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Overview

Research progress on biological effects of deuterium-depleted water

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[Abstract] Deuterium-depleted water (DDW) is water with a deuterium volume fraction of less than 0.015%, also known as deuterium-depleted water or ultra-light water. Deuterium-depleted water has a series of biological effects, such as anti-tumor, antioxidant, hypoglycemic, anti-depressant, etc., which can affect the biochemical metabolic process of organisms. Moreover, deuterium-depleted water is easy to use and has no adverse reactions. It can be used as an adjuvant in clinical treatment. This article reviews the research progress on the biological effects of deuterium-depleted water.

[Keywords] Deuterium-depleted water; biological effects; adjuvant therapeutic agent

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Research progress of biological effects of deuterium-depleted water

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[Abstract] When the deuterium concentration of water is lower than 0.015%, the water is known as deuterium-depleted water (DDW), deuterium-poor water or super light water. Deuterium-depleted water may affect the biochemical and metabolic processes of living organisms, for it has some biological effects such as anticancer effect, antioxidant effect, hypoglycemic effect, antidepressant effect and so on. Deuterium-depleted water appears to have little toxic side effects and is convenient to administer, so it may act as an adjuvant therapeutic agent in clinical treatment of diseases. In this paper, advances in research on biological effects of deuterium-depleted water were reviewed.

[Key words] deuterium-depleted water; biological effects; adjuvant therapeutic agent

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Water molecules are composed of hydrogen atoms and oxygen atoms. Hydrogen has three isotopes: protium (1H), deuterium (2D) and tritium (3T). H and D are non-radioactive stable isotopes, while T is a radioactive element. In nature, H is the most abundant, D is the least abundant, and T is the least abundant. If the H in the water molecule H2O is replaced by D and T respectively, heavy water D2O and super-heavy water T2O are formed. Natural water is a mixture of H2O and D2O , in which the ratio of deuterium to hydrogen (D/H) is about 1:6,600, that is, the volume fraction of deuterium in water is 0.015%[1] . Usually, water with a deuterium concentration below 0.015% (150 ppm) is called deuterium-depleted water (DDW), also known as deuterium-depleted water or super-light water.

In 1931, American chemist Harold Clayton Urey first discovered the element deuterium. The difference in mass between hydrogen and deuterium leads to differences in their physical and chemical properties. The density, viscosity, melting point and boiling point of D2O are all higher than those of H2O[2] . High concentrations of deuterium can cause stagnation of cell mitosis, changes in cell metabolism and related enzyme activity, and changes in the physiological state and morphological structure of cells, which can be toxic to the nervous system and [3-4] Kushner et al. [5] It is reported that when the deuterium concentration rises to 25%, heavy water will liver of living organisms, causing neurological diseases, Anemia and other complications. On the contrary, deuterium-depleted water has a certain positive effect on living organisms. In the process of inducing cell apoptosis, deuterium-depleted water activatesDNA repair system, significantly reducing single-strand DNA breaks and improving the efficiency of the cell's defense system ÿ [6-7]

In 1993, Somlyai et al. Studies have found that deuterium-depleted water can reduce the growth rate of L929 fibroblast cell lines and inhibit the growth of mouse transplanted tumors, thus proposing that the natural abundance of deuterium can trigger and maintain normal cell proliferation. Since then, the biological effects of deuterium-depleted water have gradually attracted the attention of many researchers. The deuterium concentration of water on Earth ranges from 14 to 150 ppm. Deuterium-depleted water mainly exists in the form of glacial water with a deuterium concentration of about 130 ppm[8] . The deuterium concentration range of the researchers' study of deuterium-depleted water is 20 to 110 ppm, which Deuterium-depleted water prepared by isotope vacuum distillation [9-10] can be used. Deuterium-depleted water has a series of biological effects. has many physical effects, such as anti-depression, anti-oxidation, anti-aging, anti-radiation, hypoglycemic, cardiovascular system protection, anti-tumor, etc. It can be seen that deuterium-depleted water has potential application value in health care products, cosmetics and medicine. This article reviews the research progress of the biological effects of deuterium-depleted water in recent years.

1 Anti-tumor effect of deuterium-depleted water

The anti-tumor effect of deuterium-depleted water is a hot topic in the research of the biological effects of deuterium-depleted water. Deuterium-depleted water has an inhibitory effect on the proliferation of various tumor cells and can be used as an adjuvant therapeutic agent for cancer. In 2010, the first international academic conference on deuterium-depleted water research focused on the anti-tumor effect of deuterium-depleted water, explored its biological effects, and proposed to carry out application research of deuterium-depleted water in ÿ other fields. In recent years, in vitro cell culture experiments have shown that deuterium-depleted water alone has an effect on lung cancer cells A549, nasopharyngeal carcinoma cells (CNE-1, CNE-2, 5-8F, 6-10B, Sune-1), prostate cancer cell PC-3, breast cancer cell (MDA, MCF-7), colon cancer cell HT-29 and melanoma cell research (M14, HT-199) and others have obvious anti-tumor effects. Cong et al. found that deuterium-depleted water can inhibit the proliferation of human lung adenocarcinoma A549 cells in vitro, change the morphological structure and cell cycle of cancer cells (S phase arrest), and induce cancer cell apoptosis. Wang et al. found that deuterium-depleted water can inhibit the [13] Deuterium-depleted water has been reported to increase the proliferation of nasopharyngeal carcinoma cells. proliferation, colony formation and invasion of cancer cells, and also block the growth cycle of

cancer cells. By detecting the expression level of cell proteins, it was found that deuterium-depleted water promotes the expression of quinone oxidoreductase-1 (NADPH: quinone oxidoreductase-1, NQO1), while inhibiting the expression of proliferating cell nuclear antigen (PCNA) and matrix metalloproteinase-9 (MMP-9). NQO1 protein is closely related to the detoxification of quinone substances, bioactivation of anticancer drugs, regulation of p53 protein stability and apoptosis induced by tumor necrosis factor-ÿ (TNF-ÿ), thus playing an important role in cell transformation, apoptosis and protection; PCNA protein is related to cell growth rate; MMP-9 protein is related to promoting cancer cell metastasis. Therefore, the inhibitory effect of deuterium-depleted water on cancer cell proliferation may be related to its promotion of NQO1 protein expression and inhibition of PCNA and MMP9 protein expression.

It has an inhibitory effect on cancer cell proliferation, and the inhibitory effect on MDA-MB-231 cancer cell proliferation is the most obvious, while it has no inhibitory effect on HCT-116 cancer cell proliferation. Different studies have given different answers to whether deuterium-depleted water alone has an inhibitory effect on cancer cell proliferation. Some scholars believe that the reason for this contradiction may be the limitation of the types and numbers of cancer cells used in the experiment, the different analytical techniques for measuring cell growth, etc. [17] The anti-tumor effect of deuterium-depleted water and paclitaxel under synergistic action may be due to the commonality of the two - inducing cell apoptosis and blocking the cell cycle. Some studies have studied polymers to

[18] Paclitaxel stabilizes microtubules during cell mitosisprevent them from disassembling in the cytoskeleton, further inhibiting the formation of spindles, and ultimately leading to cell apoptosis or G phase arrest. Some studies have reported that deuterium-depleted water also has this characteristic of an anti-cancer adjuvant [12] Therefore, deuterium-depleted water is considered to be a new therapeutic agent. In addition to paclitaxel, deuterium-depleted water and other anticancer drugs such as etoposide, doxorubicin and platinum compounds also have synergistic anti-tumor effects. In early 1990, a study by the Hungarian National [15], Cancer Institute found that drinking deuterium-depleted water can completely or partially inhibit the growth of [19] The animal use survey was successfully completed. Through the nude mouse . Cong et al.transplant tumor model study, it was found that deuterium-depleted water can reduce the tumor weight of nude spontaneous malignant tumors in cats and dogs; therefore, in 1999, an application for registration of deuterium-depleted water as an anticancer agent in animals was filed. mouse transplant tumors to a certain extent and inhibit the growth of transplant tumors. Gyongyi et al. measured the [20-21] Mice were injected intraperitoneally with the carcinogen 2,2-dihydroxymethylbutyric acid (2, gene expression of 6 tissues (spleen, lung, thymus, kidney, liver and lymph node) after adding 2-dimethylolbutanoic acid (DMBA). The results showed that deuterium-depleted water can downregulate the oncogenes C-myc, Ha-ras, It can also downregulate the expression of Kras, Bcl2, and Myc , and upregulate the expression of the tumor suppressor gene p53 .

In recent years, the anti-cancer adjuvant therapy of deuterium-depleted water has also been applied to clinical treatment. Krempels et al. used 4 patients [22] The effect of deuterium-depleted water on patients with brain metastases from lung cancer was studied. who drank deuterium-depleted water (instead of ordinary drinking water) on a daily basis in addition to receiving conventional chemotherapy and

radiotherapy. The results showed that the use of deuterium-depleted water combined with conventional clinical treatment can prolong the survival of patients. In general, the average survival time of patients with brain metastases from lung cancer is 8 months, and the average survival time of patients who have undergone radiotherapy is 18 months. The average survival time of the 4 patients in this study was 26.6, 54.6, 21.9, and 33.4 months, respectively. Among them, 2 patients had complete remission of brain metastases from lung cancer, and 1 patient had partial remission.

1 patient showed no significant change. Kovács et al. conducted a phase II [23] sing deuterium-depleted water double-blind clinical trial on prostate cancer patients in combination with conventional clinical treatment. The results showed that this therapy can reduce the volume of the prostate, lower the serum prostate-specific antigen (PSA) concentration, delay the progression of cancer, and prolong the survival of patients.

Krempels et al. showed [24] Deuterium-depleted water adjuvant therapy can prolong the duration of breast cancer that the survival time of patients with high-dose deuterium-depleted water and repeated treatments was more significant. Gyongyi et al. [21] A total of 129 cases of lung cancer (including small cell lung cancer, non-small cell lung cancer, A clinical trial was conducted on patients with lung cancer (cell lung cancer, lung cancer brain metastasis, and lung cancer the survival of patients, with more significant effects on female patients.

In clinical trials, cancer patients who drank deuterium-depleted water showed no significant changes in their physical indicators and no adverse reactions. This shows that deuterium-depleted water has no Deuterium-depleted water has no significant adverse reactions to blood cell indices and can be used as an anti-cancer adjuvant therapy. The anti-tumor effect of deuterium-depleted water and conventional clinical treatment is mainly manifested in reducing tumor size, alleviating cancer symptoms, delaying disease progression and prolonging patient survival. Deuterium-depleted water can cause complete or partial regression of tumor tissue. The D/H ratio in the body changes during the cell cycle. Cells can adjust the D/H ratio. Changes in the D/H ratio will trigger certain molecular mechanisms in the cell cycle regulation process.

There are studies on the It has been shown that deuterium-depleted water can directly interfere with cell cycle regulation process and signal transduction pathways, which lead to the regression of tumor tissue. The anti-tumor effect of deuterium-depleted water may be related to factors such as induction of cell apoptosis, cell cycle arrest, expression of cell cycle-related regulatory proteins, expression of cancer metastasis-related proteins, downregulation of proto-oncogenes, and upregulation of tumor suppressor genes. Its specific molecular mechanism is still unclear and needs further study to facilitate the more systematic application of deuterium-depleted water in the field of cancer treatment.

2. Anti-oxidation, anti-aging and anti-radiation effects of low-deuterium water

People's pursuit of beauty has led to the development of anti-oxidation, anti-aging and anti-radiation research. This research field has attracted extensive attention from researchers. The effect of deuterium-depleted water on the antioxidant capacity of D-galactose-induced aging mouse model was studied for the first time through experiments. It was found that deuterium-depleted water had a significant effect on the antioxidant indicators of the serum, myocardium, brain, liver and other tissues of aging mice, such as total antioxidant

capacity (T-AOC), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), It has a significant effect on Na+ -K+ -ATPase, monoamine oxidase (MAO), and malondialdehyde (MDA), and can slow down the aging process. Deuterium-depleted water can delay the aging process of mice by increasing the activity of endogenous anti-aging substances, inhibiting lipid peroxidation reactions, and scavenging free radicals. Therefore, deuterium-depleted water has a certain positive regulatory effect on the antioxidant capacity of aging model mice. In a short period of time, deuterium-depleted water has a certain pro-oxidation effect on normal mice; but after a period of time, deuterium-depleted water has an antioxidant effect on normal mice. Deuterium-depleted water can reduce the oxidative damage caused by chromium and cadmium poisoning in mice, activate the antioxidant defense system in mice, and protect the liver and kidneys from poisoning. In addition to the mouse model, deuterium-depleted water can also reduce the toxic effects of manganese on Caenorhabditis elegans by regulating DAF-16 (a lifespan regulating factor.

Harmful Water has a certain scavenging effect on toxic elements, and it may be an effective [28-29] Therefore, low deuteriumpreventive or therapeutic agent for different pathological diseases. Zhang Yaru et al. [30] The effect of deuterium-depleted water on normal human skin fibroblasts and The effect of deuterium-depleted water on melanoma cells was studied. It was found that deuterium-depleted water significantly inhibited the activity of tyrosinase in melanoma cells and reduced the production of melanin. Moreover, the study also found that deuterium-depleted water can reduce the damage of ultraviolet radiation to fibroblast proliferation. In addition, some studies have found that deuterium-depleted water can also reduce the damage of X-rays and ÿ-rays to the liver of mice, which may be related to the [31] This shows that deuterium-depleted water has an anti-radiation damage effect. improvement of the body's immune system function. Lian Lu et al. analyzed the effect of deuterium- depleted water on the immunoregulatory effect of normal mice and found that deuterium-depleted water can significantly increase the spleen index of mice, indicating that deuterium-depleted water can enhance the nonspecific immune function of mice; deuterium-depleted water can also significantly increase the content of immunoglobulin M (IgM), indicating that deuterium-depleted water can improve the humoral immunity of mice; moreover, deuterium-depleted water will not damage and destroy the spleen and thymus, and will not change the normal tissue structure. Therefore, deuterium-depleted water can improve the immunity of normal mice to a certain extent. Since deuterium-depleted water has immunomodulatory effects and can reduce the impact of bacterial endotoxins in the body, it may also have anti-inflammatory effects. The antioxidant, anti-aging, and anti-radiation effects of deuterium-depleted water indicate that deuterium-depleted water has potential application value in the fields of health products and cosmetics. [33]

3. Deuterium-depleted water and diabetes, cardiovascular disease

Early Japanese Studies It shows that hydrogen-rich water has a positive effect on glucose and lipid metabolism.[35] It has a polarizing effect and can prevent or delay the development of type 2 diabetes. Zhou Zhenyu used streptozotocin (STZ) to induce a diabetic rat model and found that low-deuterium water can reduce fasting blood sugar levels, increase fasting plasma insulin levels, improve the number, volume, morphology and distribution of stained particles of pancreatic islet cells, and has the effect of reducing and repairing pancreatic cell damage. Molnár et al. found

that glucose transporter 4 (GLUT4) in the body was translocated from the intracellular to the cell membrane, and the glucose uptake level increased. Further studies have

[36] Experiments on diabetic rat models have found that deuterium-depleted water can promotefound that low-deuterium water can intervene in glucose metabolism in diabetic patients, improve insulin sensitivity, alleviate insulin resistance, and reduce fasting blood sugar levels. Xia Honglei's effect on the metabolism of tumor-bearing nude mice is mainly manifested as a decrease in the content of sugar substances in serum metabolites. This shows that low-deuterium water can affect the body's sugar metabolism, further confirming the blood sugar-lowering effect of low-deuterium water. The hypoglycemic [37] Metabolomics analysis revealed that deuterium-depleted water has an important effect on the metastasis of in situ lung cancer. mechanism of low-deuterium water may be related to its improvement of damaged pancreatic islet cell function and promotion of insulin secretion.

Previous research [38] It was found that deuterium-depleted water can increase vascular reactivity and promote vasoconstriction responses induced by norepinephrine and angiotensin, which indicates that deuterium-depleted water has a regulatory effect on vascular relaxation and contraction. [39] Experiments on hyperlipidemic rats found that the high-density lipoprotein content in the hyperlipidemic rats drinking low-deuterium water increased significantly, the activity of tissue-type plasminogen activator was significantly enhanced, and the activity of active plasminogen activator inhibitor-1 was significantly decreased. The results show that deuterium-depleted water can improve the blood lipid level and fibrinolytic system activity of hyperlipidemia rats, and may have the effect of protecting the cardiovascular system.

Rehakova et al. [8] Studies have found that deuterium-depleted water can not only increase the plasma insulin level in normal rats and enhance the activity of nitric oxide synthase (NOS) in the rat heart, but also reduce the overall levels of cholesterol and triglycerides in rats (possibly with a lipid-lowering effect), and significantly change the cardiovascular metabolic index parameters of normal rats. Studies have shown that insulin can activate endothelial NOS activity, indicating that insulin may have anti-atherosclerotic effects. Since deuterium-depleted water [40-41] can increase the insulin level in the body, it suggests that deuterium-depleted water may have a beneficial effect on anti-atherosclerosis. In summary, deuterium-depleted water may have the effect of preventing cardiovascular complications of diabetes.

Deuterium-depleted water not only affects sugar metabolism and cardiovascular metabolism in living organisms, but also has a positive effect on some other metabolic indicators, such as creatinine, bilirubin, alkaline phosphatase, amino acid transaminase, etc. Among them, creatinine and bilirubin are important indicators of kidney and liver function, respectively. When an organism suffers from endotoxemia, deuterium-depleted water can activate the body's non-specific defense system, stabilize metabolic indicators within the normal range, and maintain metabolic balance in the body. [42]

4 Neuromodulatory effects of deuterium-depleted water

The regulatory effects of deuterium-depleted water on the nervous system mainly include enhancing memory and Antidepressant effect.

Mladin et al. [43] Through the mouse maze experiment, it was found that drinking deuterium-depleted water had no significant effect on the spatial working memory ability (short-term memory ability) and

autonomous activity of mice, but it could enhance the spatial reference memory ability of mice, that is, deuterium-depleted water has a promoting effect on the long-term memory of mice. This promoting effect may be related to acid-sensing ion channels (ASICs). ASICs are important channels for nerve cell membrane transport, related to learning and memory functions, and most of them are present in the hippocampus.

[44] . As the deuterium content in the brain tissue of mice drinking deuterium-depleted water decreases, ASIC is activated, the synaptic efficiency of hippocampal neurons is improved, and long-term memory is strengthened. Therefore, deuterium-depleted water has a promoting effect potential application value.

Strekalova etc. [45] Through epidemiological analysis and a series of mouse experiments, it is proposed that deuterium-depleted water has an anti-depressant effect. First, an epidemiological analysis method was used to analyze the relationship between the incidence of depression among residents in various states in the United States and the deuterium content of drinking water. The results showed that the incidence rate of the surveyed population was 5.3% to 13.7%, and the deuterium content of drinking water was 135 to 155 ppm; for every 10 ppm increase in deuterium content, the incidence rate increased by 1.8%, indicating that deuterium-depleted water may have a preventive effect on depression. Then, stress was applied to the mice to make them depressed, and anhedonia induction tests, Porsolt forced swimming tests, body mass tests and Transcriptomics analysis, etc.; it was found that deuterium-depleted water can reduce the expression level of serotonin transporter (SERT) in mice, increase the number of BrdU-positive neurons in mice, and alleviate the depressive symptoms of mice. Finally, the effect of deuterium-depleted water on the EEG parameters of normal mice during sleep was analyzed experimentally; it was found that deuterium-depleted water can improve the wakefulness level of mice and shorten the sleep quality, which is also helpful to improve the insomnia of patients with depression.

Deuterium-depleted water can alleviate depressive symptoms and improve sleep quality; however, The mechanism of the antidepressant properties of deuterium-depleted water has not been elaborated in detail. The mechanism may be: ÿ After deuterium-depleted water replaces ordinary water, a physical and chemical reaction occurs, which increases the fluidity of the cell membrane and weakens the rigid structure of the phospholipid bilayer, thereby changing the distribution of neurotransmitter receptors, enhancing the affinity of neurotransmitter receptors, and affecting the permeability of the blood-brain barrier and arachidonic acid metabolism, thereby promoting neural activity and alleviating depressive symptoms. ÿ Based on the difference in restrictive gene expression, the antidepressant mechanism of deuterium-depleted water can be explored from the two aspects of epigenetics and post-translational regulation, which may be related to synaptic plasticity and BDNF/TrkB signaling. According to statistics, 33% to 95% of patients with depression often have anxiety. The elevated cross maze experiment was conducted on mice, and it was found that low Mladin et al. deuterated water can relieve mice's fear of unfamiliar environments and reduce their aversion to open spaces, indicating that low-deuterium water has an anti-anxiety effect. The anti-anxiety effect of low-deuterium water may be related to its antioxidant effect. There may be a certain relationship between the state of oxidants such as Hogas and the [50] The study found that anxiety mechanism. Bouayed et al. found that there is a linear relationship between some oxidative stress indicators and [51] The study found that in tissue from the cerebellum, hippocampus

and brain regions different anxiety-related indicators in granulocytes, lymphocytes, monocytes and glial cells.

5. Outlook

In summary, deuterium-depleted water has the potential to become an auxiliary agent for the prevention and treatment of some diseases, such as cancer, diabetes, cardiovascular and cerebrovascular diseases, depression and anxiety, etc.; but the specific molecular mechanism of action is still unclear. Since deuterium-depleted water affects the metabolic process of living organisms, we can start with metabolomics analysis and combine it with bioinformatics analysis to study the mechanism of action of deuterium-depleted water. We can also study the transcriptional regulation of some special genes at the genetic level, and explore the specific molecular mechanism of deuterium-depleted water from both the metabolic and transcriptional levels to confirm the possibility of deuterium-depleted water as an auxiliary therapeutic agent for certain diseases, develop deuterium-depleted water from the laboratory research stage to clinical treatment, and make deuterium-depleted water actually used in health care products, cosmetics, and medical fields.

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