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Review Article

Radioprotective effect and other biological benefits associated with flavonoids

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Abstract

Ionizing radiation has the potential to cause extensive damage to living organisms. It can directly act on DNA, proteins and lipids, resulting in ionizing excitation and chemical bond cleavage, which can lead to molecular and cellular damage. Ionizing radiation can hydrolyze water molecules in the body, resulting in increased numbers of free radicals with strong oxidation ability. This process indirectly leads to tissue degeneration and necrosis, which can possibly result in cancer. In this paper, the intervention mechanism of flavonoids on ionizing radiation was analyzed. It has been revealed that the intervention mechanism associated with flavonoids may offer protective properties for DNA, prevent scavenging free radicals, and protect against auto-immune damage. In addition, this invention mechanism can protect the hematopoietic system and reduce inflammation

Keywords: *Ionizing radiation, Flavonoids, Radioprotective mechanisms, Molecular and cellular damage, DNA, Hematopoietic system, Inflammation*

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INTRODUCTION

In recent years, with the development of modern science and technology, ionizing radiation technology has been used extensively in several fields including military, medicine, agriculture and industry. As a result, humans are being exposed to greater levels of ionizing radiation than ever before [1,2]. Radiation causes excess production of free radicals in the human body. Free radicals play a significant role in the human body because they can induce damage to cell structure, damage to DNA, protein oxidation, and lipid peroxidation [3-5]. These harmful effects can lead to the dysfunction of hematopoietic and immune systems, accelerate the aging process, and promote degenerative pathological changes [6,7].

Consequently, there is increased importance in the field of radiation protection in the field of radiation therapy. In the early 1920s, the activity of flavonoids was uncovered. Flavonoids were found to offer several benefits including radiation resistance, reducing inflammation, and slowing the anti-aging process. Currently, studies are focusing on the mechanisms of flavonoids separation and radiation protection. Therefore, it is necessary to analyze the radiation protection mechanism associated with flavonoids.

Flavonoids are polyphenol compounds with 2-phenylchromone as the mother nucleus. These compounds most often exist in the free state or in the presence of sugar [8]. Two phenolic hydroxyl benzene rings (A ring and B ring) are connected into a C6-C3-C6 compound by the central three carbon atoms. The structure is shown in the

Figure 1. Flavonoids are widely distributed in the plant stems, leaves, and fruits, and generally exist in the plant secondary metabolism.

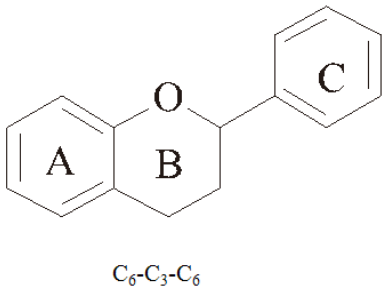

Figure 1: Flavonoid compounds nuclear structure

Classification of flavonoids

Flavonoids are classified according to the chemical properties of the carbon ring and the number and distribution of phenolic hydroxyl groups. Currently, flavonoids can be classified in over 10 different categories. [9,10].

DAMAGE DUE TO IONIZING RADIATION

Ionizing radiation naturally occurs in several different forms including X-ray, alpha, beta, gamma, and neutrons [11]. The effects of ionizing radiation on the human body may result in a series of complex biochemical changes [12]. Consequently, these changes can lead to several harmful biological effects on the body, resulting in injury or necrosis of the organization [13].

Studies have shown that [14] damage to the human body caused by ionizing radiation can occur through direct and indirect methods (Figure 2). The direct damage of the ionizing radiation occurs when various biological macromolecules in the living organism physically come into contact with ionizing radiation, therefore, directly leading to acute radiation injury. The primary method of indirect radiation damage is caused by free radicals which are derived from water molecules in the irradiated body. Ionizing radiation stimulates the organism to produce strong oxidizing free radicals such as ·OH, $\cdot O^{2-}$, H_2O_2 and NO. These free radicals can interact with the body's biological macromolecules, causing significant changes in the structure and function of the biological macromolecules, resulting in serious radiation damage [15,16].

In general, [17] the main injuries caused by ionizing radiation are DNA damage, immune system damage, and injury of the hematopoietic system. Ionizing radiation can cause DNA damage, resulting in the loss of cell information and degradation of normal cell function which progresses until the cell ultimately dies. Studies have shown that the immune system and hematopoietic system are highly sensitive to radiation. With regards to the immune system, ionizing radiation damage may lead to a reduction in immune cells, decreased immune function, and a reduction in specific and non-specific immunity within the human body. With regards to the hematopoietic system, in addition to reducing the number of blood cells, ionizing radiation can also lead to suppression of bone marrow microcirculation [18].

RADIOPROTECTIVE MECHANISMS OF FLAVONOIDS

Natural radioprotection refers to the non-toxic or low-toxic compounds isolated from natural products, which can be used before or after exposure to ionizing radiation to reduce the damage of radiation exposure.

Flavonoids offer several beneficial properties, such as anti-radiation, anti-free radical, antioxidant, antibacterial, antiviral, anticancer, and cancer prevention. In mice, flavonoids have been proven to significantly increase the radiation 30-day survival rate and reduce cell apoptosis and necrosis induced by ionizing radiation [19-21]. The radio-protective mechanisms of flavonoids primarily offer the following benefits: the protection of DNA, antioxidant, immune system protection, hematopoietic system protection, and inflammation reduction.

Reducing DNA damage and genotoxicity

DNA is the primary target of ionizing radiation damage. DNA damage secondary to exposure to ionizing radiation can result in many harmful effects to the human body. Consequently, reducing the harmful effects of ionizing radiation to DNA is one of the important issues in radio-protective research.

Gandhi [22] used alkaline comet assay technology to investigate the radio-protective effects of bailcalein on DNA damage in irradiated mice. The study found that administration of baicalein, prior to the whole-body exposure to radiation, offered protection against DNA damage. This protection was measured in the blood cells of irradiated mice by alkaline comet assay. The reduced damage in the bone marrow was measured by micronucleus assay.

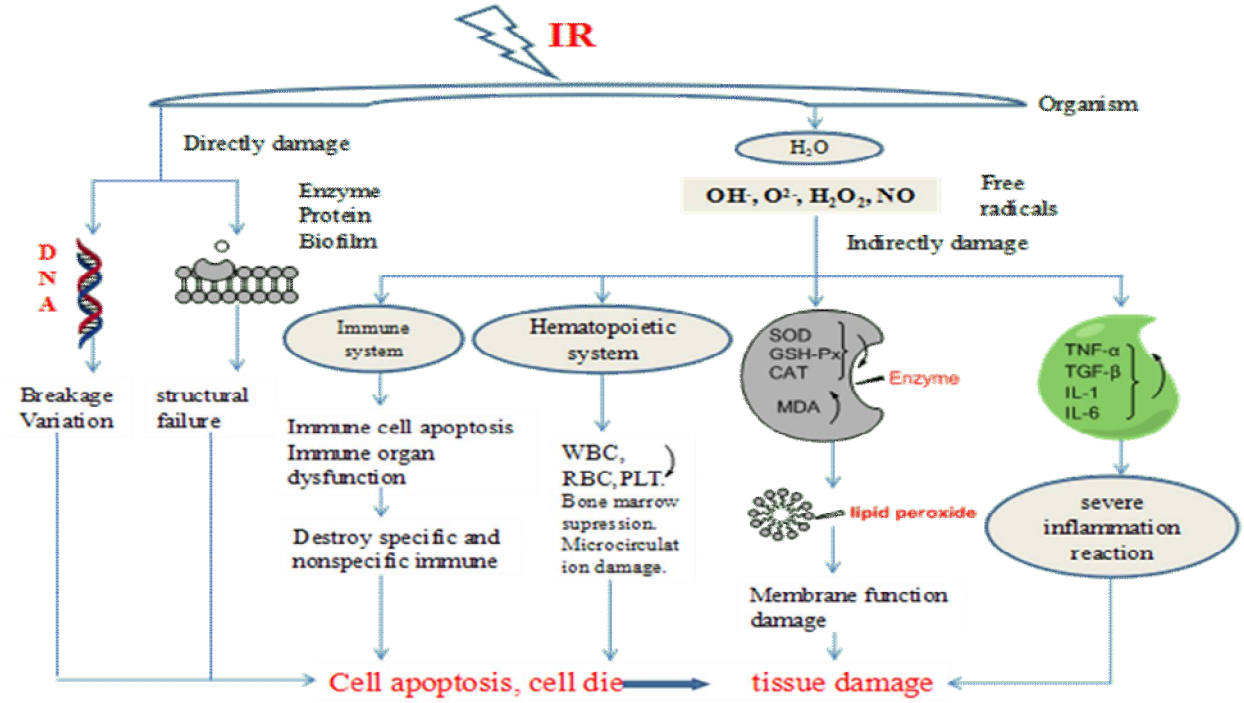

Figure 2: Radiation damage in the body. The mainly direct damage made by the ionizing radiation is directly attack all sorts of biological macromolecules in organisms, such as DNA, protein and phospholipid. Ionizing radiation can cause DNA damage leading to cell information barriers and loss of normal function, until they die. Exposure to ionizing radiation promotes the production of ·OH, $\cdot O^{2-}$, H_2O_2 and NO free radiation as a result to water hydrolysis. These free radicals can result in disorders of the immune system and hematopoietic system, membrane function damage, and excessive inflammation leading to tissue damage and cell death

The radiation protection of silibilin was studied in cell and animal experiments. When cells were exposed to 3 Gy radiation, silibinin was proven to reduce the DNA damage and micronuclei formation in lymphocytes. At the same time, oral administration of silibinin to mice prior to whole-body-γ-exposure (7.5 Gy) resulted in significant protection for radiation-induced mortality and DNA damage in blood leukocytes. The study indicated that silibinin had a strong potential to prevent radiation-induced DNA damage *in vitro* and *in vivo* [23]. Rithidech *et al* [24] used the cytokinesis-block micronucleus (CBMN) assay to evaluate the radiation protection mechanisms of apigenin. The data showed that apigenin has the radio-protective effect on radiation induced chromosome damage in human lymphocyte cells. Otherwise stated, in a dose dependent manner, apigenin significantly reduces the rate of micronucleus formation.

Xu Ping *et al* [25] investigated the protective effects of an extract from Guipi Pill against radiation-induced damage. The extract of water extraction-alcohol precipitation (WAP) from Guipi Pill was administered orally to the mice for 6 days prior to whole body radiation (8 Gy). The experiment found that the pretreatment prior to irradiation with WAP resulted in a significantly higher 30-day survival rate of mice after exposure to a potentially lethal dose of 8-Gy radiation. It has been proven that WAP significantly increases the total white body cell count and DNA content of bone marrow. WAP was also found to be beneficial for increasing the activity of various antioxidant enzymes in liver tissue of mice. In the presence of WAP, malondialdehyde levels and bone marrow micronucleus rate decreased significantly, compared with 6 Gy irradiation group.

In addition, ocimum flavonoids, narigin, procyanidins, hesperidin, propolis flavonoids, and gentianella austriaca flavonoids could also effectively reduce the genetic toxicity which was induced by radiation, and protect DNA from radiation damage [26-31].

Scavenging free radicals and antioxidant effect

Ionizing radiation can stimulate an increase in body moisture to produce a large number of free radicals. Excessive free radicals can decrease SOD, GSH-Px and CAT activities in vivo, resulting in lipid peroxidation, which has the

potential to cause significant damage to cell membranes of high lipid content. Flavonoids have the ability to effectively remove the oxygen free radicals and eliminate the indirect effects of radiation on the human body, thereby, eliminating the radiation damage *in vivo*.

Antioxidant capacity of total flavonoids of hops was studied *in vitro*, which showed that flavonoids from hops had an effective anti-oxygenation [32]. Flavonoids of hops could enhance the activities of SOD, GSH-Px and CAT, and reduce the content of MDA in irradiated mice. At the same time, it can improve the number of peripheral blood leukocytes, reduce the number of scavenging free radicals *in vivo*, and offer a protective effect on immune system in irradiated mice. These data indicated that the flavonoids of hops had valuable radio-protective activity *in vivo*, and the mechanism may be related to the antioxidant activity of flavonoids and modulation of the immune system.

Di [33] investigated the anti-oxidative and protective effect of quercetin, polydatin, and genistein on HaCaT cells injured by UVB radiation. The results showed that each of these compounds had the ability to rid the body of DPPH and ·OH free radicals. The scavenging ability of these compounds was as follow: genistein < polydatin < quercetin. These drugs were applied to act on HaCaT cells and compared with those treated by UVB irradiation only. The activity of SOD in HaCaT cells was increased ($p < 0.05$) and accompanied by a decrease of TNF-α and MDA level ($p < 0.05$). Those three drugs could inhibit UVB irradiation-induced HaCaT cell damage. Yu Jin [34] reported that when PC12 cells were incubated with different concentrations of breviscapine for a period of 2 h prior to being irradiated by 4 Gy X-rays, a significant decrease could be observed in the level of ROS and MDA. In addition, a significant increase could be observed in function of SOD and T-AOC in PC12 cells, when compared with the irradiation only.

Breviscapine has been proven to effectively remove free radicals induced by radiation, reduce lipid peroxidation, and increase total antioxidant capacity within cells to play the role of radiation protective agent. Ping *et al* [35] investigated the radio-protective effects of amentoflavone by examining cell viability, apoptosis, relative contents of intracellular ROS, and relative mitochondrial mass by flow cytometry after 60Co irradiation. Pretreatment with amentoflavone for a period of 24 h prior to 8 Gy 60Co γ-ray irradiation significantly inhibited apoptosis, promoted the G2 phase, and decreased the concentration of ROS and mitochondrial mass. These results collectively indicate that amentoflavone is an effective radio-protective agent.

In addition, hawthorn [36], mimosa, citrus [37] and Chinese wolfberry [38] containing flavonoids also have the ability of removing various free radicals, thus exhibiting significant antioxidant activity.

Immune system protection

The immune system is an extremely sensitive system in terms of radiation damage. Exposure to ionizing radiation could result in immune function disorders. Exposure to high levels of ionizing radiation can cause failure of the immune system and even death due to decreasing the number of immune cells. Ionizing radiation also has the ability to cause a disorder in antibody formation and cytokine network adjustment [39].

Isoflavones are an important class of flavonoids. These flavonoids primarily exist in leguminous plants and offer many benefits such as anti-cancer, anti-aging, anti-oxidation, regulating cell gene expression, inhibiting apoptosis, and regulating immune function. The immune function of mice treated with 4 Gy radiation, was decreased significantly, especially in thymus and spleen through experimental animal model [40].

The group which added soybean isoflavones showed obvious improvement in the index of the thymus and spleen in mice, reduction of apoptosis of the thymus and spleen cells, reduction in the percentage phase of G0-G1, an increase in the percentage phase of G2-M in irradiated thymus and spleen cells, an increase in the cell proliferation index, and an acceleration of cellular renewal. At the same time, the group that added soybean isoflavones showed a significant increase in macrophage phagocytosis, serum hemolysin level, auricle swelling rate and immune globulin IgA, IgG, IgM levels. These levels were significantly higher than the radiation control group. This indicated that soybean isoflavone had certain protective effect on the immune function of irradiated mice, especially in reducing the radiation injury in the thymus and spleen lymphocytes [41,42].

Tong [43] has found that when mice were pretreated with tartary buckwheat flavonoids (TBF) prior to radiation, TBF could increase the spleen index, thymus index, reduce spleen cells apoptosis, alleviate the disorder of spleen T cells and peripheral blood T cell subsets, and promote peripheral blood WBC recovery in 4.0 Gy γ - ray irradiated mice. These results indicate that tartary buckwheat flavonoid offer radio-protective mechanisms on the hematopoietic system and immune system.

Studies have shown that flavonoids, such as hesperidin [44-47], apigenin [48,49], quercetin [50-52] and rutin [53-55] could significantly promote lymphocyte proliferation and cytokine secretion, reduce the injury of peripheral blood lymphocytes, and have a significant protective effect on the immune system.

Hematopoietic system protection

The hematopoietic system is highly sensitive to ionizing radiation. Ionizing radiation targets all types of hematopoietic stem cells and proliferation cells. Therefore, the protection of the hematopoietic system is an important factor to prevent the radiation damage. Experimental research shows that flavonoids can protect hematopoietic organs from radiation damage, and promote the recovery of the hematopoietic system to improve the body's ability to resist radiation damage.

Lin *et al* [56] treated irradiated mice with the flavonoids of Astragali complanali (FAC). The results of this study found that FAC could increase the number of white blood cells, red blood cells, platelets, and hemoglobin in peripheral blood of irradiated mice. It was also shown that FAC has the ability to improve the 21-day survival rate of irradiated mice, and prolong the survival time of mice exposed to ionizing radiation.

Benkovic [57,58] used white blood cell count and comet assay to study the injury of white blood cells in irradiated mice. These studies found that quercetin, water-soluble derivate of propolis (WSDP), and ethanol extract of propolis (EEP), all of which contain a large number of flavonoids, could significantly increase the number of white blood cells in irradiated mice and decrease the damage of leukocyte DNA. Zhou *et al* [59] found that mice that were pre-treated with genistein before radiation could promote the mice hematopoietic system and increase the survival rate. In addition, genistein also stimulated the recovery of leukocytes, erythrocytes, lymphocytes, and thrombocytes in irradiated mice. At the same time, pre-treatment with genistein could increase the formation of granulocyte colony stimulating factors in irradiated mice and promote the regeneration of the hematopoietic stem cells. In experimental mice, Ping *et al* [60] found that administration of troxerutin before irradiation provided a higher survival rate, improvement of biochemical parameters, and preserved major histological parameters of the liver. These results collectively indicate that troxerutin is an effective radio-protective agent.

Wenxiu *et al* [61] used a nanoparticle suspension of genistein, instead of genistein dissolved in water, to evaluate the radio-protective effect on survival and hematopoietic recovery in mice exposed to total-body gamma radiation. Genstein nanosuspension resulted in a 30-day survival rate of 95 % compared to 25 % in vehicle-treated animals, increased mouse bone marrow cellularity from approximately 2.9 % (vehicle treated) to 28.3 % on day 7 of post-irradiation, decreased hematopoietic stem and progenitor cell death from 77 to 43.9 %, and attenuated the radiation-induced elevation of pro-inflammatory factors interleukin 1 beta (IL-1β), IL-6 and cyclooxygenase-2 (COX-2) in mouse bone marrow and spleen, which may assist in the protection of the hematopoietic system and prevent pro-inflammatory factors activation.

Reduction in inflammation

Exposure to large amounts of ionizing radiation could result in a severe inflammation reaction. Inflammatory cytokines could be applied to tissues and organs of each part of the body, causing damage to tissue cells and causing degeneration and necrosis in tissue cells. This type of damage most commonly occurs in the lungs and kidneys.

In mice, Hillman *et al* [62] investigated the role of soy isoflavones in the radiation protection of lung tissue. Histological examination of irradiated lungs revealed a chronic inflammatory infiltration involving the alveoli and bronchioles and a progressive increase in fibrosis. These adverse effects of radiation were alleviated by soy isoflavones administered either before or after radiation.

Wang [63] administered flavonoids extracted from *Astragalus complanatus* to mice after exposure to 10 Gy radiation. The study showed

that flavonoids could significantly increase the serum level of SOD, decrease the serum level of TGF-β1, TNF-α and IL-6 in irradiated mice, and alleviated the lung injury induced by radiation. Yuan Hu [64] had found that administering green tea polyphenols to mice before radiation could increase the 21-day survival rate and reduce the elevated serum inflammatory cytokines (TNF-α, IL-1 and IL-6), which can be developed as radio-protective agents against radiation-induced toxicity.

Lee [65] found that baicalein can suppress radiation-induced inflammatory response by negatively regulating NF-κB and up-regulating FOXOs activation, CAT, and SOD activities. Furthermore, baicalein could inhibit radiation-induced phosphorylation of MAPKs and Akt, which were the upstream kinases of NF-κB and FOXOs. These studies concluded that baicalein had a radio-protective effect against NF-κB mediated inflammatory response through the MAPKs and Akt pathway, which had a significant radio-protective effect in the kidneys of mice.

Additionally, propolis flavonoids [66-68], glabridin [69], austragalus [70,71] and flavonoids of *Oxytropis falcate* Bunge also inhibited the secretion of inflammatory factors secondary to radiation exposure, and reduced the body's inflammatory response.

Other protective effects

Flavonoids not only offer a significant radio-protective effect, but also have obvious anti-tumor, anti-viral, anti-bacterial, and anti-inflammatory effects.

The study showed that 5, 7-dihydroxy flavonoids had the ability to weaken the body lipid peroxidation, improve the activity of xanthine oxidase, and decrease P38 activation and the expression of P53 phosphorylation, which could inhibit colon cancer induced by cisplatin [72]. The study examining 13 flavonoids, separated from Humifuse Euphorbia Herb extraction, had been found that the flavonoids had the anti-HBV activity. The antiviral activity of flavonoids, which used apigenin as parent nucleus, was obviously higher than those that used luteolin and quercetin as parent nucleus. The study had also found that the antiviral activity (flavonoid glycoside > yellow ketone glucoside) and toxicity (yellow ketone > flavonoids single nucleotides sugar > luteolin glucoside) could significantly be influenced by the number of glucosides in the compound [73].

In addition, through investigating the antibacterial and antifungal properties of six different kinds of plant flavonoids, these compounds showed significant inhibition effect on *Pseudomonas aeruginosa, Acinetobacter baumannii, Staphylococcus*, and *Candida* in range of 32 - 128 mg/mL. Meanwhile, rutin, 5,7-dimethoxy-flavanone-4'-O-β-D-glycopyranoside and 5,7,3'-trihydroxy-flavanone-4'-O-β-D-glucopyranoside glucoside could significantly inhibit the HSV-1 herpes simplex virus [74].

MOLECULAR MECHANISMS OF RADIATION PROTECTION

Numerous studies have indicated that flavonoids offer significant benefits regarding radiation protection. The studies on the molecular mechanism of radiation protection were primarily protein molecules and signaling pathways focused on the induction of apoptosis.

Liu Wei *et al* [75] used Western and RT-PCR techniques to study the radiation protection effect of blueberry anthocyanins.

Table 1: Flavonoids Radioprotective mechanisms. (↑ denotes induction; ↓ is inhibition)

Reduce DNA damage	Decrease DNA rupture [22] Reduce micronuclei formation [23] Reduce chromosome lesion [24]
Antioxidant	Scavenging free radicals [33] Reduced lipid peroxidation [34]
Protection of immune system	The index of thymus and spleen ↑ [41] Globulin IgA, IgG, IgM level ↑ [42] Lymphocyte apoptosis ↓ [43]
Protection of hemopoietic system	Recovery of peripheral blood cells ↑ [56] Regeneration of the hematopoietic stem cells ↑ [59] Protect of bone marrow [61]
Reduce inflammation	TGF-β1, TNF-α, IL-1 and IL-6 ↓ [64] P-MAPKs and p-Akt ↓ [65]

The study showed that blueberry anthocyanins could significantly inhibit cell apoptosis and reduce the radiation injury by decreasing gene and protein expression of p53, phosphor-p53 (Ser15), and p21 in UV-irradiated HepG2 cells. Shin [76] treated a fibroblast cell with epicatechin prior to exposure to radiation to verify the radiation protection function. The study showed that epicatechin could significantly reduce the expression of p-JNK, p-38, cleaved caspase-3 compared with their significant increase after radiation treatment, and inhibited radiation-induced ROS generation, mitochondrial dysfunction, and cell death. At the same time, epicatechin could attenuate the radiation-induced embryotoxicity in a zebrafish model. This represented an effective means of reducing cellular damage and facilitating wound healing after radiation exposure.

Singh [77] treated mice with genistein for a period of 24 hours prior to radiation (7 Gy 60Co), quantified serum cytokine levels by multiplex Luminex, and also investigated numerous cytokines using cytokine assays. Genistein administration stimulated serum granulocyte colony stimulating factor (G-CSF) and interleukin-6 (IL-6) after irradiation. Considering G-CSF and IL-6 are important hematopoietic factors, these results indicated that the radio-protective efficacy of genistein may result in the recovery of hematopoietic cells due to enhancing the production of G-CSF and IL-6.

CONCLUSION

Flavonoids offer a variety of beneficial properties including protection from ionizing radiation, DNA protection, immune system protection, hemopoietic system protection, scavenging of free radicals, antioxidant properties, antitumor properties, antiviral properties, antibacterial properties, and anti-inflammatory properties. Despite great advances, the specific protective mechanism and the relationship between the protective mechanism is not yet clear and further investigation is required.

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CONFLICT OF INTEREST

No conflict of interest associated with this work.

CONTRIBUTION OF AUTHORS

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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