Review

Confirmation of efficacy, elucidation of mechanism, and new search for indications of radon therapy

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Indications of radon therapy include various diseases related to respiratory, painful, digestive, chronic degenerative, senile, etc. derived from reactive oxygen species, but most are based on empirical prescriptions. For this reason, we have evaluated the relation between the biological response caused by radon and the tissue/organ absorbed dose more quantitatively, and have promoted the elucidation of mechanisms related to the indication and searching newly. As a result, as a mechanism, a series of moderate physiological stimulative effects accompanying a small amount of oxidative stress by radon inhalation are being elucidated. That is, hyperfunction of anti-oxidation/immune regulation/damage repair, promotion of anti-inflammation/circulating metabolism/hormone secretion, induction of apoptosis/heat shock protein, etc. Also, new indications include inflammatory/neuropathic pain, hepatic/renal injury, colitis, type 1 diabetes, complication kidney injury, hyperuricemia, transient cerebral ischemia, and inflammatory edema. Furthermore, we examined the combined antioxidant effect of radon inhalation and antioxidants or therapeutic agents. As a result, it was clear that any combination treatment could enhance the suppression effect of disease. It can be expected that radon therapy can be used effectively by applying it in addition to usual treatment, since reduction in its dosage can also be expected by concomitant use for drugs with strong side effects.

***Key Words*:** **radon therapy, indication, physiological stimulative effect, antioxidant function, anti-inflammatory effect, combined antioxidant effect**

Radon (^{222}Rn) therapy, utilizing radon-rich hot-air baths near hot springs or at the site of a tunnel, is being implemented not only in Japan but also in Europe. Despite several reports[1] regarding its therapeutic effect in clinical trials, very few reports have elucidated the underlying mechanism. Therefore, most studies have been conducted due to prescription by the doctors based on their experience and intuition. Detailed elucidation of the mechanism of radon therapy will contribute to the discovery of new indications and establishment of optimal treatment methods. Therefore, we have promoted the elucidation of mechanism of indications and suggested new studies after further quantitative evaluation of the relationship between the biological response to radon and the absorbed dose in tissues and organs. In a previous report,[2] we had presented the enhancement of antioxidant function by low-dose irradiation and its applicability to the treatment of reactive oxygen species-related diseases. The current review aimed to outline the research progress till date regarding the confirmation of efficacy, elucidation of mechanism, and new search for the indications of radon therapy.

Indications and Physiological Effects

As shown in Table 1, the main indications of radon therapy include diseases due to active oxygen species, such as respiratory diseases (bronchial asthma/emphysema), painful diseases [rheumatoid arthritis/osteoarthritis/spondylosis deformans/Bekhterev's disease (ankylosing spondylitis)], gastrointestinal diseases (liver disease/peptic ulcer/gastroenteritis), chronic degenerative diseases (hypertension/arteriosclerosis/diabetes), and presbycusis; there are approximately 70 painful diseases. However, some contraindications have also been reported.

Radon is an inert gas, most of which is ingested by respiration; it is constantly carried throughout the body via the bloodstream, and gets attenuated to half in approximately 30 min. Owing to its high lipophilicity, it easily accumulates in endocrine glands and nerve fibers.[3] Since it is an α-ray source, its range is short (approximately 20 μm), with relatively large energy (5.49 MeV) provided to tissues. Thus, radon exhibits an effective physiological stimulating effect on organs and tissues.

On the other hand, long-term high-concentration radon inhalation is considered to be a risk factor for lung cancer, possibly via the deposition of radon progeny nuclides in the respiratory tract. For this reason, the International Commission on Radiological Protection (ICRP) has proposed an indoor reference level equivalent to 10 mSv per year. However, radon therapy is safe, since it involves an exposure to only 0.04 mSv.

Table 1. Main indications and contraindications for radon therapy

Indications
• respiratory diseases, such as bronchial asthma and emphysema
• painful diseases, such as rheumatoid arthritis, osteoarthritis, neuralgia, spondylosis deformans, and Bekhterev's disease (ankylosing spondylitis)
• gastrointestinal diseases, such as liver disease, peptic ulcer, and gastroenteritis
• chronic degenerative diseases, such as hypertension, arteriosclerosis, and diabetes
• presbycusis
• atopic dermatitis, rehabilitation after gait system injury, etc.
Contraindications
• acute illness with fever
• severe heart/kidney disease
• leukemia

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Table 2-1. Studies on inhibitory effects in various diseases: Example 1

Inhibitory effects of pre-radon inhalation in various diseases		
Diseases	Inducer	References
Inflammatory pain	Formalin	(4)
Inflammatory paw edema	Carrageenan	(5)
Gastric mucosal injury	Alcohol	(6)
Ulcerative colitis	Dextran sulfate sodium	(7)
Hyperuricemia	Potassium oxoate	(8)
Type 1 diabetes	Streptozotocin	(9)
Acute hepatopathy	Alcohol	(10)
Nephropathy	Cisplatin	(11)
Hepatic and renal damage	Carbon tetrachloride	(12)
Transient ischemic attack	Ischemia	(13)
Inhibitory effects of pre- and/or post-radon inhalation in various diseases		
Neuropathic pain	Chronic constriction injury	(14)
Type 1 diabetic nephropathy	Streptozotocin	(15)
Depression	Forced swimming test	(16)
Oxidative disorders	Carbon tetrachloride	(17)

Table 2-2. Studies on inhibitory effects in various diseases: Example 2

Comparison of each inhibitory effect or its combined effects of radon inhalation and other treatments		
Diseases	Inhibitor	References
Transient ischemic attack	Radon inhalation or ascorbic acid administration	(18)
Hepatic/renal disorders	Radon inhalation or antioxidant vitamin administration	(19, 20)
Acute alcoholic hepatopathy	Combined use of radon inhalation and antioxidant vitamins administration	(21)
Neuropathic pain	Combined use of radon inhalation and pregabalin administration	(22)
Normal	Antioxidant activity of radon or thoron inhalation	(23)
Rheumatoid arthritis/diabetes	Combined use of thoron inhalation and hyperthermia	(24)
Mechanism of radon therapy		
Mechanism of increase in Mn-SOD activity by radon inhalation		(26)
Redox status of each organ by radon inhalation		(27)

Studies on the Inhibitory Effects of Pre-radon Inhalation in Various Diseases

Table 2 lists the results of our studies related to the inhibitory effects of pre- or post-radon inhalation in various diseases. In the following outline, experiments are described in which mice were made to inhale 2,000 Bq/m^3 radon for 24 h before or after administration of the disease inducer (other concentrations and times are noted in the relevant section). The results were compared with those of pseudo (sham) inhalation experiments. Most cases suggested that radon inhalation enhances antioxidant function and suppresses various diseases.

Formalin-induced inflammatory pain. Formalin was administered subcutaneously to the sole of the hind limb after radon inhalation. Radon inhalation significantly suppressed the inflammatory pain-like behavior and decreased the levels of tumor necrosis factor-α (TNF-α) and nitric oxide (NO) in the serum, which was otherwise significantly increased by formalin administration in the sham.[4] On the other hand, the significantly increased serum and foot antioxidant functions were decreased with formalin administration. The findings suggested that radon inhalation suppresses inflammatory pain.

Carrageenan-induced inflammatory paw edema. Carrageenan (1%) was administered (50 μl) to the foot after radon inhalation. Radon inhalation had significantly reduced inflammatory foot edema, significantly increased the levels of TNF-α and NO, and superoxide dismutase (SOD) activity in serum.[5] The findings suggested that radon inhalation suppresses inflammatory oedema.

Alcohol-induced gastric mucosal injury. Alcohol (60%) was administered directly to the stomach after radon inhalation. Radon inhalation significantly reduced gastric mucosal damage and gastric lipid peroxide (LPO) level.[6] This suggested that radon inhalation suppresses gastric mucosal damage.

Dextran sulfate sodium (DSS)-induced ulcerative colitis. After radon inhalation, DSS (3%) was administered orally for 7 days. During DSS treatment, radon inhalation was continued. Radon inhalation was found to significantly increase the SOD activity and total glutathione (t-GSH) level in the colon tissue and significantly decrease the LPO level.[7] Ulcerative colitis was improved, and the myeloperoxidase activity and the levels of plasma NO, TNF-α, and LPO in colon tissue were significantly reduced. The findings suggested that radon inhalation suppresses ulcerative colitis.

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Potassium oxoate-induced hyperuricemia. Potassium oxoate (500 mg/kg body weight) was intraperitoneally administered after radon inhalation. The increased serum uric acid level and xanthine oxidase (XOD) activity due to potassium oxoate were decreased by radon inhalation.[8] In addition, radon inhalation significantly increased the SOD activities and t-GSH levels in the liver and kidneys. The results suggested that radon inhalation inhibits XOD synthesis and suppresses the production of uric acid, thereby reducing the amount of uric acid; it would, therefore, be effective in the prevention and treatment of hyperuricemia.

Streptozotocin (STZ)-induced type 1 diabetes. After radon (1,000, 2,500, or 5,500 Bq/m^3) inhalation, STZ (200 mg/kg body weight) was intraperitoneally administered. Radon inhalation slowly, yet significantly, decreased the blood glucose levels.[9] While antioxidant enzymes and substances were significantly decreased and LPO level significantly increased, radon inhalation significantly suppressed them and showed improvement in antioxidant function. Pathological observations revealed significant alleviation of islet atrophy. These findings suggested that radon inhalation alleviates the decrease in insulin secretory function to suppress type 1 diabetes.

Acute alcoholic hepatopathy. Alcohol (50%, 5 g/kg body weight) was intraperitoneally administered after radon inhalation (4,000 Bq/m^3). Activities of both glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) in serum and levels of both triglycerides and LPO in the liver, which are otherwise significantly increased after alcohol administration, were suppressed due to radon inhalation.[10] This suggested that radon inhalation suppresses liver damage.

Cisplatin-induced nephropathy. Two strains of mice with different radiosensitivities were allowed to inhale radon (1,000 or 2,000 Bq/m^3) before cisplatin administration. C57BL/6J mice showed improvement in their hair condition due to radon inhalation.[11] Similarly, 1,000 Bq/m^3 radon inhalation decreased the creatinine level and increased SOD activity in BALB/c mice. The findings suggested that radon inhalation alleviates renal damage.

Carbon tetrachloride (CCl_4)-induced hepatic and renal damage. CCl_4 was intraperitoneally administered after 6 h inhalation of radon (18,000 Bq/m^3). Radon inhalation significantly increased t-GSH levels and glutathione peroxidase (GPx) activities in the liver and kidney.[12] In addition, activities of both GOT and alkaline phosphatase (ALP) and creatinine level in the serum, which otherwise increased significantly with CCl_4 administration, were significantly decreased by radon inhalation. These findings suggested that radon inhalation suppresses liver and renal disorders.

Transient ischemic attack. After radon inhalation, the common carotid arteries on both sides were occluded with a small vessel clip for 10 min. The rate of cytotoxicity in the hippocampal CA1 region significantly increased with loading, but was significantly suppressed by radon inhalation; the hippocampus maintained a near-normal morphology.[13] In addition, radon inhalation significantly increased SOD activity in the brain. These findings suggested that radon inhalation alleviates the neuronal damage associated with cerebral ischemia.

Studies on the Inhibitory Effects of Pre- and/or Post-radon Inhalation in Various Diseases

Neuropathic pain. Radon was inhaled by a mouse model of neuropathic pain. The inhalation decreased the number of escape behaviors in response to mechanical stimuli, and suppressed the increased noradrenaline (NE) level and decreased SOD activity in plasma.[14] These findings suggested that radon inhalation relieves neuropathic pain and is involved in the suppression of NE level, representing central sensitization.

STZ-induced type 1 diabetic nephropathy. STZ was administered for 5 consecutive days, and after 4 weeks, the mice with a blood glucose level of 300 mg/dl or higher were divided into two groups. Subsequently, radon inhalation for 4 weeks enhanced the antioxidant function in the kidney and improved the fibrotic changes in urinary albumin and renal glomeruli that were exacerbated by hyperglycemia.[15] These findings suggested that radon inhalation suppresses type 1 diabetic nephropathy.

Forced swimming-induced depression. Radon was inhaled before and after the forced swimming test. Depression was reduced and decreased levels of monoamines, such as NE and dopamine, in the brain were increased upon radon inhalation.[16] The findings suggested that radon inhalation exerts an antidepressant effect.

CCl_4-induced oxidative disorders in various organs. Radon (18,000 Bq/m^3) was inhaled 6 h before or after CCl_4 administration. Both before and after inhalation, the t-GSH levels and catalase activities in the brain, heart, lungs, liver, and kidneys, and SOD activities in the heart and lungs increased significantly, whereas the LPO levels decreased.[17] The effect of suppressing these oxidative disorders was greater in pre-radon inhalation than in post-radon inhalation.

Comparison of Each Inhibitory Effect or Its Combined Effects of Radon Inhalation and Other Treatments

Radon inhalation or ascorbic acid administration for transient ischemic attack. Radon inhalation or ascorbic acid (100, 300, or 500 mg/kg body weight) administration was performed intraperitoneally. Immediately after that, a transient ischemic animal model was created. The exacerbated cytotoxicity was ameliorated by radon inhalation or ascorbic acid ingestion, and the effect was similar to that of radon inhalation and ascorbic acid administration at 500 mg/kg body weight.[18]

Radon inhalation or antioxidant vitamin administration for CCl_4-induced hepatic/renal disorders. After radon inhalation, CCl_4 (4 ml/kg body weight, 5% in olive oil) was administered intraperitoneally. On the other hand, ascorbic acid or α-tocopherol (100, 300, or 500 mg/kg body weight) was intraperitoneally administered, followed by CCl_4 administration in the same manner. From the degree of suppression of liver function, fatty liver, pathological observation, and oxidative damage, the degree of suppression of liver damage by radon inhalation was found to be similar to that by ascorbic acid administration (500 mg/kg body weight) or α-tocopherol administration (300 mg/kg body weight).[19,20] This could be because radon inhalation significantly increased the activities of SOD, catalase, and GPx in the liver.

On the other hand, radon inhalation or α-tocopherol (300 and 500 mg/kg body weight) administration significantly decreased the levels of creatinine in the serum and LPO in the kidney, suggesting the suppression of both renal damage and oxidative damage. Although the mechanism is different, the degree of suppression of renal damage by radon inhalation was equivalent to that by the administration of 300–500 mg/kg body weight α-tocopherol.

Combined use of radon inhalation and antioxidant vitamin administration for acute alcoholic hepatopathy. Alcohol (5 g/kg body weight, 50%) was intraperitoneally administered after radon inhalation and intraperitoneal administration of 300–500 mg/kg body weight of ascorbic acid or α-tocopherol. The combined use of radon inhalation and ascorbic acid or α-tocopherol significantly reduced liver function and approached normal values.[21] In addition, the degree of suppression of oxidative stress by radon inhalation was equivalent to that due to the administration of 300–500 mg/kg body weight of ascorbic acid or α-tocopherol, regardless of organs and tissues; therefore, it was suggested to have a relatively strong antioxidant effect and its

combined use would have an additive effect without antagonizing the enhancement of antioxidant function.

Combined use of radon inhalation and pregabalin administration for neuropathic pain. Pregabalin, a pain treatment drug, was administered after radon (1,000 Bq/m^3) inhalation into the mouse model of neuropathic pain. Regarding the pain-suppressing effect, radon inhalation corresponded to pregabalin administration of approximately 1.4 mg/kg body weight, and combination of radon inhalation and pregabalin administration (3 mg/kg body weight) corresponded to pregabalin administration of approximately 4.1 mg/kg body weight.[22] This suggested the occurrence of an additive effect.

Radon inhalation or thoron inhalation. Radon or thoron inhalation of 500 or 2,000 Bq/m^3 was administered, respectively. The SOD activity and t-GSH levels were found to be significantly increased, whereas the LPO level was significantly decreased.[23] The phenomena were generally observed with radon inhalation of 2,000 Bq/m^3 and thoron inhalation of 500 Bq/m^3. Difference in the optimal concentration could be attributed to the difference in radioactivity characteristics, such as emitted energy and half-life.

Combined use of thoron inhalation and hyperthermia for rheumatoid arthritis/diabetes. In clinical trials, patients with rheumatoid arthritis or diabetes were treated with thoron (4,900 Bq/m^3) and hyperthermia for 2 weeks. α-Human atrial natriuretic peptide (ANP) levels increased, blood pressure significantly decreased, and SOD activity significantly increased.[24] In addition, the concanavalin A-induced mitogen response and the number of CD4-positive cells increased, whereas the number of CD8-positive cells decreased. The findings suggested partial mechanism of alleviation of diabetes and rheumatoid arthritis by the combined use of thoron inhalation and hyperthermia.

As mentioned above, since radon inhalation suppressed oxidative stress-induced diseases, the occurrence of new indications is possible, including inflammatory/neuropathic pain and inflammatory edema, liver/renal/gastric mucosa disorders, colitis, hyperuric acid blood, type 1 diabetes and renal disorder, transient cerebral ischemia, and depression. In future, further search for new indications will be possible by examining the above-mentioned physiological characteristics of radon, radon distribution for each organ/tissue due to inhalation,[3] and changes in antioxidant function[25] and radiosensitivity. Regarding the combined effect of radon inhalation and antioxidant vitamins, such as ascorbic acid and α-tocopherol, or analgesics, such as pregabalin, both combinations were found to enhance the disease-suppressing effect. Since the effect of pain relief is strong and prolonged, and dosage of drugs with strong side effects may be reduced by concomitant use, the characteristics of radon therapy may be effectively utilized by implementing it in addition to the usual treatment.

Mechanism of Radon Therapy

Based on the above-mentioned physiological characteristics of radon, as shown in Fig. 1 and 2, a series of appropriate physiological stimulations associated with a small amount of oxidative stress due to radon inhalation may be considered as the mechanism underlying radon therapy. Hypotheses, such as hyperfunctions of antioxidation, immunomodulation, and damage repair, promotion of anti-inflammatory action, blood circulation/cell metabolism, and hormone secretion, and induction of apoptosis (mutated cell self-destruction) and heat shock protein (HSP, cell protection), have been proven and elucidated.

Below we have outlined a part of antioxidant function enhancement.

Mechanism of increase in Mn-SOD activity by radon inhalation. Regarding the mechanism by which radon inhalation increases SOD activities in various organs, mitochondrial SOD (Mn-SOD) activities, in particular, was found to have increased.[26] It involved an increase in ataxia telangiectasia mutated (ATM), nuclear factor (NF)-κB-inducible kinase (NIK), and the downstream protein NF-κB, which are associated with the synthesis of Mn-SOD.

Redox status of each organ by radon inhalation. The relationship between antioxidant function and oxidative stress was evaluated using principal component analysis (PCA) of the data from various organs after inhalation (1, 3, or 10 days) of radon (2,000 or 20,000 Bq/m^3). Both liver and kidneys have high antioxidant capacity, the brain, pancreas, and stomach have low antioxidant capacity and low LPO levels, and the lung, heart,

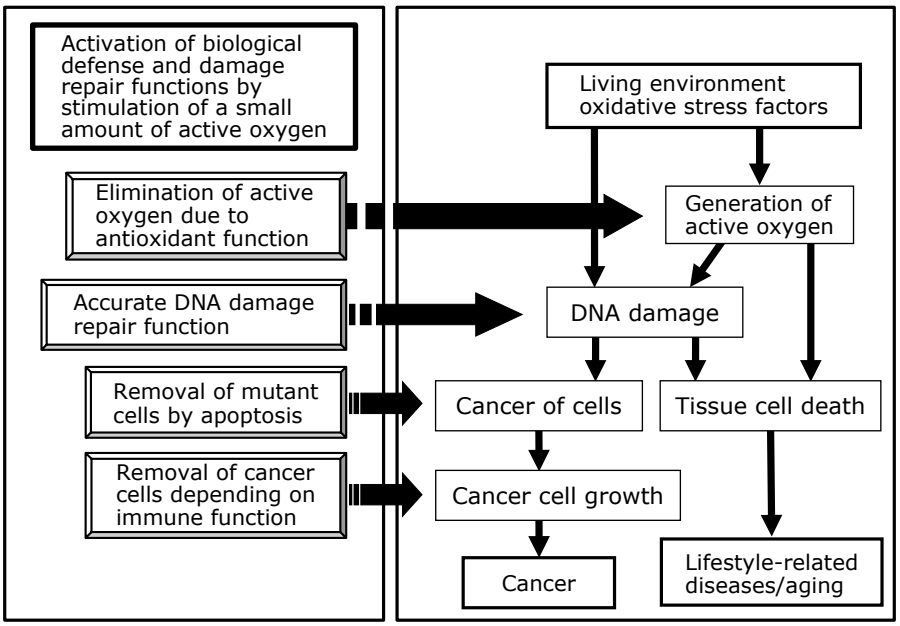

Fig. 1. Mechanism of disease suppression by radon therapy hypothesis: Example 1.

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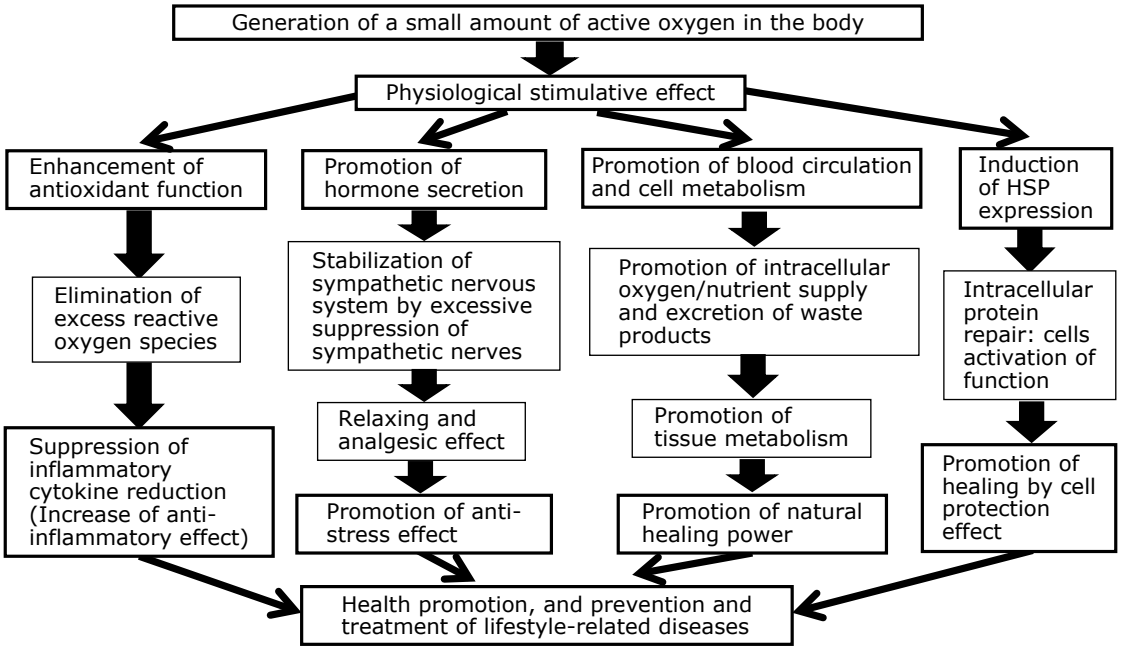

Fig. 2. Mechanism of disease suppression by radon therapy hypothesis: Example 2.

small intestine, and large intestine have high LPO levels but low antioxidant capacity.[27] These findings suggested that radon inhalation changes the oxidation status of the organ depending on factors like the total antioxidant capacity of the organ, radon concentration, and inhalation time.

Radon inhalation, which produces a small amount of reactive oxygen species in the body, induces and increases the levels of antioxidants, such as GSH, and the activities of antioxidant enzymes, such as SOD and catalase. This enhancement of antioxidant function is considered to be involved in the suppression of diseases derived from active oxygen by scavenging the excess active oxygen species and free radicals involved in the induction of diseases. We have also clarified that radon inhalation improves tissue circulation and has an anti-inflammatory effect.[2] Furthermore, no significant difference in radiosensitivity has been reported depending on the presence or absence of catalase in the body,[28] and it was found to be effective in maintaining the physiological function of liver grafts by refrigeration after low-dose X-ray irradiation.[29]

Reactive oxygen species are produced *in vivo* due to various environmental oxidative stresses; however, radiation including radon inhalation can also produce reactive oxygen species depending on the dose.[30] If the antioxidant functions are enhanced by a small amount of physiological stimulation associated with low-dose irradiation containing radon, good health may be promoted and maintained.[31,32] In this regard, we reported that the DNA damage in mouse organs due to excess reactive oxygen species was suppressed by radon inhalation.[33] On the other hand, it has been suggested that the amount of melanin-derived radicals in the skin may be an endogenous marker for the health effects of long-term low-dose irradiation.[34] In the future, it may be necessary to consider this method in order to confirm the safety of long-term use of radon therapy.

Unlike the case of high-dose irradiation, the health effect of radon inhalation may be due to the enhancement of bioadaptive response (biodefense) associated with the small amount of physiological stimulation specific to low-dose irradiation.[2]

Conclusion

Radon therapy has high potential in suppressing disorders and diseases caused by active oxygen. As a promising mechanism, hyperfunctions of immunomodulation and damage repair, promotion of anti-inflammatory action, blood circulation/cell metabolism, and hormone secretion, and induction of apoptosis and HSP may be conceivable due to enhancement of antioxidant function. Furthermore, new indications for radon therapy might occur accordingly.

A small amount of active oxygen generated from radon becomes a physiological stimulus that activates the biological defense system; when used in combination with radon inhalation, the amount of therapeutic drug used may be reduced, which eventually reduces side effects and related costs. In this way, the medical utilization of radon, which accounts for approximately half of the natural radiation, becomes meaningful; we recommend development of further research related to preventive medicine, which will eventually aid the super-aging society.

Author Contributions

KY, review concept and design, drafting of the manuscript; TK, drafting of the manuscript.

Abbreviations

ALP	alkaline phosphatase
ATM	ataxia telangiectasia mutated
CCl_4	carbon tetrachloride
GOT	glutamic oxaloacetic transaminase
GPT	glutamic pyruvic transaminase
GPx	glutathione peroxidase
HSP	heat shock protein
ICRP	International Commission on Radiological Protection
LPO	lipid peroxide
Mn-SOD	mitochondrial SOD
NE	noradrenaline

NF	nuclear factor
NIK	NF-κB-inducing kinase
NO	nitric oxide
SOD	superoxide dismutase
STZ	streptozotocin
t-GSH	total glutathione
TNF-α	tumor necrosis factor-α
XOD	xanthine oxidase

Conflict of Interest

No potential conflicts of interest were disclosed.

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