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Research progress of deuterium-depleted water in biomedicine

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AbstractDepleted deuterium water has an impact on various biological effects of living organisms. Excessive deuterium concentration can cause various damages to the body. At the same time, deuterium is also one of the important factors that induce cancer. Natural deuterium-depleted water mainly exists in alpine glacier water and the North and South Poles. In addition, the deuterium concentration in natural water can be reduced through physical and chemical methods to obtain deuterium-depleted water (also known as ultra-light water). The life process of organisms is very sensitive to changes in deuterium concentration. The reduction of deuterium concentration can stimulate the growth of living organisms. It is effective in resisting the aging of biological organisms, reducing diabetes and cardiovascular diseases, resisting cancer tumors, and protecting tissues and organs and radiation damage. In summary, this article briefly describes the role and influence of deuterium-depleted water in the above aspects. Keywords Depleted deuterium water Aging Tumor Radiation ÿesearch Progress of Deuterium Depleted Water in Biomedical Field

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Abstract Deuterium depleted water has an impact on biological effects of living organismsÿ The high concentra-

tion of Deuterium can cause various damages of the organismsÿand deuterium is also one of the important predisposing factors of cancerÿ Natural deuterium depleted water mainly exists in the alpine glacier water and the north and South polesÿ In additionÿ deuterium depleted water (was also called ultra light water) can be obtained through reducing the deuterium concentrations of natural water by physical and chemical methodsÿ Changes of deuterium concentration is highly sensitive to the progress of living organismsÿthe reduce of deuterium concentration can stimulate growth of liv-ing organismsÿand also have an effect on resisting biological caducityÿreducing diabetes and cardiovascularÿresisting tumourÿprotecting organ and radiation damageÿ In conclusionÿthis paper makes a brief exposition on the effects of deuterium depleted water in above several aspectsÿ

Keywords Deuterium depleted water caducity tumour radiation

The deuterium content in natural water is about 0.015%. The water formed by deuterium (D) replacing protium (H) is heavy water. Deuterium-depleted water (DDW or deuterium-depleted water) is water with a deuterium content of less than 0.015% [1-3]. At present, the main method for preparing deuterium-depleted water is to use tap water as raw material and separate deuterium by physical or chemical methods. The distribution of deuterium-depleted water in human tissues and organs is different. Zhimak In 2013 and 2014, [12-13] et al. observed laboratory animals for 42 days and tested various biochemical indicators (phosphatase, creatinine, bilirubin) to analyze the content of deuterium water in different tissues and organs. The deuterium water content in the heart reached 8.5%, in the liver tissue it reached 9.3%, and in the metabolically active kidney tissue it reached 10.9%. 15. 8%. This indicates that the content of deuterium-depleted water in different organs may be related to the function of the organs. Early studies have found that reducing the deuterium content in water can effectively enhance the body's antioxidant capacity [4, 5]. And with the deepening of related research, it has also been found that deuterium-depleted water has the effects of enhancing biological metabolism, promoting growth, delaying aging, and prolonging life [6-8] . In addition, deuterium-depleted water can also reduce insulin resistance, slow down blood sugar levels in diabetic patients [9-11], and enhance vascular reactivity [14]. It is worth mentioning that deuterium-depleted water has a significant effect on the auxiliary treatment of certain cancer diseases [15-24] and can improve the survival rate of irradiated organisms [25-30].

1. Effects of Deuterium-Depleted Water on Aging

Deuterium-depleted water can slow down the expression of various oxidases in plantsÿ29ÿ and enhance resistance by increasing the content of catechinsÿ7ÿ in plants . In 2014, Tanase C et al. [28]

found that polyphenols from the bark extract of safflower (SBPE) and deuterated water play an extremely important role in the metabolic process of corn plants. When corn plants were treated with deuterated water and the expression levels of different enzymes in their leaves and roots were detected, it was found that the content of catalase and superoxide dismutase was significantly reduced, and the activity of catalase in the roots was reduced. However, when corn plants were treated with polyphenols from the bark extract of safflower, the expression levels of catalase and superoxide dismutase were significantly increased, and the activity of catalase was also increased accordingly. In the same year, Tanase C [4] used deuterated water to treat sunflower plants and found that polyphenols from the bark extract of safflower (SBPE) combined with deuterated water can stimulate plants (sunflowers) to produce photosynthetic pigments such as chlorophyll a, chlorophyll b, and carotene, and increase the content of catechins in sunflower leaves, enhance plant resistance, and promote leaf growth and development. The combination of deuterium-depleted water and polyphenol extracts can be used as a natural bioregulator to increase the yield of crops such as sunflowers. It also has great development prospects in ecological agricultural production and stabilizing crop yields. The length of a person's life depends on a variety of internal genetic or external environmental factors. In 2014, Bulgaria et al. [6] investigated the long-lived population in Bulgarian residential areas. Excluding various genetic and gender factors, they found that the long-term drinking water of residents - mountain water (low-deuterium water) is the most important factor leading to the extension of the life expectancy of the population in Bulgaria's long-lived residential areas. Although there is controversy, after long-term research and observation, it is found that low-deuterium water affects cell morphology and its metabolic mechanism. A 20%-30% reduction in the deuterium content in normal water is beneficial to health. The average hydrogen bond values in water of various samples and human serum were detected under infrared spectra at -0,1387 eV and wavelength 8,95 nm. The results showed that the local values under the infrared spectrum of patients who were critically ill and had tumors were larger than those of the control group. This shows that drinking water has a positive effect on cell morphology and its metabolic mechanism. The use of a certain amount of deuterium-depleted water is necessary in the life process.

2 Effects of Deuterium-depleted Water on Diabetes

In 2008, Aneta et al. [8] reported that rats that had undergone chemotherapy were treated with deuterium-depleted water. The results showed that the total plasma glycoprotein and glycosylation levels of all rats in the deuterium-depleted water treatment group were significantly lower than those in the control group. In 2012, Zhou Zhenyu et al. [9] from the School of Agriculture and Biology of Shanghai Jiao Tong University established a diabetic Wistar rat model induced by a single intraperitoneal injection of streptozotocin (STZ) and found that drinking deuterium-depleted liquor could significantly reduce fasting blood glucose levels, effectively increase plasma insulin levels, and reduce pancreatic cell damage caused by excessive drinking. It also effectively improved the morphology, volume and distribution of pancreatic cells. In the same year, Molnár et al. [13] found that deuterium-depleted water could effectively promote the transfer of glucose transporter 4 (GLUT4) from the intracellular to the cell membrane in diabetic rats induced by streptozotocin (STZ), and greatly enhanced glucose uptake. The researchers also conducted an investigation on diabetic patients, recruiting 30 diabetic volunteers aged between 18 and 60 to drink low-deuterium water. They drank different amounts of water every day. The results showed that 11 diabetic volunteers (36.6% of the total number of people in the experiment) who drank 1.5 L of low-deuterium water every day had reduced insulin resistance, and the volunteers' systemic glucose intake increased from 0.2 mg per minute to 4.2 mg per kilogram per minute. The results showed that low-deuterium water can not only effectively reduce fasting blood sugar levels, but also slow down insulin resistance.

3. Effects of Deuterium-depleted Water on Cardiovascular and Cerebrovascular Diseases

Since the molecular clusters of deuterium-depleted water are 50% smaller than those of natural ÿ water, their movement speed and permeability have been effectively improved, so they can pass through the water channels on the cell membrane smoothly. In 1998, Haulic et al. [12] found that heavy water (D2O) can antagonize the effects of angiotensin, thereby inducing arterial dilation. Deuterium-depleted water can effectively enhance the vasoconstriction response induced by adrenaline and angiotensin, increase vascular tension, and studies have shown that deuterium-depleted water has a regulatory

effect on vascular dilation and contraction.

Krempels [15] found that deuterium-depleted water can pass through the blood-brain barrier in a clinical study of lung cancer patients with brain metastasis. The blood-brain barrier hinders the operation of most anticancer chemotherapy drugs, resulting in the ineffectiveness of the drugs against brain metastasis tumors. When experimental mice drank heavy water (D2O), it was found that the deuterium content in brain tissue and other tissues increased to a certain extent. However, after replacing heavy water with deuterium-depleted water, it was found that the deuterium content of both integrated and unintegrated brain tissue of mice was effectively reduced. The experiment showed that deuterium-depleted water can quickly pass through the blood-brain barrier. Therefore, deuterium-depleted water as an adjuvant therapeutic agent can have important application prospects in the treatment of cerebrovascular diseases.

Cardiovascular and cerebrovascular diseases are one of the major diseases that affect human health. Most of these patients also suffer from atherosclerosis. The oxidation theory of atherosclerosis proposed by researchers such as Steinberg believes that reactive oxygen species and their related oxidation products can damage the endothelium, induce endothelial cells to release various pro-inflammatory factors, and thus trigger atherosclerotic inflammatory reactions. Antioxidant stress may inhibit the process of atherosclerosis. In the section on the anti-aging effect of deuterium-depleted water, it is mentioned that when corn plants were treated with deuterium-depleted water and the expression levels of different enzymes in their leaves and roots were detected, it was found that the levels of catalase and superoxide dismutase were significantly reduced, and the activity of catalase in the roots was also reduced; similarly, as early as 2007 , Olariu et al. [5] observed the effects of drinking deuterium-depleted water on the antioxidant enzymes of red blood cells in the body and found that the malondialdehyde (MDA) content of rats drinking deuterium-depleted water was lower than that of rats drinking natural water. In addition, the reduced glutathione (GSH) value, glutathione reductase (GSH-Red) activity and superoxide dismutase (SOD) activity of rats drinking deuterium-depleted water were higher than those of rats drinking tap water. The above results indicate that deuterium-depleted water can effectively affect the antioxidant system of animals and plants, and drinking deuterium-depleted water for a

long time can play an antioxidant role, which further suggests that cardiovascular diseases caused by atherosclerosis may be effectively improved by drinking deuterium-depleted water.

4.Anti-tumor and adjuvant therapeutic effects of deuterium-depleted water

Although the world's medical level has developed rapidly, cancer is still a disease that the public is afraid of. The formation of tumor cells is closely related to the expression of many genes. As an important member of the myc gene family, the c-myc gene can make cells proliferate indefinitely and achieve immortality. The c-myc gene can participate in cell apoptosis and is related to the generation and development of various tumors. p53 is a tumor suppressor gene. Among all malignant tumors, more than 50% will have mutations in the p53 gene. After the p53 gene mutates, the spatial conformation of the gene changes, thereby losing its regulatory effect on cell growth, apoptosis and DNA repair. Therefore, the gene changes from a tumor suppressor gene to an oncogene. In 2000, Gyÿngyi Z [14] et al. found in their study that the lack of deuterium-depleted water can lead to the regression growth of tumor cells. After inbred mice were given deuterium-depleted water to drink, 48 hours after RNA expression, the expression of myc and p53 genes in six different tissues and organs (spleen, lung, thymus, kidney, liver, and lymph nodes) was inhibited, indicating that the genes that promote tumor formation are sensitive to deuterium-depleted water. Feng-Song Cong et al. [16] studied the inhibitory effects of deuterium-depleted water on lung cancer cells in vivo and in vitro in 2010 and studied its mechanism. They treated human lung cancer cells with deuterium-depleted water at different concentrations. A549, through observation, it was found that the cytoskeleton and cell cycle of A549 changed, and the proliferation of cells was inhibited at a certain time point. Scanning electron microscopy and transmission electron microscopy also found that the morphological characteristics of cell apoptosis also changed. Feng-Song Cong [16] et al. also established a tumor model by subcutaneously injecting H490 tumor cells into BalB/c mice and found that by giving tumor-bearing mice drinking deuterium-depleted water for 60 days, the growth of tumor cells was significantly inhibited. The tumor inhibition rate of mice in the deuterium-depleted water group reached 30%. Gyÿngyi Z [18] et al. found through research in 2011 that deuterium-depleted water can inhibit the growth of lung cancer cells and the expression of proto-oncogenes. They made 129 patients

with small cell and non-small cell lung cancer drink deuterium-depleted water in clinical practice, combined with traditional radiotherapy and chemotherapy for treatment. After observation, it was found that the survival rate of patients treated with deuterium-depleted water was 2-3 times higher than that of patients receiving traditional treatment, and the survival rate of female patients was significantly higher than that of males. At the same time, deuterium-depleted water also resisted the expression of Bcl2, Kras and Myc genes induced by dihydroxymethylbutyric acid. Therefore, deuterium-depleted water can be used as a non-toxic anti-cancer dietary supplement to prolong the survival rate of lung

cancer patients, especially for female patients with overexpression of tumor-related genes. In 2013, Wang H, Zhu Bÿ20ÿ et al. cultured nasopharyngeal carcinoma cells (NPC) and normal mouse preosteoblast cells MC3T3-E1 in 1640 medium containing deuterium-depleted water (50-150 ppm), and used MTT, plate cloning and Transwell experiments to detect the proliferation, migration and invasion ability of NPC and MC3T3-E1. It was found that deuterium-depleted water can inhibit the proliferation, migration and invasion of NPC cells. However, the growth ability of normal mouse preosteoblast cells MC3T3-E1 cells was effectively promoted when cultured in deuterium-depleted water medium. Through the detection of NPC cell cycle, it was found that low-deuterium water blocked the transition of cells from G1 phase to S phase, significantly reduced S phase cells, and significantly accumulated G1 phase cells. Through western-blot experiments, it was also found that the expression of reduced coenzyme II (NADPH) in NPC cells treated with low-deuterium water increased significantly, while the expression of proliferating cell nuclear antigen (PCNA) and matrix metalloproteinase 9 (MMP9) decreased. The results show that low-deuterium water can be used as a new non-toxic adjuvant product for the treatment of nasopharyngeal carcinoma, and has broad application prospects in the future. Globally, cervical cancer ranks third among common malignant tumors in women, and is also one of the four tumors that are prone to cause death in female cancer patients, accounting for 10% and 8% of the total number of newly diagnosed cancer cases and cancer deaths, respectively. At present, the main treatments for cervical cancer are surgery, radiotherapy and chemotherapy. In 2014, Zhang Li et al. [22] from the Sino-American Cancer Research Institute of Guangdong Medical

College treated Hela cells with culture media of different deuterium-depleted water concentrations and used the MTT method and streaking to detect the presence of The scratch test showed that the proliferation and invasion and metastasis of Hela cells were significantly inhibited as the deuterium concentration in the culture medium decreased. In the low-deuterium water culture medium with a deuterium concentration of 50 × 10-6 , the Hela cell proliferation inhibition rate reached 39.54% ($P < 0.01$) after 72 h. In addition, the scratch test results showed that low-deuterium water also had an effective inhibitory effect on the invasion of cervical cancer cells, and the difference was most obvious when the deuterium concentration was 50 × 10-6 ($P < 0.01$). The expression of related proteins was detected by immunoblotting and immunohistochemistry, and it was observed that low-deuterium water could up-regulate and down-regulate the expression level of p21 protein and Na + /K + -ATPase in Hela cells, respectively. The p21waf gene is an important downstream gene of the p53 gene. The p21 protein, as the expression product of the p21waf gene, is currently the most extensive cell cycle inhibitory protein with kinase inhibitory activity. The p21 gene can form the G1 phase checkpoint of the cell cycle with the p53 gene. Once the DNA is damaged and not repaired, it cannot pass the G1 phase checkpoint, which can effectively reduce the replication and accumulation of damaged DNA. A series of studies have shown that deuterium-depleted water plays an important role in inhibiting tumors. It is believed that in the near future, deuterium-depleted water is expected to become a new anti-tumor strategy.

5. Anti-radiation effect of deuterium-depleted water

Once the human body is exposed to a certain dose of radiation in a short period of time, it will cause radiation damage to the relevant organs, resulting in anemia, reduced immune function and endocrine disorders. As early as 1983 to 1987, Laissue JA [25, 26] found through hematological research that deuterium-depleted water can protect mice irradiated with whole-body gamma rays, significantly increasing their survival rate after irradiation. The experimental results show that the anti-radiation damage effect of deuterium-depleted water is directly related to its ability to improve the defense function of the relevant immune system, especially it can effectively enhance the nonspecific immune defense function and promote the proliferation of peripheral blood cells. Gabriel [27] and other researchers also conducted

experiments on mice irradiated with a half-lethal dose of X-rays and found that drinking deuterium-depleted water can effectively enhance the anti-radiation effect of Aralia dasyphylla extract. In 2010, Corneanu GC, Corneanu M [30] and others used deuterium-depleted water and 0. 0.1% deuterium-depleted water containing polyphenols was injected intraperitoneally into mice and irradiated with X-rays (5.28Gy). After one day of exposure, stress factors were generated. Whether deuterium-depleted water alone or in combination with polyphenols, it has a radiation protection effect, especially the combination of deuterium-depleted water and phenols. Although the mechanism is still unclear, this unique anti-radiation damage property of deuterium-depleted water will have great potential for clinical application.

6 Outlook

In the human body, water accounts for 65% to 70% of the total mass, so water is called the source of life. DNA is an important factor in the stability of the molecule, and it is involved in almost all life reactions of the body. Deuterium, as an isotope of hydrogen, affects the inheritance and replication of DNA in this way. At present, the global research on the application of deuterium-depleted water is still in its infancy, and researchers are still very vague about the mechanism of action of deuterium-depleted water on various diseases, especially the mechanism of deuterium-depleted water's resistance to tumors, which is worthy of in-depth study. With the rapid development of modern molecular biology technology, deuterium-depleted water will be used more widely than ever in the field of biomedicine.

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