Volume 20, No 4 | International Journal of Radiation Research, October 2022

Treatment strategies for radiation-induced brain injury

Y. Zhang[1,2], G. Ou[1], Q. Li[1,2], S. Ma[2*], L. Du[1,2*]

[1]Department of Pharmaceutical Sciences, Beijing Institute of Radiation Medicine, Beijing 100850, China
[2]School of Medicine, Shandong University of Traditional Chinese Medicine, Jinan 250355, China

► ***Review article***

Corresponding authors:
Shan Ma and Du Lina, Ph.D.,
E-mail: *mashan76@sina.com, dulina@188.com*

Received: July 2021
Final revised: February 2022
Accepted: May 2022

Int. J. Radiat. Res., October 2022; 20(4): 727-736

DOI: 10.52547/ijrr.20.4.1

Keywords: *Radiation-induced brain injury (RIBI), conventional medicine, pathogenesis, hyperbaric oxygen (HBO), protective agents.*

ABSTRACT

Radiation-induced brain injury (RIBI) is a common complication in patients with head and neck tumors. RIBI usually occurs six months to three years after therapy and is often accompanied by cognitive dysfunction, epilepsy, and other neurological dysfunctions. In severe cases, RIBI can cause a wide range of cerebral edema and herniation. A systematic search was conducted through PubMed/Medline, EMBASE, and Cochrane library databases and articles with the keywords radiation-induced brain injury, pathogenesis and protective agents were collected. The commonly known pathogenesis of RIBI includes vascular injury, immune-inflammatory response, glial cell damage, and neuronal damage. Therapeutic agents, hyperbaric oxygen, surgery, and stem cells transplantation are the most common treatment for RIBI. Tamoxifen, curcumin, and quercetin can prevent glial cell activation, proliferation, and oxidative stress caused by irradiation. Over recent years, the RIBI remission rate has gradually increased; however, there are still no effective prevention and treatment methods. This review summarized recent progress in the treatment for RIBI, as well as the pathogenesis of RIBI, including vascular injury, glial cell injury, immune-inflammatory response, and neuronal damage.

INTRODUCTION

Radiotherapy is widely used to treat recurrent cancer, such as brain and breast carcinomas. Radiation exposure usually depends on the type of malignancy. Whole-brain radiotherapy (WBRT) is the treatment of choice for local recurrence after surgical resection of brain metastases. Yet, radiation to the brain may cause certain side effects. RIBI is a common complication caused by radiation treatment for head and neck tumors [1]. The longer the radiation exposure, the more malignant the disease. Acute injury and subsequent long-term damage often lead to multifocal hypometabolism and persistent neuroinflammation of the brain [2].

According to clinical symptoms, RIBI can be classified into three stages: an acute stage, an early delayed stage, and a late delayed stage [3,4]. Acute RIBI often occurs days or weeks after irradiation [5], mainly due to cerebral edema, increased intracranial pressure, and transient neurological impairment caused by increased blood-brain barrier (BBB) permeability. Its main clinical manifestations include headache, nausea, vomiting, increased body temperature, disturbance of consciousness, and convulsions, which are generally recoverable. Early delayed RIBI is usually a temporary and reversible white matter injury that occurs after a few weeks to 3 months after brain radiotherapy and is mainly characterized by demyelinating lesions of oligodendrocytes with axonal edema. Its clinical manifestations include lethargy, nausea, and irritability, which can usually be cured after active treatment during this period. Late delayed RIBI complicated with abnormal vascular changes and demyelination [6], and white matter necrosis often occurs 6 months after irradiation [7,8]; this stage is commonly irreversible and progressive (figure 1). According to the volume range of therapeutic radiation, late RIBI (3 months to several years) is accompanied by local nerve tissue abnormalities and increased intracranial pressure, and its diagnosis, which is based on the clinical manifestations alone, is difficult to establish. During this stage, low-density areas of white matter increase with irregular enhancement effects on the computed tomography (CT) images, accompanied by diffusing edema around the lesion and varying degrees of space-occupying effects [9]. Similar changes are shown on magnetic resonance imaging (MRI). Under MRI, RIBI is usually seen as peripheral enhancement accompanied by mild mass effect and peripheral edema. The important microscopic changes of RIBI include fibroid necrosis of vessels, coagulative necrosis, peripheral reactive gliosis, and vascular hyalinization with luminal stenosis [10]. The most obvious clinical features are personality changes, memory loss, decreased concentration, and dementia. The main

[DOI: 10.52547/ijrr.20.4.1]

manifestations among children are growth delay and mental retardation, which eventually lead to severe dementia.

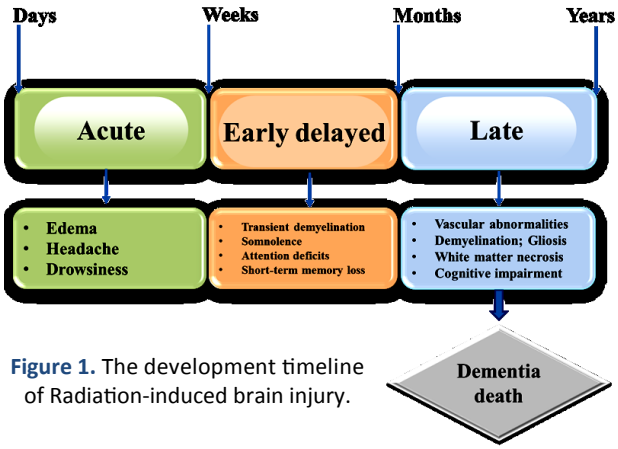


Figure 1. The development timeline of Radiation-induced brain injury.

Currently, the mechanism leading to RIBI is believed to involve vascular injury, glial cell injury, autoimmunity, inflammation, and nerve injury. The most conventional therapeutic protocols include steroid hormones, vasodilators, dehydrating agents, neuroprotective agents, hyperbaric oxygen therapy (HBO), and surgery.

In this review, we summarized recent progress in the treatment for RIBI (primarily focusing on the therapeutic agents) as well as the pathogenesis of RIBI, including vascular injury, glial cell injury, immune-inflammatory response, and neuronal damage. By exploring the mechanism and treatment options, we can seek more effective drugs to treat RIBI patients.

MATERIALS AND METHODS

A systematic search was conducted through PubMed/Medline, EMBASE, and Cochrane library databases about the articles with the keywords of radiation-induced brain injury, pathogenesis and protective agents.

RIBI pathogenesis

The current pathological changes of RIBI include vascular injury, immune-inflammatory response, and neuronal damage (figure 2).

Vascular injury

Radiation causes vascular tissue damage and affects oxygen diffusion between the brain and blood vessels. Also, the expression of hypoxia-inducible factor (HIF)-1α in the brain increases and then activates the astrocytes, which secrete the vascular endothelial growth factor (VEGF), thus promoting angiogenesis. These new blood vessels, which have high permeability, further promote the infiltration of surrounding tissue fluid and consequently lead to cerebral edema (figure 2b) [11]. Vascular injury is represented by loss of endothelial cells and increased blood vessel permeability, which would leads to late delayed RIBI [12]. Compared with healthy individuals, patients who undergo radiotherapy suffer from more plaque formation, hemodynamic abnormalities, and common thickening of intima-media thickness [13]. Some studies suggested that RIBI is a multifocal cerebrovascular injury manifested as perivascular edema and abnormal angiogenesis [14]. In a mouse model of RIBI, established using a single large dose of radiation, the number of vascular endothelial cells was significantly reduced in the early stage after irradiation [15]. The number of endothelial cells and density of blood vessels were found to decrease in a time- and dose-dependent manner [15, 16]. Previous studies have suggested that vascular endothelial cells lose collagen connectivity after radiation, which affects the smoothness of the endothelium, and even results in endothelial defects [17]. Moreover, radiation can also cause DNA damage. The p53-dependent apoptosis mechanism in the mitochondria and the death receptor pathways regulated by neuroamide often lead to the death of endothelial cells [18].

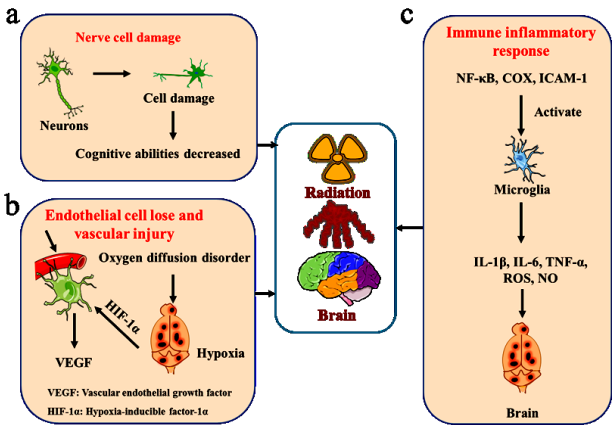


Figure 2. Illustration schemes of Radiation-induced brain injury.

Radiation induces an immune and inflammatory reaction in the brain

An inflammatory response occurs in the damaged tissues when the whole brain is irradiated. Nerve cells mainly include myelin-producing glial cells, astrocytes, and microglia. Microglia are important immune cells of the CNS [19]. In the healthy brain, healthy neurons express and secrete molecules (CD47, CD55, CD20, and CX3CL1), maintaining adjacent microglial cell stationery. Cerebral vascular endothelial cells are also in a quiescent state, allowing a continuous flow of blood lymphocytes (figure 3).

After radiation, neurons and microglia are directly affected (cellular damage and activation). Damaged neurons secrete pro-inflammatory cytokines activating microglia (figure 2c). The brain's immune and inflammatory responses may be activated in different ways, which are explained in the following paragraphs (figure 4).

[DOI: 10.52547/ijrr.20.4.1]

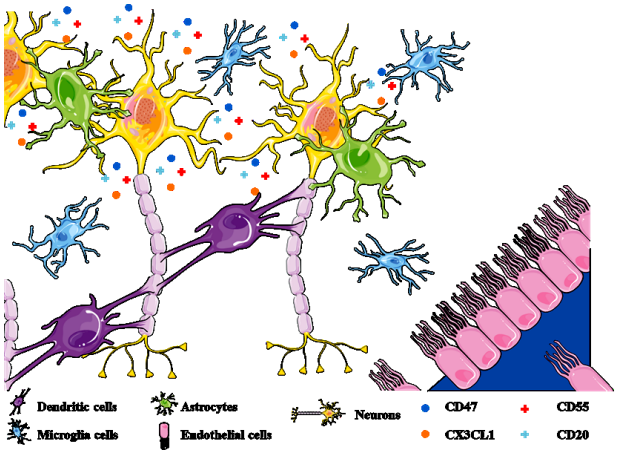


Figure 3. Cells in the healthy brain.

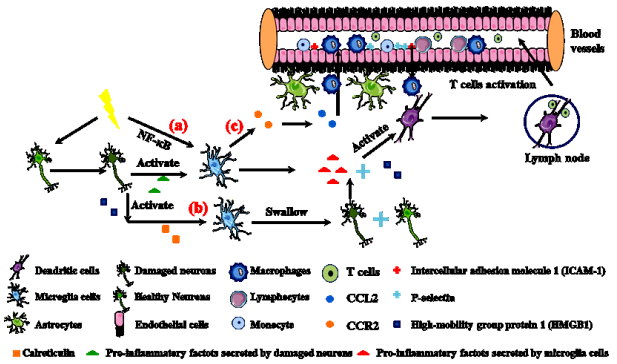


Figure 4. The immune and inflammatory reaction in brain induced by radiation.

Microglia are activated through the NF-κB pathway (figure 4a), which then activate MHC molecules. At the same time, microglial cells secrete pro-inflammatory cytokines (COX, IL1-β, IL-6, and TNF-α) [20, 21], chemokines (CX3, CL1, CCL3), which activate antigen-presenting cells (APCs) in the brain [22, 23].

Damaged neurons secrete the high-mobility group protein 1 (HMGB1), which then activates microglia that swallow damaged and healthy neurons (figure 4b). Moreover, pro-inflammatory signals emitted by microglia and HMGB1 activate dendritic cells, which migrate to regional lymph nodes due to increased BBB permeability and induce immune activation in the brain. The most commonly activated immune cells are regulatory T cells [24, 25], which produce IL-10 and TGF-β.

CCL2 could induce peripheral macrophages to express CCR2, which penetrate the BBB. Activated microglia also increase CCL2 and CCR2 expression (figure 4c). At the same time, radiation upregulates the adhesion markers (ICAM-1, P-selectin), which allows peripheral lymphocytes and monocytes to adhere to endothelial cells and migrate through the microvessel wall [26].

Immune and inflammatory reaction induced by radiation is a complicated process that involves various cellular components and the surrounding immune system [27]. The extent of radiation-induced injury, such as inflammation or immune response, is determined by the radiation type, dose, delivery method, and total cumulative dose [28].

Neuronal damage and cognition dysfunction

One of the severe outcomes in patients with fractionated partial brain irradiation is significant cognitive impairment at > 6 months after irradiation [29], which significantly affects the quality of patients' life. Cognitive deficits usually include a decrease in memory. Studies on memory of RIBI animals evaluated using Morris water maze [30-33] showed increased average escape latency and decreased number of crossing platforms compared to control animals, which suggested that the learning and memory ability of animals is decreased

It is well known that radiotherapy can prolong survival in patients with brain tumors; yet, previous studies have also suggested that 50 - 90% of adult patients with brain tumors usually present cognitive impairment (decreased memory ability (learn, verbal, and work) even dementia) after fractionated irradiation lasting six months [18,34]. Once the patient receives radiotherapy, the hippocampus and temporal lobes damage lead to a cognitive function decrease [35]. Therefore, selectively avoiding critical brain areas for irradiation may be essential to preserving cognitive function.

Damage to neurons is well known to cause reduced memory function. After brain inflammation, inducible NO synthase (iNOS) expressed in macrophages, neutrophils, and microglia increase NO levels in the brain. Radiation oxidizes water, which in turn produces hydroxyl radicals [36]. Hydroxyl radicals are also indirectly produced by forming secondary partial active oxygen, including superoxide, hydroxyl, and NO radicals (figure 2a and figure 5). Several reports suggested that free radicals lead to the loss of neurons [37]. Spatial memory and learning deficits have also been correlated with hippocampal neurons damaged [38-40]. Neurons are known to underlie endogenous synapses and control cognitive behavior. The impaired neuronal function can cause mental retardation, memory loss, dementia, and ataxia. *In vivo* and *in vitro* studies have shown that radiation induces changes in hippocampal cell activity, synaptic efficiency, synaptic production, and neuronal gene expression [3]. Yet, the acute effects of radiation on synaptic function on neurons are still not well understood.

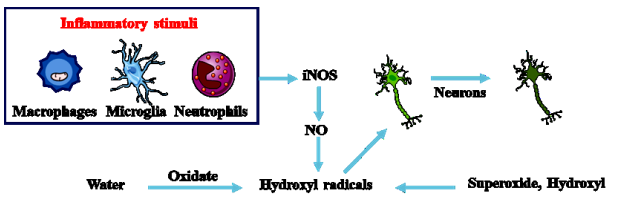


Figure 5. The relationship between apoptosis in hippocampal neurons and oxidative stress.

Therapeutic protocols of RIBI

The occurrence and extent of RIBI are related to

[DOI: 10.52547/ijrr.20.4.1]

the radiation dose, exposure volume range, age, time, physical condition, etc. Hyperbaric oxygen (HBO), glucocorticoids, nerve growth factor, bevacizumab, and craniotomy are common treatments used for RIBI. A craniotomy is a highly invasive and risky procedure that is usually only considered when extensive cerebral edema and space-occupation are detected. In addition to surgery, the therapeutic protocols of RIBI include the therapeutic agents, HBO, and stem cells transplantation. Therapeutic agents are those used to decrease apoptosis, inhibit immune responses, improve microcirculation, and eliminate reactive oxygen [41]. However, RIBI patients with increased intracranial pressure need long-term dependence on dehydrating agents and hormone maintenance therapy.

Therapeutic agents

Glucocorticoids (GC)

The main clinical manifestations of RIBI are increased intracranial pressure caused by cerebral edema and localized symptoms or signs caused by necrotic brain tissue. Moreover, an inflammatory response occurs in the damaged tissues when CNS is irradiated [42]. Dehydration combined with immunosuppressive agents (such as GC) is a common treatment for RIBI [43-45]. GC is a steroid hormone with strong immunosuppressive and anti-inflammatory that has an important role in regulating the immune system and is the endocrine basis of inflammatory diseases. GC binds to the GC receptor (GR) in the cytoplasm and then moves through the nuclear pore (NP) to the nucleus. The complex then binds to GC-responsive elements (GRE) and activates gene transcription (figure 6). The expression of anti-inflammatory proteins is then upregulated, and the expression of pro-inflammatory proteins in the cytosol is suppressed [46].

Some studies have found that GC could reduce the permeability of BBB in mouse vascular brain endothelial cells [47, 48]. However, this relief is temporary and cannot reverse or inhibit the clinical progress of RIBI, and its effective rate is only about 20% [49]. Long-term use of hormones can also cause complications, such as infection, ulcers, high blood pressure, osteoporosis, and muscle atrophy. There is still a controversy as to whether select a high-dose attack regimen or low dose maintenance.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody targeting VEGF, which has been used to treat RIBI by reducing vascular injury and permeability brain edema [50,51]. In addition, bevacizumab has a long half-life (approximately three weeks) [52, 53], and a good therapeutic effect for patients with RIBI with poor hormone effects [54]. Neuroimaging studies demonstrated that bevacizumab could alleviate brain radiation necrosis [55,56]. A recent study included 17 RIBI patients with head and neck tumors treated with bevacizumab. Except for one case that had no obvious therapeutic effect, the brain injury lesions of the other patients showed significant improvement in imaging [57]. The bevacizumab application after radiotherapy could significantly prolong the survival of RIBI patients, improve clinical effects and cognitive function, and finally reduce the RIBI incidence [58]. Yet, considering that necrotic brain tissue has no blood vessels, bevacizumab has been shown ineffective in RIBI patients with necrotic brain tissue [11].

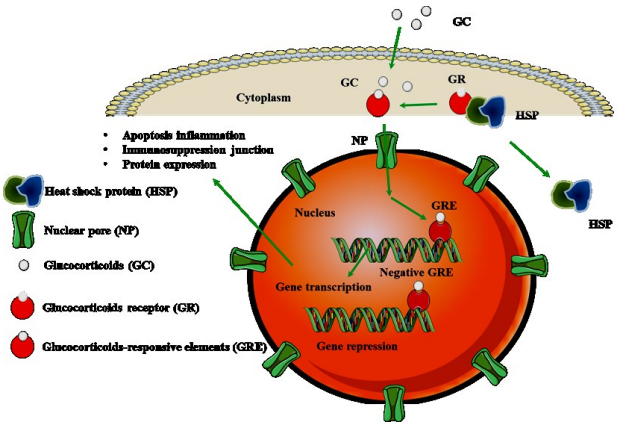


Figure 6. Mechanisms of glucocorticoid (GC) action.

Edaravone

There is a relationship between apoptosis in hippocampal neurons and oxidative stress. Edaravone, a new free radical scavenger, positively affects the pro-inflammatory response, nitric oxide production, and apoptotic cell death [59, 60]. The neurological symptoms of nasopharyngeal carcinoma were significantly improved after radiotherapy with edaravone treatment. The brain edema and brain necrosis volume of patients significantly decreased [61]. Recently, it has been found that cognitive dysfunction after brain radiation therapy may be related to hippocampal neurogenesis damage caused by oxidative stress. This damage is induced by proliferating neural stem cells (NSCs) or progenitor cells [62]. Edaravone can protect NSCs from cell death and restore differentiation after irradiation, while edaravone has no obvious protective effect on human brain tumor cells [63].

Cyclooxygenase-2 (COX-2) inhibitor

Cyclooxygenases are the main mediators of inflammation, which act by catalyzing the metabolism of arachidonic acid and prostaglandin synthesis [64, 65]. A previous study found that radiation induced an increase in the expression of COX-2 protein after brain irradiation in male C57/BL6 mice, as well as the increase in prostaglandin E(2) and thromboxane A(2) [66]. Furthermore, it showed that NS-398, a selective COX-2 inhibitor, could reduce prostaglandin induction and edema formation against RIBI. The production of prostaglandin E2, which is a COX-2 biological product, was reduced by 75% in irradiated

[DOI: 10.52547/ijrr.20.4.1]

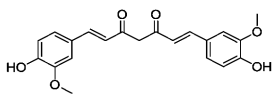
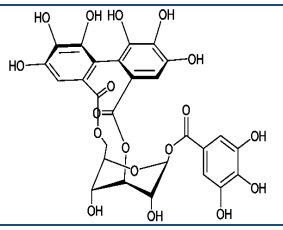
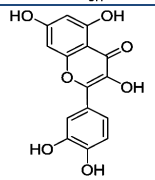
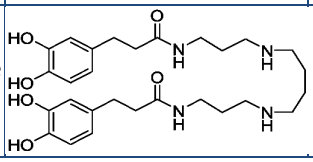
brains after giving meloxicam [67, 68]. Celecoxib is a paradigm-selective inhibitor of cyclooxygenase-2, which can reduce the damage of BBB and brain edema after radiotherapy. By inhibiting the expressions of NF-κB and vascular endothelial growth factors, the level of radiation inflammation and cerebrovascular damage could be alleviated [69].

Table 1. Commercial drugs for the treatment of RIBI.

Drugs	Company	Formulations	Mechanisms
Edaravone	Nanjing Xiansheng Dongyuan Pharmaceutical Co., Ltd.	Injection	Reduce cerebral edema [61]. Protect ischemic neurons [63] Promote the recovery of nerve function [63]
Bevacizumab	Qilu Pharmaceutical Co., Ltd.	Injection	Reduce cerebral edema [50,51] Reduce vascular injury [50,51]
Celecoxib	Pfizer Pharmaceuticals LLC	Capsules	Reduce the damage of brain edema and BBB [69]

Chinese medicine has also attracted much attention due to its advantages of multiple targets and low toxicity (table 2, https://m.chemicalbook.com/).

Table 2. Chinese medicine for the treatment of RIBI.

Main ingredients	Chemical formula	Mechanism of treating RIBI
Curcumin		Reduce cerebral edema [70] Neuroregeneration [71]
Corilagin		Enhance angiogenesis [72] Anti-inflammatory [73,74]
Quercetin		Anti-oxidation [75] Anti-inflammatory [76]
Kukoamine A		Neuroprotection [77] Anti-inflammation [78]

Curcumin

Curcumin is a natural ingredient in turmeric rhizomes with anti-oxidation, anti-inflammation, inhibition of angiogenesis, and antitumor properties. Curcumin can restrain NF-κB and iκB kinase, inhibiting proliferation and inducing cell apoptosis [79, 80]. It can also effectively reduce cerebral edema in rats with intracerebral hemorrhage by inhibiting the NF-κB pathway and subsequent aquaporin expression [70]. *In vitro* showed that curcumin can stimulate neurogenesis, synaptogenesis, and cell migration of brain-derived adult neural stem cells, thus could be used as a suitable drug candidate for radiation-induced neuropathic applications [71]. Curcumin could also significantly ameliorate the BBB damage in the brain to treat RIBI, which is mainly manifested in the decreased expression of glial fibrillary acidic protein and the increased expression of cyclic nucleotide 3' phosphohydrolase in the hippocampus [81].

Corilagin

Corilagin is a type of tannin family with anti-inflammatory activities that can enhance angiogenesis and reduce oxidative stress by regulating the Nrf2 signaling pathway against cerebral ischemic injury [72]. Another study showed that corilagin mitigated the cognitive impairment in RIBI mice and partially protected the BBB integrity from RIBI. Corilagin could inhibit the activation of microglia by the NF-κB pathway and reduce the expression of inflammatory cytokines against RIBI [73, 74].

Quercetin

Quercetin has strong antioxidant activity. Histopathological data showed that the degradation and infiltration of cells were significantly reduced with quercetin, which demonstrated its obvious neuroprotective effects [82]. The administration of quercetin before radiation could significantly increase the cytoskeletal protein Tuj1 and the neurotrophin brain-derived neurotrophic factor in the neuron, suggesting its neuroprotective effect on the brain against radiation-induced inflammatory responses [83]. Quercetin can also effectively protect oligodendrocyte precursor cells from radiation injury by oxygen-glucose deprivation *in vitro*, and this mechanism may be related to the activation of the phosphatidylinositol-3-kinase/alanine aminotransferase assay signaling pathway [75]. It could repair brain injury by inhibiting inflammation and apoptosis, thus promoting recovery of nerve function [76].

Kukoamine A

Kukoamine A (KuA) is a natural bioactive alkaloid found in wolfberry root bark, which has diverse therapeutic effects, including anti-oxidation, neuroprotection, and anti-inflammation. KuA can reduce malondialdehyde levels, increase glutathione and superoxide dismutase levels by regulating the expressions of caspase-3, cytochrome C, Bax, and Bcl2 catalase, and inhibit the apoptosis of neuron cells after whole-brain irradiation [77]. In addition, KuA can reduce the activation of hippocampal microglia in rats [78]. Therefore, KuA can serve as a neuroprotective agent on RIBI by inhibiting neuronal

[DOI: 10.52547/ijrr.20.4.1]

oxidative stress and cell apoptosis.

Other drugs

There are some other reported effective drugs for RIBI treatment. (1) Magnesium can exert protective effects against RIBI by reducing calcium overloading, improving oxidation-reduction, and inhibiting apoptosis [84]. In addition, it can significantly reduce the protein or mRNA levels of NF-κB and intercellular adhesion molecule-1 [85]. (2) Valproic acid can inhibit the generation of reactive oxygen species by regulating the nuclear factor erythroid-2-related factor 2/heme oxygenase-1, which may improve cognitive behavior following RIBI [86]. It could also improve the effectiveness of glioma radiotherapy by protecting normal hippocampal neurons [87]. (3) Tamoxifen is a selective estrogen receptor modulator approved by FDA for its diverse neuroprotective properties. It can regulate antioxidants, anti-inflammatory and anti-glial hyperplastic responses [88]. Tamoxifen can significantly reduce the activation of astrocytes and neuronal apoptosis after radiation therapy, which is conducive to the structural reconstruction and functional recovery of the brain [89]. (4) Chinese medicine Shenqi Fuzheng injection could effectively reduce RIBI by inhibiting the NF-κB signal pathway and microglial activation [90, 91]. Tanshinone IIA has also been found to restore RIBI by reducing apoptosis and brain edema [92]. *Acanthopanax senticosus* (AS) is a widely used Chinese herbal medicine rich in phenolic compounds with antioxidant and anti-inflammatory properties [93]. It can maintain the normal activity of the nervous system of rats by regulating various signaling pathways, which has a positive effect on the movement, fission, structure, adhesion, and phagocytosis of nerve cells [94, 95].

HBO

During HBO therapy, the patient inhales 100% oxygen at a pressure of at least 1.5 atmospheres absolute (150 kPa) [96]. HBO can be used as a radiosensitizer to enhance the effect of radiation or as a therapeutic agent to reduce delayed radiation damage [96-99]. It helps oxygen dissolve in plasma and reach the brain independent of hemoglobin. In addition, HBO could promote the formation of new blood vessels in areas where the partial pressure of oxygen is reduced due to vascular damage, which can restore radiation-induced damage.

Combined with HBO, radiotherapy can destroy tumor cells and control the growth of tumor cells and reduce the incidence of RIBI, as well as prolong the survival time [100, 101]. A clinical trial involving 505 patients with various cancers studied the effects of HBO on radiotherapy. Compared with patients only receiving radiotherapy, patients with cervical or bronchial cancer receiving maximum-dose radiotherapy and hyperbaric oxygen showed higher survival [102, 103].

HBO is a non-invasive treatment that promotes tissue repair and accelerates the recovery of the nervous system [104, 105]. Small retrospective studies have shown that the stability or improvement rate is higher in 70-80% of the patients receiving treatment [106-108]. Also, data from patients with symptomatic brain radiation necrosis treated with HBO between 2008 and 2018 showed that HBO could improve clinical and radiologic effects in most cases [109]. The prophylactic effect of HBO therapy for RIBI patients with brain metastasis was evaluated. The rate of white matter damage in the HBO group (2%) was lower than that in the non-HBO group (36%) [110].

Many patients receiving radiotherapy can reduce the dose of hormonal drugs during or after HBO therapy. Despite common complications, HBO is considered relatively safe with tolerable toxicity. Clinically, it is also often combined with other interventions (such as bevacizumab) to treat RIBI. Endostar® (a commercial recombinant human endostatin injection) combined with short-term HBO therapy reduces the necrosis area of the radiated brain with non-recurrence [111].

Stem cells transplantation

Stem cell transplantation is a promising treatment protocol for CNS damage. Stem cells are pluripotent cells that can differentiate into cells with different functions and structures. Mesenchymal stromal cells (MSCs) can potently alleviate radiation-induced fever by inhibiting activation of the related domain [112]. A combination of MSCs and nimodipine has a good therapeutic effect in RIBI mice, which was mainly reflected by improved exercise and cognitive ability, and decreased percentage of necrotic neurons and astrocytes in mice. Combination therapy with other methods is more effective than MSC alone. After receiving treatment, the expression of pro-apoptotic indicators (p53, Bax) and anti-apoptotic indicator Bcl -2 increases, thus protecting brain cells from further injury. The therapeutic effects of the combination of MSCs and nimodipine may be related to the inhibition of cell apoptosis and the promotion of mesenchymal stem cells to move to damaged brain sites [113].

In addition, stem cells powered by electric vehicles can effectively treat brain injuries, including cognitive deficits caused by radiation [114]. Adult stem cells can also restore cognitive function in mice with neurodegenerative diseases and brain damage by reducing oxidative stress and promoting hippocampal neurogenesis [115]. After neural stem cells were transplanted into the brain of rats exposed to radiation, the cognitive dysfunction of these rats was restored, and the defects of hippocampal function induced by radiation were improved, suggesting that stem cell transplantation is feasible for the treatment of RIBI [116].

It should be noted that there may be safety concerns about grafting foreign stem cells into the

[DOI: 10.52547/ijrr.20.4.1]

brain. Therefore, cell-free alternatives are necessary. Stem cell-derived extracellular vesicles are nano-sized lipid-bound vesicles that could easily pass through BBB [117]. They may be effective in treating RIBI, especially radiation-induced cognitive deficits.

DISCUSSION

Radiotherapy is an important treatment strategy for head and neck tumors. However, the related RIBI cannot be ignored. Many long-term studies have been conducted on the diagnosis, mechanism and treatment of RIBI. Yet, so far, no fully effective treatment method for RIBI has been developed, which is mainly attributed to the complexity of the CNS. Due to the complex structure of the brain and the indivisible human body, the mechanism that causes RIBI is not associated with a single factor. The above mechanisms may have a hierarchical relationship or different pathogenesis and vary from patient to patient. For RIBI, prevention may be more important than treatment due to the complicated injury mechanism. On the one hand, precise localized radiation and a detailed dose fractionation regimen are necessary [118-120]. On the other hand, efficient radiation protectants are needed to treat or prevent RIBI by eradicating free radicals, anti-inflammation or neuron restoration. Due to the complex damage mechanism of RIBI, traditional Chinese medicine may be more effective and superior to the treatment of RIBI than the use of single drugs due to its multiple targets.

Currently, the diagnosis of RIBI relies heavily on magnetic resonance imaging (MRI)[9, 121]. However, its diagnostic value is limited because white matter edema and demyelination commonly reveal diseases at a later stage. A radiodiagnosis approach can also help address microstructural changes in the temporal lobe that are not visible to human eyes, enabling precise prediction of RIBI, especially at early stages. Preclinical studies have shown that white matter lesions are the earliest form of radiation injury [122, 123]. The three radiodiagnosis models using T2-weighted images can help to better detect white matter lesions [121]. Contrast-enhanced T1-weighted images better indicate radiation-induced vascular changes. The combination of different MRI measures can therefore improve the predictive performance of RIBI. Recently, functional imaging techniques such as dynamic contrast enhancement (DCE), diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI) have been also used to provide functional and metabolic information [124-127].

In-vivo experiments are conductive and important to study the pathogenesis, intervention, and optimization of the treatment strategies for RIBI. Many novel protocols are confirmed to effectively treat RIBI in various animal models. Rats and mice remain the most commonly used RIBI models [128]. On this basis, neuronal regeneration, inflammatory mechanism, and glial cell function related to RIBI are evaluated, which is important to study the damage mechanism of RIBI. Nevertheless, the differences between rodents or cells and humans are substantial. Therefore, transforming RIBI treatment strategies from animal to clinical applications remains challenging. Preclinical studies can provide direction for the research on the pathogenesis of RIBI and provide reliable experimental, and theoretical support for the transformation from animal experiments to clinical experiments and applications. So, experiments are combined with actual clinical practice to find new targets or approaches for the treatment of RIBI.

CONCLUSION

Thanks to the advancements in radiotherapy technology, radiation-induced brain injury has been gradually decreased. The mechanisms causing RIBI may have a hierarchical relationship or different pathogenesis. Traditional Chinese prescriptions may be more powerful and superior for the efficient treatment of RIBI due to their multiple targets. The next study emphasis should be focused on neuronal regeneration, inflammatory mechanism, glial cell function and so on, which could provide new targets or applicable approaches for the valid treatment of RIBI.

ACKNOWLEDGMENT

None

***Conflicts of interest*:** Declared none.

***Funding*:** This work was supported by the Beijing Natural Science Foundation (7202147) and National Natural Science Foundation (82172186).

***Author's contribution*:** YZ: Searching for references and writing the manuscript; GO: Writing and revising; QL: Summarizing, writing and revising; SM: Design and editing; LD: Guidance and editing.

REFERENCES

1. Yu X, Li M, Zhu L, Li J, Zhang G, Fang R, Wu Z, Jin Y (2020) Amifostine -loaded armored dissolving microneedles for long-term prevention of ionizing radiation-induced injury. *Acta Biomater,* ***112****: 87-100.*
2. Kim JH, Brown SL, Jenrow KA, Ryu S (2008) Mechanisms of radiation -induced brain toxicity and implications for future clinical trials. *Journal of Neuro-oncology,* ***87****(3): 279-286.*
3. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD (2012) Radiation-induced brain injury: A review. *Frontiers Oncology,* ***2:*** *73.*
4. Greene-Schloesser D, Moore E, Robbins ME (2013) Molecular pathways: radiation-induced cognitive impairment. *Clinical Cancer Research,* ***19****(9):2294-2300.*
5. Robbins ME, Brunso-Bechtold JK, Peiffer AM, Tsien CI, Bailey JE, Marks LB (2012) Imaging radiation-induced normal tissue injury. *Radiation Resarch,* ***177****(4): 449-466.*

[DOI: 10.52547/ijrr.20.4.1]

6. Schultheiss TE, Stephens LC (1992) Invited review: permanent radiation myelopathy. *The British Journal of Radiology,* ***65****(777): 737-753.*
7. Tofilon PJ and Fike JR (2000) The radioresponse of the central nervous system: a dynamic process. *Radiation Research,* ***153****(4): 357-370.*
8. Sheline GE, Wara WM, Smith V (1980) Therapeutic irradiation and brain injury. *Int J Radiat Oncol Biol Phys,* ***6****(9): 1215-1228.*
9. Wang YX, King AD, Zhou H, Leung SF, Abrigo J, Chan YL, Hu CW, Yeung DK, Ahuja AT (2010) Evolution of radiation-induced brain injury: MR imaging-based study. *Radiology,* ***254****(1): 210-218.*
10. Yang J, Gao J, Han D, Li Q, Liao C, Li J, Wang R, Luo Y (2020) Hippocampal changes in inflammasomes, apoptosis, and MEMRI after radiation-induced brain injury in juvenile rats. *Radiation Oncology,* ***15****(1): 1-11.*
11. Zhuang H, Shi S, Yuan Z, Chang JY (2019) Bevacizumab treatment for radiation brain necrosis: mechanism, efficacy and issues. *Molecular Cancer,* ***18 (1):****21.*
12. Balentova S and Adamkov M (2015) Molecular, cellular and functional effects of radiation-induced brain injury: A review. *International Journal of Molecular Sciences,* ***16****(11): 27796-27815.*
13. Ye J, Rong X, Xiang Y, Xing Y, Tang Y (2012) A study of radiation-induced cerebral vascular injury in nasopharyngeal carcinoma patients with radiation-induced temporal lobe necrosis. *PLOS One,* ***7****(8): e42890.*
14. Andrews RN, Metheny-Barlow LJ, Peiffer AM, Hanbury DB, Tooze JA, Bourland JD, *et al.* (2017) Cerebrovascular remodeling and neuroinflammation is a late effect of radiation-induced brain injury in non-human primates. *Journal of Radiation Research,* ***187****(5): 599-611.*
15. Peña LA, Fuks Z, Kolesnick RN (2000) Radiation-induced apoptosis of endothelial cells in the murine central nervous system: protection by fibroblast growth factor and sphingomyelinase deficiency. *Cancer Research,* ***60****(2): 321-327.*
16. Brown WR, Blair RM, Moody DM, Thore CR, Ahmed S, Robbins ME, Wheeler KT (2007) Capillary loss precedes the cognitive impairment induced by fractionated whole-brain irradiation: apotential rat model of vascular dementia. *Journal of Neurology Science,* ***257****(1-2): 67–71.*
17. Yuan H, Gaber MW, McColgan T, Naimark MD, Kiani MF, Merchant TE (2003) Radiation-induced permeability and leukocyte adhesion in the rat blood-brain barrier: modulation with anti-ICAM -1 antibodies. *Brain Research,* ***969****(1-2): 59-69.*
18. Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ (2008) Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *Lancet Oncology,* ***9****(5): 453–461.*
19. Lewis CA, Manning J, Rossi F, Krieger C (2012) The Neuroinflammatory Response in ALS: The Roles of Microglia and T Cells. *Neurology Research International,* ***2012:*** *803701.*
20. Xue J, Dong JH, Huang GD, Qu XF, Wu G, Dong XR (2014) NF-κB signaling modulates radiationinduced microglial activation. *Oncology Reports,* ***31****(6): 2555-2560.*
21. Lee WH, Sonntag WE, Mitschelen M, Yan H, Lee YW (2010) Irradiation induces regionally specific alterations in pro-inflammatory environments in rat brain. *International Journal of Radiation Biology,* ***86****(2): 132-144.*
22. Gebicke-Haerter PJ (2001) Microglia in neurodegeneration: molecular aspects. *Microscopy Research and Technique,* ***54****(1): 47-58.*
23. Spleiss O, Appel K, Boddeke HW, Berger M, Gebicke-Haerter PJ (1998) Molecular biology of microglia cytokine and chemokine receptors and microglial activation. *Life Sciences,* ***62****(17-18): 1707-1710.*
24. O'Connor RA, Malpass KH, Anderton SM (2007) The inflamed central nervous system drives the activation and rapid proliferation of Foxp3+ regulatory T cells. *Journal of Immunology,* ***179****(2): 958-966.*
25. Zhang Z, Zhang ZY, Wu Y, Schluesener HJ (2012) Lesional accumulation of CD163+ macrophages/microglia in rat traumatic brain injury. *Brain Research,* ***1461:*** *102-110.*
26. Laman JD and Weller RO (2013) Drainage of cells and soluble antigen from the CNS to regional lymph nodes. *Journal of Neuroimmune Pharmacology,* ***8****(4): 840-856.*
27. Lumniczky K, Szatmári T, Sáfrány G (2017) Ionizing radiation-induced immune and inflammatory reactions in the brain. *Frontiers in Immunology,* ***8****: 517.*
28. McKelvey KJ, Hudson AL, Back M, Eade T, Diakos CI (2018) Radiation, inflammation and the immune response in cancer. *Mammalian Genome,* ***29****(11-12): 843-865.*
29. Sundgren PC, Cao Y (2009) Brain irradiation: effects on normal brain parenchyma and radiation injury. *Neuroimaging Clinics of North America,* ***19****(4): 657–668.*
30. Zhang L, Pang L, Zhu S, Ma J, Li R, Liu Y, Zhu L, Zhuang X, *et al.* (2020) Intranasal tetrandrine temperature-sensitive in situ hydrogels for the treatment of microwave-induced brain injury. *International Journal of Pharmaceutics,* ***583:****119384.*
31. Chen W, Li R, Zhu S, Ma J, Pang L, Ma B, Du L, Jin Y (2020) Nasal timosaponin BII dually sensitive in situ hydrogels for the prevention of Alzheimer's disease induced by lipopolysaccharides. *International Journal of Pharmaceutics,* ***578****: 119115.*
32. Ma J, Wang C, Sun Y, Pang L, Zhu S, Liu Y, Zhu L, Zhang S, Wang L, Du L (2020) Comparative study of oral and intranasal puerarin for prevention of brain injury induced by acute high-altitude hypoxia. *International Journal of Pharmaceutics,* ***591****: 120002.*
33. Zhu S, Zhang S, Pang L, Ou G, Zhu L, Ma J, Li R, Liu Y, Wang L, Wang L, Du L, Jin Y (2021) Effects of armodafinil nanocrystal nasal hydrogel on recovery of cognitive function in sleep-deprived rats. *International Journal of Pharmaceutics,* ***597****: 120343.*
34. Anderson VA, Godber T, Smibert E, Weiskop S, Ekert H (2000) Cognitive and academic outcome following cranial irradiation and chemotherapy in children: a longitudinal study. *British Journal of Cancer,* ***82(2)****: 255-262.*
35. Leyrer CM, Peiffer AM, Greene-Schloesser DM, Kearns WT, Hinson WH, *et al.* (2011) Normal tissue complication modeling of the brain: dose-volume histogram analysis of neurocognitive outcomes of two CCOP trials. *International Journal of Radiation Oncology, Biology, Physics,* ***81****: S184–S185.*
36. Riley PA (1994) Free radicals in biology: oxidative stress and the effects of ionizing radiation. *International Journal of Radiation Biology,* ***65****(1): 27-33.*
37. Poon HF, Calabrese V, Calvani M, Butterfield DA (2006) Proteomics analyses of specific protein oxidation and protein expression in aged rat brain and its modulation by L-acetylcarnitine: insights into the mechanisms of action of this proposed therapeutic agent for CNS disorders associated with oxidative stress. *Antioxid Redox Signal,* ***8****(3-4): 381-394.*
38. Ji S, Wu H, Ding X, Chen Q, Jin X, Yu J, Yang M (2020) Increased hippocampal TrkA expression ameliorates cranial radiationinduced neurogenesis impairment and cognitive deficit via PI3K/AKT signaling. *Oncology Reports,* ***44****(6): 2527-2536.*
39. Madsen TM, Kristjansen PE, Bolwig TG, Wörtwein G (2003) Arrested neuronal proliferation and impaired hippocampal function following fractionated brain irradiation in the adult rat. *Neuroscience,* ***119****(3): 635-642.*
40. Xiao H, Liu B, Chen Y, Zhang J (2016) Learning, memory and synaptic plasticity in hippocampus in rats exposed to sevoflurane. *International Journal of Developemental Neuroscience,* ***48****: 38-49.*
41. Alkis ME, Bilgin HM, Akpolat V, Dasdag S, Yegin K, Yavas MC, Akdag MZ (2019) Effect of 900-, 1800-, and 2100-MHz radiofrequency radiation on DNA and oxidative stress in brain. *Electromagnetic Biology and Medicine,* *1-16.*
42. Salvador E, Shityakov S, Förster C (2014) Glucocorticoids and endothelial cell barrier function. *Cell Tissue Research,* ***355****(3): 597-605.*
43. Straub RH, Cutolo M (2016) Glucocorticoids and chronic inflammation. *Rheumatology (Oxford),* ***55****(2): II6-II14.*
44. Ronchetti S, Migliorati G, Bruscoli S, Riccardi C (2018) Defining the role of glucocorticoids in inflammation. *Clinical Science,* ***132****(14): 1529-1543.*
45. Dixit KS, Kumthekar PU (2020) Optimal management of corticosteroids in patients with intracranial malignancies. *Current treatment options in oncology,* ***21****(9): 1-11.*
46. Rhen T, Cidlowski JA (2005) Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med,* ***353****(16): 1711-1723.*
47. Förster C, Silwedel C, Golenhofen N, Burek M, Kietz S, Mankertz J, Drenckhahn D (2005) Occludin as direct target for glucocorticoid-induced improvement of blood-brain barrier properties in a murine in vitro system. *The Journal of Physiology,* ***565(****Pt 2): 475-486.*
48. Förster C, Waschke J, Burek M, Leers J, Drenckhahn D (2006) Glucocorticoid effects on mouse microvascular endothelial barrier permeability are brain specific. *The Journal of Physiology,* ***573****(Pt 2): 413-425.*
49. Lam TC, Wong FC, Leung TW, Ng SH, Tung SY (2012) Clinical outcomes of 174 nasopharyngeal carcinoma patients with radiation-induced temporal lobe necrosis. *International of Journal Radiation Oncology, Biology, Physics,* ***82****(1): e57-e65.*
50. Matuschek C, Bolke E, Nawatny J, Hoffmann TK, Peiper M, Orth K, Gerber PA, Rusnak E, Lammering G, Budach W (2011) Bevacizumab

[DOI: 10.52547/ijrr.20.4.1]

as a treatment option for radiation-induced cerebral necrosis. *Strahlentherapie und Onkologie,* ***187****(2): 135-139.*
51. Alessandretti M, Buzaid AC, Brandao R, Brandao EP (2013) Low-dose bevacizumab is effective in radiation-induced necrosis. *Case Reports in Oncological Medicine,* ***6****(3): 598-601.*
52. Nonoguchi N, Miyatake S, Fukumoto M, Furuse M, Hiramatsu R, Kawabata S, *et al.* (2011) The distribution of vascular endothelial growth factor-producing cells in clinical radiation necrosis of the brain: pathological consideration of their potential roles. *Journal of Neuro-oncology,* ***105****(2): 423-431.*
53. Wang Y, Fei D, Vanderlaan M, Song A (2004) Biological activity of bevacizumab, a humanized anti-VEGF antibody in vitro. *Angiogenesis,* ***7****(4): 335-345.*
54. Benoit A, Ducray F, Cartalat-Carel S, Psimaras D, Ricard D, Honnorat J (2011) Favorable outcome with bevacizumab after poor outcome with steroids in a patient with temporal lobe and brainstem radiation necrosis. *Journal of Neurology,* ***258****(2): 328-329.*
55. Yonezawa S, Miwa K, Shinoda J, Nomura Y, Asano Y, Nakayama N, *et al.* (2014) Bevacizumab treatment leads to observable morphological and metabolic changes in brain radiation necrosis. *Journal of Neuro-oncology,* ***119****(1): 101-109.*
56. Sadraei NH, Dahiya S, Chao ST, Murphy ES, Osei-Boateng K, Xie H, Suh JH, *et al.* (2015) Treatment of cerebral radiation necrosis with bevacizumab: the Cleveland clinic experience. *American Journal of Clinical Oncology,* ***38****(3): 304-310.*
57. Wang Y, Pan L, Sheng X, Mao Y, Yao Y, Wang E, Zhang N, Dai J (2012) Reversal of cerebral radiation necrosis with bevacizumab treatment in 17 Chinese patients. *European Journal of Medicine Research,* ***17****(1): 25.*
58. Zhang F, Yuan T, Gao M (2019) Efficacy of chemoradiotherapy combined with bevacizumab in patients with nasopharyngeal carcinoma: A comparative study. *Journal of BUON,* ***24****(3):1252-1258.*
59. Bailly C (2019) Potential use of edaravone to reduce specific side effects of chemo-, radio- and immuno-therapy of cancers. *International Immunopharmacology,* ***77:*** *105967.*
60. Shakkour Z, Issa H, Ismail H, Ashekyan O, Habashy KJ, Nasrallah L, Jourdi H, *et al.* (2021) Drug repurposing: Promises of edaravone target drug in traumatic brain injury. *Current medicinal chemistry,* ***28****(12): 2369-2391.*
61. Tang Y, Rong X, Hu W, Li G, Yang X, Yang J, Xu P, Luo J (2014) Effect of edaravone on radiation-induced brain necrosis in patients with nasopharyngeal carcinoma after radiotherapy: a randomized controlled trial. *Journal of Neuro-oncology,* ***120****(2): 441-447.*
62. Joseph JA (1992) The putative role of free radicals in the loss of neuronal functioning in senescence. *Integrative Physiological Behavioral Science,* ***27****(3): 216-227.*
63. Ishii J, Natsume A, Wakabayashi T, Takeuchi H, Hasegawa H, Kim SU, Yoshida J (2007) The free-radical scavenger edaravone restores the differentiation of human neural precursor cells after radiation-induced oxidative stress. *Neuroscience Letters,* ***423****(3): 225-230.*
64. Ferrer MD, Busquets-Cortés C, Capó X, Tejada S, Tur JA, Pons A, Sureda A (2019) Cyclooxygenase-2 inhibitors as a therapeutic target in inflammatory diseases. *Current medicinal chemistry,* ***26*** *(18): 3225-3241.*
65. López DE and Ballaz SJ (2020) The role of brain cyclooxygenase-2 (Cox-2) beyond neuroinflammation: Neuronal homeostasis in memory and anxiety. *Molecular Neurobiology,* ***57****(12): 5167-5176.*
66. Moore AH, Olschowka JA, Williams JP, Paige SL, O'Banion MK (2004) Radiation-induced edema is dependent on cyclooxygenase 2 activity in mouse brain. *Radiation Research,* ***161****(2): 153-160.*
67. Han L and Ren Q (2014) Protective effect of meloxicam against acute radiation-induced brain injury in rats. *Chinese Journal of Cellular and Molecular Immunology,* ***30****(4): 375-378.*
68. Desmarais G, Charest G, Fortin D, Bujold R, Mathieu D, Paquette B (2015) Cyclooxygenase-2 inhibitor prevents radiation-enhanced infiltration of F98 glioma cells in brain of Fischer rat. *International Journal of Radiation Biology,* ***91****(8): 624-633.*
69. Jendrossek V (2013) Targeting apoptosis pathways by celecoxib in cancer. *Cancer Letters,* ***332****(2): 313-324.*
70. Wang BF, Cui ZW, Zhong ZH, Sun YH, Sun QF, Yang GY, Bian LG (2015) Curcumin attenuates brain edema in mice with intracerebral hemorrhage through inhibition of AQP4 and AQP9 expression. *Acta Pharmacologica Sinica,* ***36****(8): 939-948.*
71. Kim SJ, Son TG, Park HR, Park M, Kim MS, Kim HS, Chung HY, Mattson MP, Lee J (2008) Curcumin stimulates proliferation of embryonic neural progenitor cells and neurogenesis in the adult hippocampus. *The Journal of Biological Chemistry,* ***283****(21): 14497-14505.*
72. Ding Y, Ren D, Xu H, Liu W, Liu T, Li L, Li J, Li Y, Wen A (2017) Anti-oxidant and pro-angiogenic effects of corilagin in rat cerebral ischemia via Nrf2 activation. *Oncotarget,* ***8****(70): 4816-4828.*
73. Tong F, Zhang J, Liu L, Gao X, Cai Q, Wei C, Dong J, Hu Y, Wu G, Dong X (2016) Corilagin attenuates radiation-induced brain injury in mice. *Molecular Neurobiology,* ***53****(10): 6982-6996.*
74. Youn K, Lee S, Jeong WS, Ho CT, Jun M (2016) Protective role of corilagin on Aβ $_{25\text{-}35}$-induced neurotoxicity: Suppression of NF-κB signaling pathway. *Journal of Medicinal Food,* ***19****(10): 901-911.*
75. Thabet NM and Moustafa EM (2017) Protective effect of rutin against brain injury induced by acrylamide or gamma radiation: role of PI3K/AKT/GSK-3β/NRF-2 signalling pathway. *Archives of Physiology and Biochemistry,* ***124****(2): 185-193.*
76. Xu D, Hu MJ, Wang YQ, Cui YL (2019) Antioxidant Activities of Quercetin and Its Complexes for Medicinal Application. *Molecules,* ***24****(6): 1123.*
77. Zhang Y, Cheng Z, Wang C, Ma H, Meng W, Zhao Q (2016) Neuroprotective effects of kukoamine A against radiation-induced rat brain injury through inhibition of oxidative stress and neuronal apoptosis. *Neurochemical Research,* ***41****(10): 2549-2558.*
78. Zhang Y, Gao L, Cheng Z, Cai J, Niu Y, Meng W, Zhao Q (2017) Kukoamine A prevents radiation-induced neuroinflammation and preserves hippocampal neurogenesis in rats by inhibiting activation of NF-κB and AP-1. *Neurotoxicity Research,* ***31(2):*** *259-268.*
79. Shehzad A, Rehman G, Lee YS (2013) Curcumin in inflammatory diseases. *Biofactors,* ***39****(1): 69-77.*
80. Chiang IT, Liu YC, Hsu FT, Chien YC, Kao CH, Lin WJ, Chung JG, Hwang JJ (2014) Curcumin synergistically enhances the radiosensitivity of human oral squamous cell carcinoma via suppression of radiation-induced NF-kappaB activity. *Oncology Reports,* ***31****(4): 1729-1737.*
81. Hu N, Shi Y, Cheng X, Zhang Q, Shang H, Wang A, Li L, Liu Y (2018) Protective effect of cucurmin on behavior and blood brain barrier in rat model of radiation injured brain. *The Journal of Practical Medicine,* ***34****(10): 1628-1632.*
82. Kale A, Piskin O, Bas Y, Aydin BG, Can M, Elmas O, Buyukuysal C (2018) Neuroprotective effects of quercetin on radiation-induced brain injury in rats. *Journal of Radiation Research,* ***59****(4): 404-410.*
83. Chatterjee J, Langhnoja J, Pillai PP, Mustak MS (2019) Neuroprotective effect of quercetin against radiation-induced endoplasmic reticulum stress in neurons. *Journal of Biochemical and Molecular Toxicology,* ***33****(2): e22242.*
84. Shadman J, Sadeghian N, Moradi A, Bohlooli S, Panahpour H (2019) Magnesium sulfate protects blood–brain barrier integrity and reduces brain edema after acute ischemic stroke in rats. *Metabolic Brain Disease,* ***34****(4):1221-1229.*
85. Khalilzadeh M, Abdollahi A, Abdolahi F, Abdolghaffari AH, Dehpour AR, Jazaeri F (2018) Protective effects of magnesium sulfate against doxorubicin induced cardiotoxicity in rats. *Life Sciences,* ***207:*** *436-441.*
86. Liao G, Li R, Chen X, Zhang W, Du S, Yuan Y (2016) Sodium valproate prevents radiation-induced injury in hippocampal neurons via activation of the Nrf2/HO-1 pathway. *Neuroscience,* ***331:*** *40-51.*
87. Thotala D, Karvas RM, Engelbach JA, Garbow JR, Hallahan AN, DeWees TA, *et al.* (2015) Valproic acid enhances the efficacy of radiation therapy by protecting normal hippocampal neurons and sensitizing malignant glioblastoma cells. *Oncotarget,* ***6****(33): 3504-3522.*
88. Colón JM, Miranda JD (2016) Tamoxifen: an FDA approved drug with neuroprotective effects for spinal cord injury recovery. *Neural Regeneration Research,* ***11****(8): 1208-1211.*
89. Liu JL, Tian DS, Li ZW, Qu WS, Zhan Y, Xie MJ, Yu ZY, Wang W, Wu G (2010) Tamoxifen alleviates irradiation-induced brain injury by attenuating microglial inflammatory response in vitro and *in-vivo*. *Brain Research,* ***1316:*** *101-111.*
90. Zhang J, Tong F, Cai Q, Chen LJ, Dong JH, Wu G, Dong XR (2015) Shenqi fuzheng injection attenuates irradiation-induced brain injury in mice via inhibition of the NF-κB signaling pathway and microglial activation. *Acta Pharmacologica Sinica,* ***36****(11): 1288-1299.*
91. Chen LJ, Zhang RG, Yu DD, Wu G, Dong XR (2019) Shenqi Fuzheng injection ameliorates radiation-induced brain injury. *Current Medcine Science,* ***39****(6): 965-971.*
92. Dong X, Dong J, Zhang R, Fan L, Liu L, Wu G (2009) Anti-inflammatory erffects of tanshinone IIA on radiation-induced microglia BV-2 cells inflammatory response. *Cancer Biother Radiopharm,* ***24****(6) :681-687.*

[DOI: 10.52547/ijrr.20.4.1]

93. Huang L, Zhao H, Huang B, Zheng C, Peng W, Qin L (2011) *Acanthopanax senticosus*: review of botany, chemistry and pharmacology. *Die Pharmazie,* ***66****(2): 83-97.*
94. Zhou AY, Song BW, Fu CY, Baranenko DD, Wang EJ, Li FY, Lu GW (2018) *Acanthopanax senticosus* reduces brain injury in mice exposed to low linear energy transfer radiation. *Biomedicine & Pharmacotherapy,* ***99:*** *781-790.*
95. Zhou Y, Cheng C, Baranenko D, Wang J, Li Y, Lu W (2018) Effects of *Acanthopanax senticosus* on brain injury induced by simulated spatial radiation in mouse model based on pharmacokinetics and comparative proteomics. *International Journal of Molecular Science,* ***19****(1): 159.*
96. Mayer R, Hamilton-Farrell MR, van der Kleij AJ, Schmutz J, Granstrom G, *et al.* (2005) Hyperbaric oxygen and radiotherapy. *Strahlentherapie und Onkologie,* ***181****(2): 113-123.*
97. Pasquier D, Hoelscher T, Schmutz J, Dische S, Mathieu D, Baumann M, Lartigau E (2004) Hyperbaric oxygen therapy in the treatment of radio-induced lesions in normal tissues: a literature review. *Radiotherapy and Oncology,* ***72****(1): 1-13.*
98. Williamson RA (2007) An experimental study of the use of hyperbaric oxygen to reduce the side effects of radiation treatment for malignant disease. *International of Journal Oral and Maxillofac Surgery,* ***36****(6): 533-540.*
99. Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C (2012) Hyperbaric oxygen therapy for late radiation tissue injury. *The Cochrane Database Systermatic Reviews* ***(5):*** *CD005005.*
100. Bennett MH, Feldmeier J, Smee R, Milross C (2012) Hyperbaric oxygenation for tumour sensitisation to radiotherapy. *The Cochrane Database Systermatic Reviews* ***(4):*** *CD005007.*
101. Al-Waili NS, Butler GJ, Beale J, Hamilton RW, Lee BY, Lucas P (2005) Hyperbaric oxygen and malignancies: a potential role in radiotherapy, chemotherapy, tumor surgery and phototherapy. *Medicne Science Monitor,* ***11****(9): Ra279-Ra289.*
102. Cade IS, McEwen JB (1978) Clinical trials of radiotherapy in hyperbaric oxygen at Portsmouth, 1964--1976. *Clinical Radiology,* ***29****(3): 333-338.*
103. Watson ER, Halnan KE, Dische S, Saunders MI, Cade IS, McEwen JB, Wiernik G, *et al.* (1978) Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the cervix. *The British Journal of Radiology,* ***51****(611): 879-887.*
104. Feldmeier JJ and Hampson NB (2002) A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. *Undersea & Hyperbaric Medicine,* ***29****(1): 4-30.*
105. Chuba PJ, Aronin P, Bhambhani K, Eichenhorn M, Zamarano L, Cianci P, *et al.* (1997) Hyperbaric oxygen therapy for radiation-induced brain injury in children. *Cancer,* ***80****(10): 2005-2012.*
106. Wanebo JE, Kidd GA, King MC, Chung TS (2009) Hyperbaric oxygen therapy for treatment of adverse radiation effects after stereotactic radiosurgery of arteriovenous malformations: case report and review of literature. *Surgical Neurology,* ***72****(2): 162-168.*
107. Cihan YB, Uzun G, Yildiz S, Dönmez H (2009) Hyperbaric oxygen therapy for radiation-induced brain necrosis in a patient with primary central nervous system lymphoma. *Journal of Surgical Oncology,* ***100****(8): 732-735.*
108. Kohshi K, Imada H, Nomoto S, Yamaguchi R, Abe H, Yamamoto H (2003) Successful treatment of radiation-induced brain necrosis by hyperbaric oxygen therapy. *Journal of Neurological Sciences,* ***209****(1-2): 115-117.*
109. Co J, De Moraes MV, Katznelson R, Evans AW, Shultz D, Laperriere N, *et al.* (2019) Hyperbaric Oxygen for Radiation Necrosis of the Brain. *The Canidian Journal of Neurological Sciences, volume* ***(47):*** *92-99.*
110. Ohguri T, Imada H, Kohshi K, Kakeda S, Ohnari N, Morioka T, Nakano K, Konda N, Korogi Y (2007) Effect of prophylactic hyperbaric oxygen treatment for radiation-induced brain injury after stereotactic radiosurgery of brain metastases. *Int J Radiat Oncol Biol Phys,* ***67****(1): 248–255.*
111. Xing S, Fan Z, Shi L, Yang Z, Bai Y (2019) Successful treatment of brain radiation necrosis resulting from triple-negative breast cancer with Endostar and short-term hyperbaric oxygen therapy: A case report. *Onco Targets and Therapy,* ***12:*** *2729-2735.*
112. Liao H, Wang H, Rong X, Li E, Xu R-H, Peng Y (2017) Mesenchymal stem cells attenuate radiation-induced brain injury by inhibiting microglia pyroptosis. *Biomed Research International,* ***2017:*** *1948985.*
113. Wang G, Liu Y, Wu X, Lu Y, Liu J, Qin Y, Li T, Duan H (2016) Neuroprotective effects of human umbilical cord–derived mesenchymal stromal cells combined with nimodipine against radiation-induced brain injury through inhibition of apoptosis. *Cytotherapy,* ***18****(1): 53–64.*
114. Smith SM, Limoli CL (2017) Stem cell therapies for the resolution of radiation injury to the brain. *Current stem Cell Reports,* ***3****(4): 342-347.*
115. Spurlock MS, Ahmed AI, Rivera KN, Yokobori S, Lee SW, Sam PN, Shear DA, Hefferan MP, Hazel TG, Johe KK, Gajavelli S, Tortella FC, Bullock RM (2017) Amelioration of Penetrating Ballistic-Like Brain Injury Induced Cognitive Deficits after Neuronal Differentiation of Transplanted Human Neural Stem Cells. *Journal of Neurotrauma,* ***34****(11): 1981-1995.*
116. Acharya MM, Christie LA, Hazel TG, Johe KK, Limoli CL (2014) Transplantation of human fetal-derived neural stem cells improves cognitive function following cranial irradiation. *Cell Transplant,* ***23****(10): 1255-1266.*
117. Leavitt RJ, Limoli CL, Baulch JE (2019) miRNA-based therapeutic potential of stem cell-derived extracellular vesicles: a safe cell-free treatment to ameliorate radiation-induced brain injury. *International Journal of Radiation Biology,* ***95****(4): 427-435.*
118. Li Y, Huang X, Jiang J, Hu W, Hu J, Cai J, Rong X, Cheng J, Xu Y, Wu R, Luo J, Tang Y (2018) Clinical Variables for Prediction of the Therapeutic Effects of Bevacizumab Monotherapy in Nasopharyngeal Carcinoma Patients With Radiation-Induced Brain Necrosis. *Int J Radiat Oncol Biol Phys,* ***100****(3): 621-629.*
119. Na A, Haghigi N, Drummond KJ (2014) Cerebral radiation necrosis. *Asia-Pacific Journal of Clinical Oncology,* ***10****(1): 11-21.*
120. Smart D (2017) Radiation Toxicity in the Central Nervous System: Mechanisms and Strategies for Injury Reduction. *Seminars in Radiation Oncology,* ***27****(4): 332-339.*
121. Chan YL, Leung SF, King AD, Choi PH, Metreweli C (1999) Late radiation injury to the temporal lobes: morphologic evaluation at MR imaging. *Radiology,* ***213****(3): 800-807.*
122. Kennedy AS, Archambeau JO, Archambeau MH, Holshouser B, Thompson J, *et al.* (1995) Magnetic resonance imaging as a monitor of changes in the irradiated rat brain. An aid in determining the time course of events in a histologic study. *Investigative Radiology,* ***30****(4): 214-220.*
123. Rabinov JD, Brisman JL, Cole AJ, Lee PL, Bussiere MR, Chapman PH, *et al.* (2004) MRI changes in the rat hippocampus following proton radiosurgery. *Stereotactic Functional Neurosurgery,* ***82*** *(4): 156-164.*
124. Xiong WF, Qiu SJ, Wang HZ, Lv XF (2013) 1H-MR spectroscopy and diffusion tensor imaging of normal-appearing temporal white matter in patients with nasopharyngeal carcinoma after irradiation: initial experience. *Journal of Magnetic Resonance Imaging: JMRI,* ***37****(1): 101-108.*
125. Chapman CH, Nagesh V, Sundgren PC, Buchtel H, Chenevert TL, Junck L, *et al.* (2012) Diffusion tensor imaging of normal-appearing white matter as biomarker for radiation-induced late delayed cognitive decline. *International Journal of Radiation Oncololy, Biology, Physics,* ***82****(5): 2033-2040.*
126. Chan YL, Yeung DK, Leung SF, Chan PN (2003) Diffusion-weighted magnetic resonance imaging in radiation-induced cerebral necrosis. Apparent diffusion coefficient in lesion components. *Journal of Computer Assisted Tomography,* ***27****(5): 674-680.*
127. Wang HZ, Qiu SJ, Lv XF, Wang YY, Liang Y, Xiong WF, Ouyang ZB (2012) Diffusion tensor imaging and 1H-MRS study on radiation-induced brain injury after nasopharyngeal carcinoma radiotherapy. *Clinical Radiology,* ***67****(4): 340-345.*
128. Yang L, Yang J, Li G, Li Y, Wu R, Cheng J, Tang Y (2017) Pathophysiological responses in rat and mouse models of radiation-induced brain injury. *Molecular Neurobiology,* ***54****(2): 1022-1032.*

[DOI: 10.52547/ijrr.20.4.1]