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Protective Role of Molecular Hydrogen in Cancer Radiotherapy: An Update

Ziad Abuawad[1], Mousa Numan Ahmad[1]*, Slezak J[2], Lahham A[3]

[1]Department of Nutrition and Food Technology, Human Nutrition and Dietetics, University of Jordan, Amman11942, Jordan; [2]Institute for Heart Research, Slovak Academy of Sciences, Dubravskacesta 9, P.O. Box 104, 84005 Bratislava, Slovakia; [3]Department of Earth and Environmental Sciences, Al-Quds University, Jerusalem 20002, Palestine.

ABSTRACT

Nowadays, cancer presents a serious health problem worldwide. Oxidative stress has an important role in a variety of pathologies, and the search for an effective and well-tolerated antioxidant agent continues. Although cancer radiotherapy confers significant benefits, it causes remarkable tissue damage and subsequent apoptosis as a result of ionizing radiation by hydroxyl radicals (•OH) that follow the radiolysis of water. There is evidence, but inconclusive indicating that antioxidant capabilities of molecular hydrogen (H_2) alleviate this oxidative stress and subsequent cancer complications and decrease death rates. This article discusses current knowledge on the implications of H_2 in the reduction of radiation therapy-induced adverse effects in cancer. It also highlights the outcomes of recent clinical trials. Relevant articles were identified through an up-to-date online search of PubMed, Medline, Scopus, Science Direct, PsycINFO, registered clinical trials, Google Scholar, and WHO database. The available evidence shows that H_2 as a therapeutic antioxidant selectively reduces the cytotoxic oxygen radicals, in particular, •OH, and may improve cancer conditions. Despite the non-specific mechanism of H_2, researchers have reported several positive effects of H_2 in cancer therapy, including delayed cancer progression, alleviation of radiotherapy and chemotherapy complications, and improved efficacy of conventional therapy when used in combination with H_2. It seems that H_2 has protective effects in the radiotherapy of many cancers. Nonetheless, there is a general scarcity of controlled human studies that investigate direct and longitudinal clinical and biochemical effects of H_2 on key cancerous changes. Thus, further research is required.

Key Words: Antioxidants, Carcinoma, Hydrogen-rich water, Radiation therapy, Oxidative stress

INTRODUCTION

Cancer is an abnormal growth of cells that tend to proliferate in an unrestrained manner and, in some cases, to metastasize to other areas of the body.[1] It is the second leading cause of death globally, accounting for an estimated 9.6 million deaths.[2] The most common types of cancer in men are the lung, prostate, colorectal, stomach, and liver, whereas, in women, they are cancers of the breast, colorectal, lung, cervical, and thyroid.[2] Over the past half-century, progress has been achieved in basic and clinical research, resulting in a decrease in the incidence and death rates of some types of cancer, due, largely, to primary prevention and early detection of the disease, rather than the effectiveness of any drug.[3]

Cancer often necessitates multimodal therapy which includes surgery, radiotherapy (RT), and chemotherapy, or a combination.[4] RT deposits high-energy radiation and thus destroys cancerous tissues and provides a significant survival benefit.[5] The opinion that cancerous cells are more sensitive than normal cells to radiation constitutes the basis of RT. The ability of cancerous cells to repair damaged DNA is limited as they tend to divide rapidly, while normal cells surrounding tumour lesions can withstand RT and recover.[6] Despite efforts to deliver a maximum radiation dose to the target cancerous area and simultaneously protect the nearby normal tissues from radiation injury, there remains significant toxicity of RT to the latter tissues;[7] a matter that leads to several side effects such as fatigue, irritation of skin and bladder, nausea, diarrhoea, constipation, painful bowel movements, sexual problems, scarring, fibrosis, and reduced quality of life.[8,9] RT also increases long-term risks of cancer, central nervous system disorders, cardiovascular disease, and cataracts.[8,9] Local treatment of a primary tumour with RT has produced unpredictable systemic effects on tumour growth, such as enhanced growth of distant metastases or inhibition of distant tumour growth that is known as the abscopal effect.[8,9] Moreover, enhanced tumour

Corresponding Author:
Prof. Mousa Numan Ahmad, Department of Nutrition and Food Technology, Human Nutrition and Dietetics, University of Jordan, Amman 11942 Jordan; Telephone +962 772609701; +962 797509543; Fax +962-6-530-0806; Email: mosnuman@ju.edu.jo; mousanuman@gmail.com

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cell recruitment of circulating tumour cells is another adverse local effect of RT.[10] Several findings have implied that RT can paradoxically enhance tumour recurrence and metastasis via multiple pathways[6].

It is believed that most RT-induced symptoms are associated with increased oxidative stress (OS) and inflammation.[8-10] Ionizing radiation produces toxic reactive oxygen species (ROS) and free radicals.[9] ROS represents the imbalance between the production of oxidants especially free radicals and ROS and the capacity of disposing of them through antioxidants[11]. Several radioprotectors and mitigators have received substantial interests to eliminate or reduce these side effects and thus improve therapeutic efficiency; however, their role in cancer treatment is unclear.[12-14]

Molecular hydrogen (H_2) is a novel and safe medical gas.[15] It can be dissolved in water and administered through drinking, inhalation, baths, and intravenous drip infusion of H_2-rich saline.[15] Moreover, H_2 is a new antioxidant that scavenges free radicals and reduces oxidative load.[16,17] In contrast to other antioxidants, gaseous H_2 can effectively enter the cell, organelle membranes, and defuse ROS because of its neutrality and small size.[18] Therefore, H_2 is recommended as an appropriate candidate for or contributor to the therapeutic strategies for many metabolic diseases, such as certain types of cancer, especially liver carcinoma.[19] This article discusses the current literature addressing the role of H_2 in the reduction of RT-induced adverse effects in cancer and evaluates the findings of recent human clinical trials.

LITERATURE SEARCH

An up-to-date literature review was conducted on the role of H_2 in the reduction of RT-induced adverse effects in various types of cancer. The search was limited to recent English publications. Relevant articles were principally identified through an up-to-date online search of the PubMed, Medline, Scopus, Science Direct, Google Scholar, PsycINFO, registered clinical trials, WHO site, and other available databases. The search was performed using the following keywords or their combinations: hydrogen-rich water, gaseous molecular hydrogen, cancer, radiotherapy, radiotherapy-induced adverse effects, antioxidants, oxidative stress, reactive oxygen species, and free radicals. Included articles were mainly original observational, experimental, and clinical, case study, intervention, and cross-sectional researches in humans or animals. For further search accuracy, the reference lists of works were checked for additional publications from the major databases.

OXIDATIVE STRESS IN CANCER

OS is an imbalance between the production of free radicals and reactive metabolites, the so-called oxidants or ROS, and the protective mechanisms which involve their elimination referred to as antioxidants.[11] This imbalance causes damage to cells and biomolecules with a potential effect on the entire organism.[20] ROS are the products of oxygen-derived small molecules that play a role in normal cellular metabolism including oxygen radicals, such as superoxide anion ($O_2^{\bullet-}$), hydroxyl ($^{\bullet}OH$), peroxyl ($RO_2^{\bullet}$), and alkoxyl ($RO^{\bullet}$), as well as non-radicals.[11,20] The latter can be transformed into radicals or serve the purpose of an oxidizing agent and include hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), ozone (O_3), and singlet oxygen ($1O_2$). ROS enhances DNA synthesis, cellular proliferation and survival, cellular migration and invasion, tumour metastasis, and angiogenesis. In aerobic cells, endogenous metabolic reactions produce $O_2^{\bullet-}$, H_2O_2, and $^{\bullet}OH$.[21] The continuous exposition of mitochondria to high levels of ROS leads to mitochondrial DNA damage and increase O and $^{\bullet}OH$ levels in cellular apoptosis.[21] The generation of ROS in cells exists in equilibrium with a large variety of antioxidant defence mechanisms that include enzymatic scavengers such as superoxide dismutase (SOD), catalase, glutathione peroxidase and peroxiredoxins, and non-enzymatic scavengers like vitamins C and E, glutathione, lipoic acid, carotenoids, and iron chelators.[22]

Tumour cells produce ROS in larger quantities than normal cells elevating OS in these cells.[22,23] ROS damages DNA in many chronic inflammatory diseases and a wide variety of cancer types. ROS can initiate tumorigenicity and subsequent tumour promotion and progression by damaging DNA[23]. ROS also produces and introduces respectively gene mutations and structural alterations into the DNA during the initiation stage of cancer.[21,24] Furthermore, ROS plays key roles in the stimulation of cell signalling pathways in intra- and extracellular environmental conditions, regulation of gene mutations, and balance of cell proliferation and apoptosis.[25] Peroxisome proliferator-activated receptor-γ, nuclear factor-κB, β-catenin/Wnt, activator protein 1, nuclear factor erythroid 2-related factor 2, tumour protein *p53*, and hypoxia-inducible factor1-alpha are among the many transcription factors that can be activated by OS.[20] ROS controls and mediates the effects of C-radiation and various chemotherapeutic agents used to treat cancer. It is known that chronic inflammation caused by long-term ROS activates the effector molecules. ROS also alters the malignant transformation and the expression of genes involved in immune, inflammatory responses, carcinogenesis, and metastasis.[20,25] The hypermetabolic state is one of the characteristics of malignant carcinomas that results in a persistent OS state in a cellular microenvironment. As a result, the utilization of antioxidants that antagonize ROS seems to be a feasible strategy in cancer therapy.[21,26]

OXIDATIVE DAMAGE OF RADIATION

Radiation energy in the exposure pathway causes direct detrimental biological effects by targeting several biomolecules,

mainly DNA, proteins, and lipids.[26,27] Hydroxyl radicals target DNA forming 8-hydroxydeoxyguanosine (8-OHdG), a biomarker of carcinogenesis, from deoxyguanosine.[28] The initial formation of ROS, a result of H_2O radiolysis, intervenes in the radiation-induced DNA lesions, which leads to indirect detrimental biological impacts.[28] The generation of $HO^{\bullet}$, ionized water (H_2O^+), hydrogen radicals, and hydrated electrons are the quick result of exposure of water to ionizing radiation. The reaction of the initially produced radicals generates hydrogen peroxide (H_2O_2) and superoxide anion ($O_2^{-\bullet}$). The radiation-induced increase of ROS could damage cellular constituents and induce OS; this is because ROS is produced endogenously, and its level is regulated by several antioxidant defence mechanisms.[29]

Free radicals target the lipid layer of cell membranes.[28] ROS reacts with membrane polyunsaturated fatty acids.[30] The process involves the abstraction of the bis-allylic position of these fatty acids either by $HO^{\bullet}$ or by a thiyl radical ($RS^{\bullet}$) forming peroxyl radicals. The latter can abstract a hydrogen atom from another fatty acid, inducing the so-called peroxidation reactions.[29] Malondialdehyde (MDA), acrolein, and 4-hydroxy-2-nonenal are some of the break-down products of hydroperoxides that are considered chemical indicators of lipid peroxidation reactions or even indices of defective permeability and fluidity of cell membranes.[29-31]

RADIOTHERAPY IN CANCER

Cancerous cells have a degree of self-sufficiency that causes them to not respond to the signals which activate the normal cell cycle leading to uncontrolled growth and proliferation of transformed cells.[1,2] If the proliferation of cancerous cells continues, it can be fatal.[32] It is estimated that metastasis is responsible for about 90% of cancer deaths.[33] The type of cancer, its locality, and stage of progression determine the selection of treatment of cancer and its progress. Some of the traditional and most widely used treatment methods are surgery, RT, and chemotherapy, or a combination.[4] Hormone-based therapy, anti-angiogenic modalities, stem cell therapies, and immunotherapy are some of the modern modalities.[32] More than half of the cancer patients receive RT during their illness; RT is of prime importance, especially in patients with untreatable tumours or incompletely resected tumours and for those with recurrent disease.[34] RT can be used to downstage primary tumours, to reduce the risk of recurrence in the adjuvant setting, and in the palliative setting, to improve the quality of life at each stage of the disease.[10] Treatment with surgery, often followed by RT is used in most breast cancer patients in stages I, II, or III. About half of women (49%) with stage I or II breast cancer undergo breast-conserving surgery followed by RT.[35] Women (56%) diagnosed with metastatic disease (stage IV) most often receive radiation and/or chemotherapy alone.[35]

Before surgery, RT is often applied to disrupt the ability of cancer cells to grow and divide, slow their growth, and shrink tumour areas.[5] The use of RT is based on the theory that cancerous cells are more sensitive to radiation than normal cells as the former cells have a limited ability to repair damaged DNA and tend to divide more quickly, while the latter cells surrounding tumour lesions can withstand RT and recover.[36] The mechanism underlying this theory lies in the fact that the damaged DNA is unable to replicate, and thus cell division is halted, resulting in the death of cells.[36] Targeting normal cells that lie in the peripheries of the main tumorous mass is the main adverse effect of RT. Nevertheless, improved imaging techniques for accurate targeting of the cancer mass, in addition to the ability of normal cells to regain normal function faster than cancer cells, could minimize the damage caused by RT.[32] Fatigue, nausea, diarrhoea, and dry mouth, loss of appetite, hair loss, sore skin, and depression are some of the acute radiation-associated side effects. The probability of radiation-generated complications is linked to the size or area of the radiation treated body parts, the given dose of radiation and its fractionation and rate of application, and individual radio-sensitivity.[9]

RT remains the most effective non-surgical technique to achieve control of malignant tumors.[32-38] The past two decades have witnessed a rapid rise in technological advancement aimed at improving endurance, accuracy, and efficacy through RT used more than a century ago. On the other hand, there is evidence to suggest that the various changes caused by radiation in the tumour environment can also pose a metastatic risk that may offset the long-term effectiveness of treatment. Several theoretical mechanisms have been largely suggested by which radiation exposure can increase the risk of metastases. These include the direct release of tumour cells into the circulatory system, systemic effects of the tumour, irradiation of normal tissues, and changes caused by radiation in the phenotype of tumour cells.[37] It is a new scientific topic for radiologists to examine highly effective low-toxic radiation protectants. The focus has always been on deploying ideal radiation protectants in the radiation field.[28,38]

ANTIOXIDANT ACTIVITY OF MOLECULAR HYDROGEN

The oxidants in ROS are reduced by H_2. When selectively dissolved in the cultured medium, H_2 reduces the strongest oxidants, such as OH and $ONOO^-$, in cell signals.[25] However, H_2 does not disturb the cellular levels of O_2, $NO\cdot$, or H_2O_2. ROS is also involved in metabolic oxidation-reduction reactions in cell-free systems. Because OH is strong enough to interact with H_2, it can be a sign of the oxidative strength of ROS. Hydroxyl radicals ($\cdot OH$) produced by radiolysis or photolysis of H_2O significantly reduced by H_2 treatment leading to decrease levels of $^{\cdot}OH$ in cultured cells, thus protecting the mitochondria from OH.[21]

H_2 has promising physical-chemical properties as a therapeutic antioxidant. It is smaller than molecular oxygen and is electrically neutral.[18,21] This allows it to easily penetrate cell membranes and spread into cellular organelles, mainly the nucleus and mitochondria. Moreover, H_2 has a very mild reactivity so that it does not interact with important physiologically relevant ROS that is involved in cell signaling.[18,21,28] It also does not affect physiology, temperature, blood pressure, pH, or pO_2, nor has it been reported to be toxic at much higher levels than clinically effective doses. H_2 excess simply expires across the lungs when much is delivered. H_2 treatment enhances endogenous antioxidant enzymes and thus contributes to improved OS. Catalase, SOD, and glutathione peroxidase are the important cellular antioxidant enzymes.[39] Table 1 summarizes the physical-chemical properties of H_2 that determine its antioxidant therapeutic benefits.

Table 1: Physical-chemical properties and therapeutic features of molecular hydrogen

Physical-chemical properties	Therapeutic features
Low molecular weight	Easily diffuses across cellular membranes to reach subcellular compartments
Small size and high diffusivity	Can cross the blood-brain barrier
Strong covalent bond between H atoms	Stability at room and body temperature
H_2 molecule is non-polar	Slightly soluble in water at atmospheric pressure
Gas at room temperature	Multiple routes (oral, injection and inhalation)
Endogenous gas	Well tolerated
Reducing agent	Selective antioxidant effects
Selective reducing agent	No effect on redox homeostasis
Reaction with OH radicals and inhibition of lipopolysaccharide/interferon γ-induced nitric oxide production.	Anti-inflammatory
Reducing/eliminating $^{\cdot}OH$ and $ONOO^-$	Anti-apoptotic
High level of H_2 is well tolerated	Biologically inert and safe

RAIOPROTECTIVE EFFECT OF MOLECULAR HYDROGEN

Molecular hydrogen has appeared as a promising cancer treatment either as a preventive agent or in combination therapy with anticancer drugs.[40-43] The consumption of hydrogen-rich water (HRW) may reduce the side effects of anticancer drugs by reducing OS and improving metamorphosis due to decreased apoptosis.[40] H_2 also protects the immune system through radiation protection action. Moreover, H_2 may reduce radiation-induced blood injury, as well as save depletion of white blood cells and platelets.[41] HRW causes telomere shortening in cancer cells, suppressing tumour angiogenesis by clearing intracellular ROS as well as suppressing gene expression and secreting vascular endothelial growth factors.[42]

Several side effects of RT are believed to be associated with increased OS and inflammation due to ROS generation during RT.[9] Daily consumption of HRW is a potential new treatment strategy to improve the quality of life after exposure to RT. It has been reported that the life quality of patients with liver carcinoma who were given a placebo decreased significantly during the first month of RT.[43] One of the most common complaints in patients undergoing RT is symptoms of the digestive system.[43] Compared to patients consuming placebo, patients consuming HRW had significantly less appetite loss and fewer taste disorders, with no significant difference in the average degrees of vomiting or diarrhoea. The biological reaction to RT-induced OS without compromising antitumor effects was reduced by HRW consumption.[43]

It has been reported that $^{\cdot}OH$ was significantly decreased in cultured cells using H_2 treatment by radiolysis or photolysis of H_2O and thus protecting the mitochondria[21]. H_2 also penetrates the biological membranes and diffuses into organelles, thereby reducing the cellular levels of ATP synthesized in the mitochondria and the nucleus. H_2 effectively reduces cyclooxygenase-2, a marker of OS, in immune-positive neurons due to its antioxidant and anti-inflammatory neuroprotective effects[44]. Induction of inflammatory cytokines and inhibition of cell signalling factors activates the anti-inflammatory and anti-allergic properties of H_2. Moreover, H_2 has been shown to reduce the expression of several pro-inflammatory factors, including tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β, IL-10, IL-12, and chemokine ligand 2, intercellular adhesion molecule 1, nuclear factor-κB, high mobility group box 1 protein, and prostaglandin E. H_2-rich saline reduces serum diamine oxidase, TNF-α, IL-1β, IL-6, tissues MDA, protein carbonyl and myeloperoxidase activity, as well as discouraging pro-apoptotic players, including c-Jun N-terminal kinase and caspase-3.[44,45] IL-4 serum level decreased significantly after H_2 inhalation. H_2 gas inhalation upregulated SOD activity and significantly reduced the increased level of MDA and myeloperoxidase in allergic asthmatic mice.[21,46] The protective effect of H_2 against the development and invasion of the tumour enables it to act as an antitumor factor. Hence, the electrically neutral HRW was shown as an antioxidant to counteract ROS, inhibition of cancer cell proliferation, and invasion, together with the removal of intracellular oxidants.[21]

Increased antioxidant capacity as indicated by decreased levels of oxidative products, increased activities of antioxidation-related enzymes and decreased early and late levels

of pro-inflammatory cytokines in serum and tissues are the three main positive effects of the treatment with H_2 on organ damage. H_2 has also been used to treat many OS-associated diseases, such as cardiovascular disorder.[39] Regardless of the form that is used, H_2 gas or H_2 water, treatment with H_2 improves the quality of life of patients receiving chemotherapy or RT. Energy metabolism, measured by O_2 consumption and CO_2 expiration, was stimulated by drinking HRW. These results indicate the potential advantage of H_2 in improving obesity, diabetes and metabolic syndrome.[39] Consuming HRW can prevent arteriosclerosis more effectively than other antioxidants and may delay the development and progression of Parkinson's disease. The brain OS was also reduced by continuous consumption of HRW. Oral HRW is an effective antioxidant and anti-inflammatory agent that reduces chronic allograft nephropathy.[47] Accumulated data also show the possibility of H_2 as an anti-ageing solution and in wellness applications, especially sports and injuries.[48]

H_2 therapy can work with cancer treatments such as surgical removal, chemotherapy, and RT, which often lead to systemic inflammation, to restore tissue function.[40] H_2 rapidly spreads to reduce cytotoxic and inflammatory radicals in tissues. The antioxidant properties of H_2 gas or H_2 water have been shown to improve the quality of life of cancer patients during chemotherapy. Nephrotoxicity, mortality, and body weight loss caused by cisplatin were reduced by inhaling 1% of H_2 gas or drinking H_2 water. The level of renal apoptosis was also reduced by drinking H_2. Most of the symptoms caused by radiation are believed to be associated with increased ROS and inflammation during RT significantly affecting the patient's quality of life.[9] HRW consumption reduces biological interactions with the radiation-induced OS without damaging antitumor activities. Inflammation in OS-related cancer can be protected by inhaling H_2 gas and giving H_2 orally. This improves the antitumor effect of cancer management.[21] H_2 may act alone or in conjunction with another treatment to suppress tumour growth by inducing apoptosis, reducing proliferation, regulation of structural maintenance of chromosome 3, and inhibiting cell cycle-related factors.[9,49-54] Table 2 presents a summary description of some studies on the therapeutic potentials of molecular hydrogen in cancer.

Table 2: Selected studies on therapeutic potentials of molecular hydrogen in cancer

Cancer	Research design	Study population	Main findings	Reference
Tongue carcinoma	In vitro human cell line models	Human tongue squamous carcinoma-derived cell line HSC-4 (RCB1902)	Pt-NC-supplemented HD-water is a novel agent against tongue cancer due to its cancer progression-repressive abilities	49
liver cancer	A randomized, placebo-controlled study	49 patients receiving radiotherapy for liver tumour	Hydrogen-rich water reduces radiation-induced oxidative stress without affecting antitumor action	9
Lung cancer	In vitro human cell line models	Human lung epithelial cell line A549 cells	Hydrogen protects against irradiation lung damage without toxicity	50
	In vitro human cell line models	human NSCLC A549 cell line	Hydrogen-rich saline with a PI3K inhibitor, LY294002, reduces cancer proliferation and promotes apoptosis	51
	In vitro human cell line models	Cancer A549 and H1975 and normal BEAS-2B cell lines	Hydrogen inhibits cancer progression through down-regulating SMC3	52
Colorectal cancer	Controlled, randomized, single-blind trial	152 patients with colorectal cancer	Hydrogen-rich water alleviates mFOLFOX6-related liver injury	53
	Human clinical trial phase II	55 patients with stage IV colorectal carcinoma	H_2 gas reverses imbalances toward PD 1+ CD8+ T cells to improve prognosis	54

Pt-nc= Platinum nano colloid; mFOLFOX6= A chemotherapy consisting of leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin; PI3K= Phosphatidyl inositol-3 kinase; LY294002= A morpholine-containing drug; SMC3= Structural maintenance of chromosome 3; PD 1+= A protein found on T cells.

The gastrointestinal tract ranks the second-most sensitive organ to irradiation injury during cancer RT after the bone marrow.[55] Injection of H_2-rich saline before radiation in a mouse model protected the gastrointestinal endothelia from RT-induced injury, decreased plasma MDA and intestinal 8-OHdG levels, and protected plasma levels of endogenous antioxidant enzymes such as SOD and glutathione peroxidase.[28,56] Lungs are also radiosensitive to pneumonitis in acute and subacute settings and pulmonary fibrosis in chronic settings.[57,58,62] Pretreatment of H_2 reduced OS products, mainly

4-hydroxy-2-nominal and 8-OHdG. The levels of apoptosis-associated proteins, including Bax and active caspase 3 in irradiated A549 cells, after 24-hour incubation with H_2-rich solution, were significantly reduced by H_2. Five months after irradiation, lung fibrosis, Ashcroft scores, and type III collagen deposition were reduced by H_2 treatment.[28,50]

Due to their postmitotic state, cardiac myocytes are relatively resistant to radiation damage.[59] Endothelial cells are known to be sensitive to radiation, and their damage is associated with the pathophysiology of most forms of cardiac injuries, which may result from loss of alkaline phosphatase activity of capillary endothelial cells.[60,61] In addition to myocardial degeneration, perivascular and interstitial fibrosis are seen. H_2 pretreatment proved to have cardioprotective properties by decreasing MDA and 8-OHdG levels.[28]

CONCLUSION

Collectively, the role of antioxidants in preventing and treating cancer has been well studied, but the majority of research has not paid much attention to molecular hydrogen. In this context, H_2 has antioxidant, anti-inflammatory, and antiallergic effects by its selective removal of free radicals. H_2 treatment can alleviate the harmful effects of chemotherapy and RT to improve the quality of life for cancer patients. H_2 treatment may also delay the development of cancer; combined use of H_2 with other anticancer drugs may enhance anticancer effects in treatment. H_2 is then included as a treatment, with highly reactive ROS, and effective diffusive action in cells. Characteristics of the strength of body temperature in mammalian cells, a virtually event-free tolerance profile, and the ability to administer therapy in a variety of ways to fit a patient or indication treatment, with minimal cost-effective surgical intervention. The expanded nature of the effects of H_2 means that it has therapeutic potential across a wide range of medical applications. The definition of H_2, as a type of antioxidant, cannot explain all its radioprotective effects. The exact mechanism and signal pathway involved in the protective role of H_2 in ionizing radiation injury needs further studies in the future. Only a few studies describe how H_2 exerted its effect not only as an antioxidant. For the first time, H_2 may become a gaseous signaling molecule like nitric oxide, carbon monoxide, and hydrogen sulfide. However, several randomized clinical trials are needed to confirm whether H_2 treatment is applicable in the clinical setting and whether it affects the efficacy of RT. Although the field is still relatively new, H_2 appears promising in preventive care and treatment of ROS-related diseases.

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