinum-coated titanium electrodes are often used for electrolysis of water in the commercial ERW-producing apparatus. On the cathodic platinum plate, hydrogen atoms (active hydrogen) and hydrogen molecules are generated. Mineral nanoparticles and mineral nanoparticle hydrides are also formed as shown in Fig. 1B. Actually we found that ERW prepared from NaOH solution contained a small amount of Pt nanoparticles (Fig. 2C and D). Synthesized Pt nanoparticles scavenged $O_2^{\cdot-}$, $\cdot OH$, and H_2O_2 (Hamasaki *et al.*, 2008; Kajita *et al.*, 2007) (Fig. 2). Synthesized Pt nanoparticles also activated hydrogen molecules to hydrogen atoms by their catalysis action. Natural reduced waters (NRWs) such as Hita Tenryosui water in Japan and Nordenau water in Germany also exhibited ROS-scavenging activities (Li *et al.*, 2002). We propose an active hydrogen mineral nanoparticles hypothesis of reduced water to explain the mechanism of action of both ERW and NRW (Fig. 3). See supplementary information for detailed discussion.

Anti-diabetic effect of reduced water

According to a national health and nutrition survey in 2007, 22.1 million people, amounting for one sixth of the entire population, are patients with diabetes or people with suspected diabetes in Japan. Diabetes mellitus is mainly classified into two types: type 1 insulin dependent diabetes

mellitus and type 2 non-insulin dependent diabetes mellitus. Type 1 diabetes mellitus is caused by insulin deficiency due to the oxidative damage of pancreatic β cells attacked by immune cells. Type 2 diabetes mellitus is also strongly associated with the oxidative damage of myotube and adipocyte cells due to stress, hyperphagia, and lack of exercise. ERW, Hita Tenryosui water and Nordenau water have been shown to scavenge intracellular ROS in a hamster pancreatic β cell line HIT-T15 cells, and remarkably accelerate the secretion of insulin. The oxidative damage induced by alloxan, a type 1 diabetes inducer, is suppressed by ERW and NRW in cells and in alloxan-induced type 1 diabetes model mice (Li *et al.*, 2002, 2005, 2010, 2011).

ERW, Hita Tenryosui water and Nordenau water scavenge ROS in rat L6 myotube cells and enhance sugar uptake (Oda *et al.*, 1999). Nordenau water and Hita Tenryosui water promote the phosphorylation of the insulin receptor *via* suppression of the activity of tyrosine protein phosphatase, which is a redox-sensitive protein, and activate PI3 kinase and Akt, as well as promote the translocation of the sugar transport carrier GLUT4 to the cell membrane to promote sugar uptake (Shirahata *et al.*, 2001, 2007). These waters also alleviate sugar tolerance damage in type 2 diabetes model mice (Gadek & Shirahata, 2002; Osada *et al.*, 2010). ERW derived from tap water improves the symptoms of diabetes model mice (Jin *et al.*, 2006; Kim, Jung, Uhm, Leem, & Kim, 2007; Kim & Kim, 2006).

It has been reported that in 45% of 411 type 2 diabetes patients (mean age, 71.5 years) who drank 2 L of Nordenau water per day, blood glucose and HbA1c levels were significantly decreased after drinking this water for 6 days. These levels were further decreased after long term drinking. Additionally, blood cholesterol, low density lipoprotein (LDL), and creatinine levels were significantly decreased and high density lipoprotein levels were significantly increased. Drinking this water for a longer period resulted in an increase in the percentage of patients who improved (Gadek, Hamasaki, & Shirahata, 2009; Gadek, Li, & Shirahata, 2006). In an open clinical test performed at the First Central Hospital in Jilin Cangechun City in China, 65 patients with diabetes and 50 patients with hyperlipidemia drank 2 L of Hita Tenryosui water per day for 2 months. This resulted in a significant decrease in blood sugar levels in 89% of patients with diabetes. Additionally, blood triglyceride and total cholesterol levels in 92% of patients with hyperlipidemia were significantly decreased (Osada *et al.*, 2010). Furthermore, a double-blind random clinical trial for 29 patients with type 2 diabetes was performed at the Fukuoka Tokusuyukai Hospital, Fukuoka city, Japan. Urinary 8-OH dG (an internal oxidation marker) levels of patients who drank 1 L of Hita Tenryosui water per day for 6 months were significantly decreased (Matsubayashi, Hisamoto, Murao, & Hara, 2008). In addition, in a double-blind clinical trial with 100 subjects performed at Hiroshima University from November 2008 to September

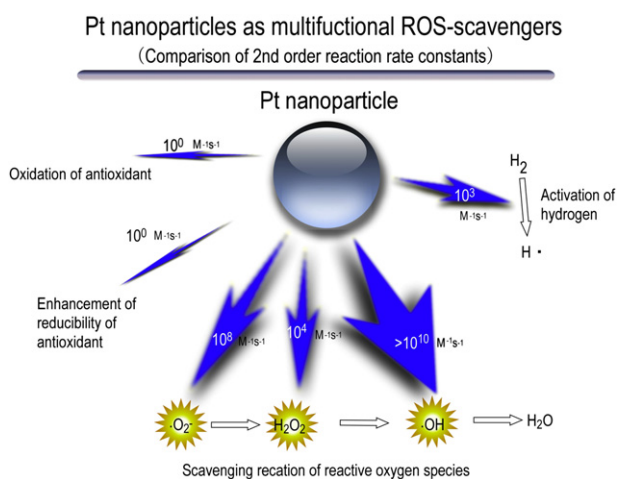


Fig. 2. Multi-functional ROS-scavenging activity of Pt nanoparticles. The 2nd order reaction rates of synthesized Pt nanoparticles of 2–3 nm were determined as reported by Hamasaki *et al.* (2008). Pt nanoparticles exhibit superoxide anion radical-scavenging activity as well as SOD enzyme activity. They also exhibit catalase-like activity. The hydroxyl radical-scavenging activity of Pt nanoparticles is as strong as that of ascorbic acid, one of the strongest scavengers. Pt nanoparticles activate hydrogen molecules to active hydrogen and stimulate the reducibility of antioxidants. The autoxidation activity of Pt nanoparticles on antioxidants is weak. The numbers show K_s values of second reaction rate constants.

Active hydrogen mineral nanoparticle reduced water hypothesis

Active agents in reduced water may be: active hydrogen, hydrogen anion, hydrogen molecule, mineral nanoparticles, mineral nanoparticle hydrides

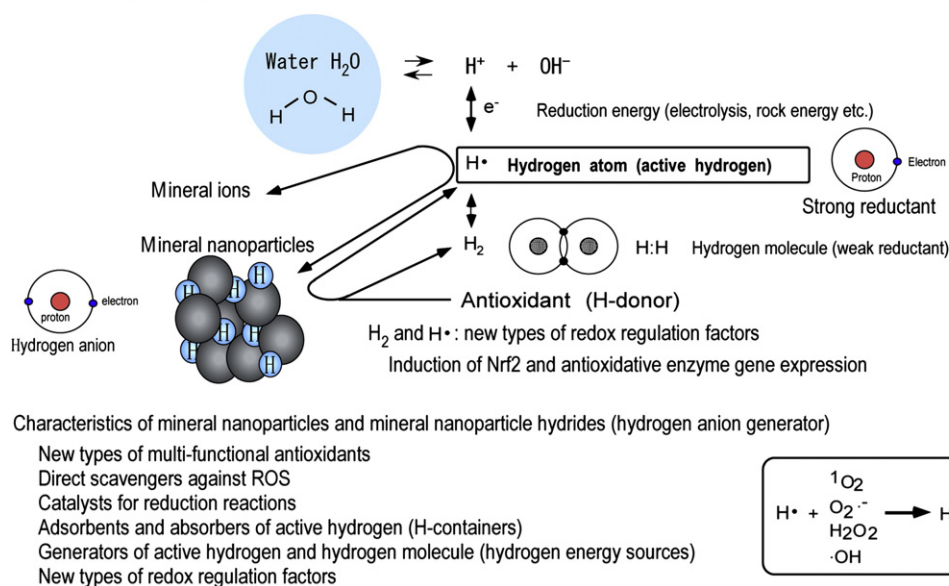


Fig. 3. Active hydrogen mineral nanoparticle reduced water hypothesis. As a common mechanism in both ERW and NRW, water is reduced by electric energy, rock energy and other energy to produce active hydrogen (H atom) and mineral nanoparticles. H atoms produce hydrogen molecules, which are weak reductants, but can function as H-donors. Mineral nanoparticles sustain reduction energy, because they gradually dissociate to mineral ions, releasing electrons. Mineral nanoparticles directly scavenge $O_2^{\bullet-}$, $\cdot OH$ and H_2O_2 by catalysis mechanisms. Mineral nanoparticles stimulate H atom release from many organic substances such as antioxidants and methanol to enhance reducibility. Mineral nanoparticle hydrides can release hydrogen anions, which can function as a reductant.

2009, when 2 L of Hita Tenryosui water was drunk a day, it was found to have anti-metabolic syndrome effects such as a significant decrease in starved blood sugar levels, blood pressure, total cholesterol, LDL cholesterol, GOT, γ -GTP, and triglyceride levels, arteriosclerosis index, and uric acid levels, and a significant increase in leptin levels, as well as improvement of constipation (Higashikawa, Kuriya, Noda, & Sugiyama, 2009). In the clinical trial, it was suggested that drinking 2 L of natural mineral water per day itself was beneficial for health.

Other physiological functions of reduced water

Elongation effect on the lifespan of nematodes

A recent theory on aging suggests that there are adequate ROS levels in living organisms to elongate lifespan, and both insufficient and excess ROS levels shorten the lifespan (Brewer, 2009). We have reported that ERW significantly extends the lifespan of nematodes (*Caenorhabditis elegans*) by scavenging ROS in nematodes (Yan et al., 2010). The active agent responsible for the lifespan extension in ERW is suggested to be Pt nanoparticles of ppb levels, but not hydrogen molecules (Yan et al., 2011). It has also been reported that Pt nanoparticles of an optimum concentration extend the lifespan of nematodes by scavenging ROS (Kim et al., 2008; Kim, Shirasawa, & Miyamoto, 2010).

Anti-cancer effects

ERW causes telomere shortening in cancer cells (Shirahata et al., 1999). It suppresses tumor angiogenesis by scavenging intracellular ROS and suppressing the gene expression and secretion of vascular endothelial growth factor (Ye et al., 2008). ERW suppresses the growth of cancer cells and microorganisms (Hamasaki et al., 2005; Komatsu et al., 2001) and induces apoptosis together with glutathione in human leukemia HL60 cells (Tsai, Hsu, Chen, Ho, & Lu, 2009). ERW induces differentiation of K562 cells to megakaryocytes (Komatsu et al., 2003), and when supplemented with Pt nanoparticles, it strongly suppresses the two step transformation of NIH3T3 cells by a carcinogen (Nishikawa et al., 2005).

Anti-arteriosclerosis effects

ERW suppresses the Cu^{2+} -catalyzed oxidation of human LDL and suppresses triglyceride levels in mice fed high fat foods (Abe et al., 2010). Hydrogen-supplemented water also suppresses arteriosclerosis (see the supplemental information).

Anti-neurodegenerative effects

ERW suppresses neural cell death by oxidative stress (Kashiwagi et al., 2005). Hydrogen-supplemented water also exhibits various anti-neurodegenerative disease effects (see the supplemental information).

Application of ERW to electrolyzed water hemodialysis

Recently, the application of ERW to hemodialysis has been intensively investigated to establish a new dialysis method using ERW (Huang, Yang, Lee, & Chien, 2003; Huang *et al.*, 2006, 2010; Nakayama *et al.*, 2007, 2009, 2010; Zhu *et al.*, 2011).

Suppressive effect of the side effects of anti-cancer drugs

Hydrogen-supplemented water suppresses the side effects of anti-cancer drugs (see the [supplemental information](#)).

Aquaporin penetration of water

Kitagawa, Liu, and Ding (2011) recently reported that extractable organic solvents and freeze-labile special components in Hita Tenryosui water promote aquaporin activity in penetration of water into cells. Such components moving via aquaporin are suggested to activate cellular immune responses, which allow prevention and/or treatment of some chronic diseases.

Other effects

Naito *et al.* (2002) reported that chronic administration with electrolyzed alkaline water inhibits aspirin-induced gastric mucosal injury in rats. Hydrogen-enriched electrolyzed water has been demonstrated to be safe in mutagenicity, genotoxicity and subchronic oral toxicity (Saitoh, Harata, Mizuhashi, Nakajima, & Miwa, 2010). ERW exhibits hepatoprotective effects against CCl₄-induced liver damage in mice (Tsai *et al.*, 2009). Ionized alkaline water improves the symptoms of metabolic acidosis in experimental animals (Abo-Enein, Gheith, Barakat, Nour, & Sharaf, 2009). ERW also exhibits an anti-hangover effect (Park *et al.*, 2009). Silica hydride found in Funza water

in Pakistan suppressed carbon tetrachloride-induced hepatotoxicity in mice (Tsu *et al.*, 2010).

Recently, many papers have been published on the suppressive effects of hydrogen molecules contained in ERW on oxidative stress-related diseases (see the [supplementary information](#)). The major functions of reduced water are summarized in Fig. 4.

Conclusions and perspective

Accumulating evidence has shown that reduced waters are health beneficial and they suppress oxidative stress-related diseases such as diabetes, cancer, arteriosclerosis, neurodegenerative diseases, and the side effects of hemodialysis. The mechanisms of action of reduced water for scavenging ROS are considered to be complicated. ERW contains hydrogen molecules and mineral nanoparticles. Hydrogen molecules and active hydrogen may be new redox regulation factors that can induce the gene expression of antioxidative enzymes. Hydrogen molecules may be converted to active hydrogen by catalyst action of metal nanoparticles to exhibit more potent reducibility. Mineral nanoparticles themselves are new types of multi-functional antioxidants. Mineral hydride nanoparticles, which are H-donors as well as organic antioxidants like ascorbic acid, are also candidates of active agents in reduced waters. NRW may have one or some of the active agents described above. Further investigation on activation methods of water by electricity, magnetic fields or light are likely to contribute to the development of energy-rich waters, which will be beneficial for human health. Reduced water may suppress harmful effects of environmental pollution on the embryo in pregnant women by purifying amniotic fluid and blood. Reduced water might also contribute to the food industry by improving the taste, texture and preservation of foods. In industries, the usage of ERW is

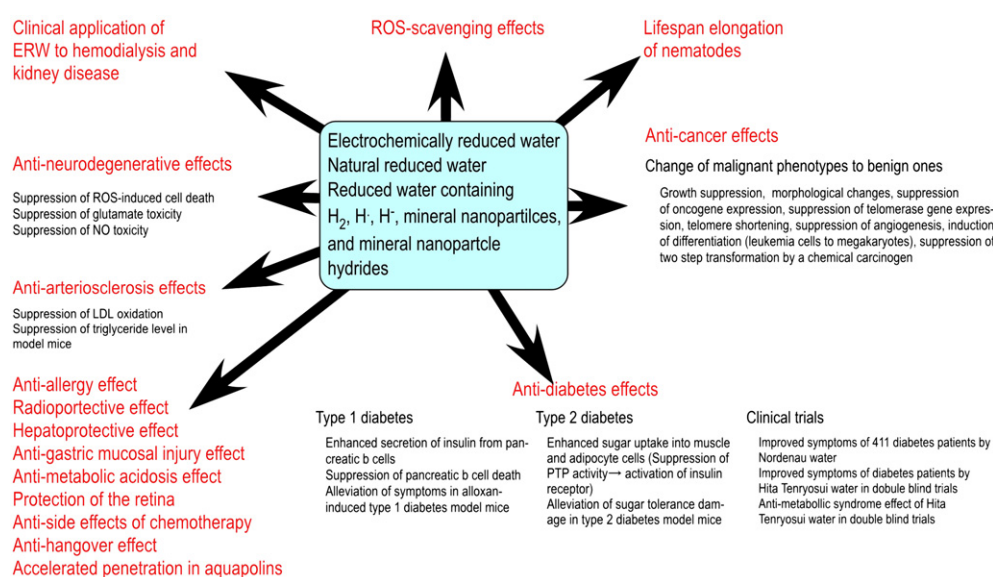


Fig. 4. Variety of functions of reduced water.

expected as washing water to prevent the rust of semiconductors. In the field of environmental remediation, reduced water will prevent the rotting of river and lake water, because the proliferation of bacteria or organisms causing the rotting will be suppressed in a reduced circumstance. Further research on water itself may ultimately reveal the secret of the origin of life.

Acknowledgments

We are grateful to Mr. Shinkatsu Morisawa, Nihon Trim Co. Ltd. and Mr. Yoshitoki Ishii, Hita Tenryosui Co. Ltd. for their technical and financial support for our reduced water research. Our research on anti-diabetic effects of reduced water by ERW was partly supported by Grants-in-aid for Scientific Research (KAKENHI) of Japan (No. 11876073). The authors are thankful to Dr. Munenori Kawamura, Kyowa Medical Clinic, and Dr. Zbigniew Gadek, Nordenau, Germany, for their clinical collaboration. The authors also express their sincere thanks to all staff, research fellows and graduate students who performed the research on reduced water in the laboratory of Cellular Regulation Technology, Faculty of Agriculture, Kyushu University.

Supplementary material

Supplementary data related to this article can be found online at [doi:10.1016/j.tifs.2011.10.009](https://doi.org/10.1016/j.tifs.2011.10.009).

References

- Abe, M., Sato, S., Toh, K., Hamasaki, T., Nakamichi, N., Teruya, K., et al. (2010). Suppressive effect of ERW on lipid peroxidation and plasma triglyceride level. In M. Kamihira, et al. (Eds.), *Animal cell technology: Basic & applied aspects, Vol. 16* (pp. 315–321). Dordrecht: Springer.
- Abo-Enein, H., Gheith, O. A., Barakat, N., Nour, E., & Sharaf, A.-E. (2009). Ionized alkaline water: new strategy for management of metabolic acidosis in experimental animals. *Therapeutic Apheresis and Dialysis, 13*, 220–224.
- Bari, M. L., Sabina, Y., Isobe, S., Uemura, T., & Isshiki, K. (2003). Effectiveness of electrolyzed acidic water in killing *Escherichia coli* O157:H7, *Salmonella enteritidis*, and *Listeria monocytogenes* on the surface of tomatoes. *Journal of Food Protection, 66*, 542–548.
- Brewer, G. J. (2009). Epigenetic oxidative redox shift (EORS) theory of aging unifies the free radical and insulin signaling theories. *Experimental Gerontology, 45*, 173–179.
- Gadek, Z., & Shirahata, S. (2002). Changes in the relevant test parameters of 101 diabetes patients under the influence of the so-called “Nordenau-phenomenon”. In S. Shirahata, et al. (Eds.), *Animal cell technology: Basic & applied aspects, Vol. 12* (pp. 427–431). Dordrecht: Kluwer Academic Publishers.
- Gadek, Z., Hamasaki, T., & Shirahata, S. (2009). “Nordenau phenomenon” – application of natural reduced water to therapy. Follow-up study upon 411 diabetes patients. In K. Ikura, et al. (Eds.), *Animal cell technology: Basic & applied aspects, Vol. 15* (pp. 265–271). Dordrecht: Springer.
- Gadek, Z., Li, Y., & Shirahata, S. (2006). Influence of natural reduced water on relevant test parameters and reactive oxygen species concentration in blood of 320 diabetes patients in the prospective observation procedure. In S. Iijima, & K.-I. Nishijima (Eds.), *Animal cell technology: Basic & applied aspects, Vol. 14* (pp. 377–385). Dordrecht: Springer.
- Hamasaki, T., Kashiwagi, T., Aramaki, S., Imada, T., Komatsu, T., Li, Y., et al. (2005). Suppression of cell growth by platinum nanocolloids as scavengers against reactive oxygen species. In F. Godia, & M. Fussenegger (Eds.), *Animal cell technology meets genomics* (pp. 249–251). Dordrecht: Springer.
- Hamasaki, T., Kashiwagi, T., Imada, T., Nakamichi, N., Aramaki, S., Toh, K., et al. (2008). Kinetic analysis of superoxide anion radical-scavenging and hydroxyl radical-scavenging activities of platinum nanoparticles. *Langmuir, 24*, 7354–7364.
- Hayakawa, T. (1999). Functions and application of alkali-ion suit water. *Food Style, 21*(3), 49–55.
- Hayashi, H., & Kawamura, M. (2002). Clinical application of electrolyzed-reduced water. In S. Shirahata, et al. (Eds.), *Animal cell technology: Basic & applied aspects, Vol. 12* (pp. 31–36). Dordrecht: Kluwer Academic Publishers.
- Higashikawa, F., Kuriya, T., Noda, M., & Sugiyama, M. (2009). Verification of improving action of mineral water on lipid metabolism in clinical trials. In *Abstract book of the 7th meeting of the Japanese Society of Preventive Medicine* (pp. 20).
- Hirokawa, N., Tanaka, Y., Okada, Y., & Takeda, S. (2006). Nodal flow and the generation of left-right asymmetry. *Cell, 125*, 33–45.
- Hove, J. R., Koster, R. W., Forouhar, A. S., Acevedo-Bolton, G., Fraser, S. E., & Gharib, M. (2003). Intracardiac fluid forces are an essential epigenetic factor for embryonic cardiogenesis. *Nature, 421*, 172–177.
- Huang, K.-C., Hsu, S.-P., Yang, C.-C., Ou-Yang, P., Lee, K.-T., Morisawa, S., et al. (2010). Electrolyzed-reduced water improves T-cell damage in end-stage renal disease patients with chronic hemodialysis. *Nephrology, Dialysis, Transplantation, 25*, 2730–2737.
- Huang, K.-C., Yang, C.-C., Hsu, S.-P., Lee, K.-T., Liu, H.-W., Morisawa, S., et al. (2006). Electrolyzed-reduced water reduced hemodialysis-induced erythrocyte impairment in end-stage renal disease patients. *Kidney International, 70*, 391–398.
- Huang, K.-C., Yang, C.-C., Lee, K.-T., & Chien, C.-T. (2003). Reduced hemodialysis-induced oxidative stress in end-stage renal disease patients by electrolyzed reduced water. *Kidney International, 64*, 704–714.
- Iwaki, M., Iwane, A. H., Shimokawa, T., Cooke, R., & Yanagida, T. (2009). Brownian search-and-catch mechanism for myosin-VI steps. *Nature Chemical Biology, 5*, 403–405.
- Jin, D., Ryu, S.-H., Kim, H.-W., Yang, E.-J., Lim, S.-J., Ryang, Y.-S., et al. (2006). Anti-diabetic effect of alkaline-reduced water on OLETF rats. *Bioscience, Biotechnology, and Biochemistry, 70*, 31–37.
- Kajita, M., Hikosaka, K., Iitsuka, M., Kanayama, A., Toshima, N., & Miyamoto, Y. (2007). Platinum nanoparticle is a useful scavenger of superoxide anion and hydrogen peroxide. *Free Radical Research, 41*, 615–626.
- Kashiwagi, T., Hamasaki, T., Kabayama, S., Takaki, M., Teruya, K., Katakura, Y., et al. (2005). Suppression of oxidative stress-induced apoptosis of neuronal cells by electrolyzed reduced water. In F. Godia, & M. Fussenegger (Eds.), *Animal cell technology meets genomics* (pp. 257–259). Dordrecht: Springer.
- Kim, M.-J., & Kim, H.-K. (2006). Anti-diabetic effects of electrolyzed reduced water in streptozotocin-induced and genetic diabetic mice. *Life Sciences, 79*, 2288–2292.
- Kim, M.-J., Jung, K.-H., Uhm, Y.-K., Leem, K.-H., & Kim, H.-K. (2007). Preservative effect of electrolyzed reduced water on pancreatic β -cell mass in diabetic *db/db* mice. *Biological and Pharmaceutical Bulletin, 30*, 234–236.
- Kim, J., Shirasawa, T., & Miyamoto, Y. (2010). The effect of TAT conjugated platinum nanoparticles on lifespan in a nematode *Caenorhabditis elegans* model. *Biomaterials, 31*, 5849–5854.

- Kim, J., Takahashi, M., Shimizu, T., Shirasawa, T., Kajita, M., Kanayama, A., et al. (2008). Effects of a potent antioxidant, platinum nanoparticle, on the lifespan of *Caenorhabditis elegans*. *Mechanism of Ageing and Development*, *129*, 322–331.
- Kitagawa, Y., Liu, C., & Ding, X. (2011). The influence of natural mineral water on aquaporin water permeability and human natural killer cell activity. *Biochemical and Biophysical Research Communications*, *409*, 40–45.
- Komatsu, T., Kabayama, S., Hayashida, A., Nogami, H., Teruya, K., Katakura, Y., et al. (2001). Suppressive effect of electrolyzed reduced water on the growth of cancer cells and microorganisms. In E. Lindner-Olsson, N. Chatzissavidou, & L. Elke (Eds.), *Animal cell technology: From target to market* (pp. 220–223). Dordrecht: Kluwer Academic Publishers.
- Komatsu, T., Katakura, Y., Teruya, K., Otsubo, K., Morisawa, S., & Shirahata, S. (2003). Electrolyzed reduced water induces differentiation in K-562 human leukemia cells. In K. Yagasaki (Ed.), *Animal cell technology: Basic & applied aspects* (pp. 387–391). Dordrecht: Kluwer Academic Publishers.
- Li, Y.-P., Hamasaki, T., Nakamichi, N., Kashiwagi, T., Komatsu, T., Ye, J., et al. (2010). Suppressive effects of electrolyzed reduced water on alloxan-induced apoptosis and type 1 diabetes mellitus. *Cytotechnology*, doi:10.1007/s10616-010-9317-6.
- Li, Y.-P., Hamasaki, T., Teruya, K., Nakamichi, N., Gadek, Z., Kashiwagi, T., et al. (2011). Suppressive effects of natural reduced waters on alloxan-induced apoptosis and type 1 diabetes mellitus. *Cytotechnology*, in press.
- Li, Y.-P., Nishimura, T., Teruya, K., Maki, T., Komatsu, T., Hamasaki, T., et al. (2002). Protective mechanism of reduced water against alloxan-induced pancreatic β -cell damage: scavenging effect against reactive oxygen species. *Cytotechnology*, *40*, 139–149.
- Li, Y.-P., Teruya, K., Katakura, Y., Kabayama, S., Otsubo, K., Morisawa, S., et al. (2005). Effect of reduced water on the apoptotic cell death triggered by oxidative stress in pancreatic β HIT-T15 cell. In F. Godia, & M. Fussenegger (Eds.), *Animal cell technology meets genomics* (pp. 121–124). Dordrecht: Springer.
- Matsubayashi, N., Hisamoto, T., Muraio, N., & Hara, T. (2008). About effect of so called reduced water on diabetes patients. In The abstract book of the 46th Kyushu Regional Meeting of Japan Diabetes Society (pp. 82).
- Naito, Y., Takagi, T., Uchiyama, K., Tomatsuri, N., Matsuyama, K., Fujii, T., et al. (2002). Chronic administration with electrolyzed alkaline water inhibits aspirin-induced gastric mucosal injury in rats through the inhibition of tumor necrosis factor- α expression. *Journal of Clinical Biochemistry and Nutrition*, *32*, 69–81.
- Nakayama, M., Kabayama, S., Nakano, H., Zhu, W.-J., Terewaki, H., Nakayama, K., et al. (2009). Biological effects of electrolyzed water in hemodialysis. *Clinical Practice*, *112*, c9–c15.
- Nakayama, M., Kabayama, S., Terawaki, H., Nakayama, K., Kato, K., Sato, T., et al. (2007). Less-oxidative hemodialysis solution rendered by cathode-side application of electrolyzed water. *Hemodialysis International*. International Symposium on Home Hemodialysis. *11*, 322–327.
- Nakayama, M., Nakano, H., Hamada, H., Itami, N., Nakazawa, R., & Ito, S. (2010). A novel bioactive haemodialysis system using dissolved dihydrogen (H_2) produced by water electrolysis: a clinical trial. *Nephrology, Dialysis, Transplantation*, *25*, 3026–3033.
- Nishikawa, R., Teruya, K., Katakura, Y., Osada, K., Hamasaki, T., Kashiwagi, T., et al. (2005). Electrolyzed reduced water supplemented with platinum nanoparticles suppresses promotion of two-stage cell transformation. *Cytotechnology*, *47*, 97–105.
- Obolenskaya, M. Y., Teplyuk, N. M., Divi, R. L., Poirier, M. C., Filimonova, N. B., Zadrozna, M., et al. (2010). Human placental glutathione S-transferase activity and polycyclic aromatic hydrocarbon DNA adducts as biomarkers for environmental oxidative stress in placentas from pregnant women living in radioactivity- and chemically-polluted regions. *Toxicology Letters*, *196*, 80–86.
- Oda, M., Kusumoto, K., Teruya, K., Hara, T., Maki, S., Kabayama, S., et al. (1999). Electrolyzed and natural reduced water exhibit insulin-like activity on glucose uptake into muscle cells and adipocytes. In A. Bernard, B. Griffiths, W. Noe, & F. Wurm (Eds.), *Animal cell technology: Products from cells, cells as products* (pp. 425–427). Dordrecht: Kluwer Academic Publishers.
- Osada, K., Li, Y.-P., Hamasaki, T., Abe, M., Nakamichi, N., Teruya, K., et al. (2010). Anti-diabetes effects of Hita Tenryosui water, a natural reduced water. In K. Ikura, et al. (Eds.), *Animal cell technology: Basic & applied aspects, Vol. 15* (pp. 307–313). Dordrecht: Springer.
- Park, S. K., Qi, X. F., Song, S. B., Kim, D. H., Teng, Y. C., Yoon, Y. S., et al. (2009). Electrolyzed-reduced water inhibits acute ethanol-induced hangovers in Sprague-Dawley rats. *Biomedical Research*, *30*, 263–269.
- Saitoh, Y., Harata, Y., Mizuhashi, F., Nakajima, M., & Miwa, N. (2010). Biological safety of neutral-pH hydrogen-enriched electrolyzed water upon mutagenicity, genotoxicity and subchronic oral toxicity. *Toxicology and Industrial Health*, *26*, 203–216.
- Shirahata, S. (2002). Reduced water for prevention of diseases. In S. Shirahata, et al. (Eds.), *Animal cell technology: Basic & applied aspects, Vol. 12* (pp. 25–30). Dordrecht: Kluwer Academic Publishers.
- Shirahata, S. (2004). Reduced water. In *Characteristics and application technology – Application to the fields of agriculture, foods, and medical therapy* (pp. 33–45). Tokyo: N.T.S.
- Shirahata, S., Kabayama, S., Nakano, M., Miura, T., Kusumoto, K., Gotoh, M., et al. (1997). Electrolyzed-reduced water scavenges active oxygen species and protects DNA from oxidative damage. *Biochemical and Biophysical Research Communications*, *234*, 269–274.
- Shirahata, S., Li, Y., Hamasaki, T., Gadek, Z., Teruya, K., Kabayama, S., et al. (2007). Redox regulation by reduced water as active hydrogen donors and intracellular ROS scavengers for prevention of type 2 diabetes. In E. Smith (Ed.), *Cell technology for cell products* (pp. 99–101). Dordrecht: Springer.
- Shirahata, S., Murakami, E., Kusumoto, K.-I., Yamashita, M., Oda, M., Teruya, K., et al. (1999). Telomere shortening in cancer cells by electrolyzed-reduced water. In K. Ikura (Ed.), *Animal cell technology: Challenges for the 21st century* (pp. 355–359). Dordrecht: Kluwer Academic Publishers.
- Shirahata, S., Nishimura, T., Kabayama, S., Aki, D., Teruya, K., Otsubo, K., et al. (2001). Anti-oxidative water improves diabetes. In E. Lindner-Olsson, et al. (Eds.), *Animal cell technology: From target to market* (pp. 574–577). Dordrecht: Kluwer Academic Publishers.
- Tashiro, H., Kitahara, T., Fujiyama, Y., & Banba, T. (2000). Clinical evaluation of alkali-ionized water for chronic diarrhea – placebo-controlled double-blind study. *Digestion & Absorption*, *23*, 52–56.
- Tsai, C.-F., Hsu, Y.-W., Chen, W.-K., Chang, W.-H., Yen, C.-C., Ho, Y.-C., et al. (2009). Hepatoprotective effect of electrolyzed reduced water against carbon tetrachloride-induced liver damage in mice. *Food and Chemical Toxicology*, *47*, 2031–2036.
- Tsai, C.-F., Hsu, Y.-W., Chen, W.-K., Ho, Y.-C., & Lu, F.-J. (2009). Enhanced induction of mitochondrial damage and apoptosis in human leukemia HL-60 cells due to electrolyzed-reduced water and glutathione. *Bioscience, Biotechnology, and Biochemistry*, *73*, 280–287.
- Tsu, Y.-W., Tsai, C.-F., Chuang, W.-C., Chen, W.-K., Ho, Y.-C., & Lu, F. J. (2010). Protective effects of silica hydride against carbon tetrachloride-induced hepatotoxicity in mice. *Food and Chemical Toxicology*, *48*, 1644–1653.

- Yan, H., Tian, H., Kinjo, T., Hamasaki, T., Tomimatsu, K., Nakamichi, N., et al. (2010). Extension of the lifespan of *Caenorhabditis elegans* by the use of electrolyzed reduced water. *Bioscience, Biotechnology, and Biochemistry*, 74, 2011–2015.
- Yan, H., Kinjo, T., Tian, H., Hamasaki, T., Teruya, K., Kabayama, S., et al. (2011). Mechanism of the lifespan extension of *Caenorhabditis elegans* by electrolyzed reduced water—participation of Pt nanoparticles. *Bioscience, Biotechnology, and Biochemistry*, 75, 1295–1299.

- Ye, J., Li, Y., Hamasaki, T., Nakamichi, N., Komatsu, T., Kashiwagi, T., et al. (2008). Inhibitory effect of electrolyzed reduced water on tumor angiogenesis. *Biological and Pharmaceutical Bulletin*, 31, 19–26.
- Zhu, W.-J., Nakayama, M., Mori, T., Nakayama, K., Katoh, J., Murata, Y., et al. (2011). Intake of water with high levels of dissolved hydrogen (H₂) suppresses ischemia-induced cardio-renal injury in Dahl salt-sensitive rats. *Nephrology, Dialysis, Transplantation*, 26, 2112–2118.



The evolution of research

With a long history of researchers relying on its peer-reviewed full text content, SciVerse ScienceDirect stands the test of time. ScienceDirect continuously enriches its offerings with efficiency increasing tools, correlating information and integrated multimedia to accelerate the research process.

info.sciverse.com/sciencedirect

