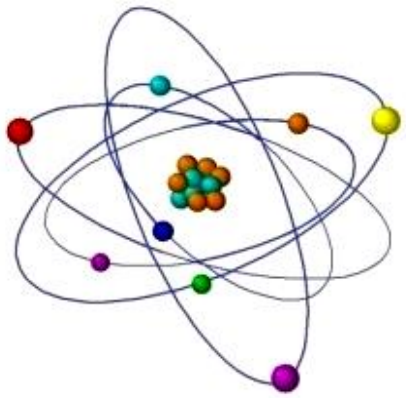
RADIOPROTECTIVE POTENTIAL OF HERNIARIN: A NATURAL COUMARIN AGAINST IONIZING RADIATION-INDUCED OXIDATIVE AND GENOTOXIC INJURY



[1,2]Sophio Kalmakhelidze*, [1]Zizi Kvaratskhelia,
[1]Vakhtang Kakhiani, [1]Mariam Vacharadze,
[3]Mariam Chkadua, [1]Nikoloz Kajaia, [1,2]Tamar Sanikidze

[1]Tbilisi State Medical University, Georgia.
[2]Ivane Beritashvili Center of Experimental Biomedicine,
Laboratory of Radiation Safety Problems, Georgia
[3]Agricultural University, Georgia.

DOI: 10.63465/rrs6202611768 *Corresponding author: s.kalmakhelidze@tsmu.edu

ABSTRACT: *The increasing use of ionizing radiation in diagnostic and therapeutic medicine has raised concern regarding radiation-induced injury to normal tissues, particularly the central nervous system. One of the earliest cellular responses to ionizing radiation is the generation of reactive oxygen and nitrogen species, leading to oxidative stress, lipid peroxidation, protein modification, mitochondrial dysfunction, DNA damage, genomic instability, inflammation, and cell death. These processes are particularly important in radiosensitive tissues and in the central nervous system, where radiation-induced oxidative and inflammatory injury may contribute to neurocognitive impairment, vascular dysfunction, and impaired neurogenesis. Therefore, increasing attention has been directed toward natural compounds with antioxidant, anti-inflammatory, and antigenotoxic properties that may reduce radiation-induced normal tissue injury. Herniarin, a naturally occurring simple coumarin, has attracted interest as a potential radioprotective compound. Coumarins are polyphenolic plant-derived compounds known for diverse pharmacological activities, including antioxidant, anti-inflammatory, cytoprotective, and antigenotoxic effects. Available experimental evidence suggests that herniarin and related coumarins may reduce oxidative DNA damage, limit genotoxicity, modulate endogenous antioxidant defence systems, and protect rapidly dividing cells from toxic injury. This review summarizes the biological mechanisms underlying ionizing radiation-induced oxidative and genotoxic damage and discusses the potential radioprotective role of herniarin, a natural coumarin compound. Although existing findings are promising, further in vivo and mechanistic studies are required to clarify optimal dose, timing, bioavailability, tissue-specific effects, and translational relevance.*

Keywords: herniarin, coumarins, radiation, oxidative stress, DNA damage, genotoxicity

INTRODUCTION

Ionizing radiation is an indispensable tool in modern medicine, particularly in cancer radiotherapy and diagnostic imaging. Despite substantial advances in treatment planning, dose optimization, and targeted delivery, exposure of normal tissues remains an important clinical concern, especially in cases involving high cumulative doses or irradiation of radiosensitive organs. Radiation-induced toxicity is not restricted to acute cellular injury; rather, it may also involve delayed and chronic biological responses that emerge weeks, months, or even years after exposure. These responses are mediated by complex and interrelated mechanisms, including oxidative stress, inflammatory signalling, mitochondrial dysfunction, impaired tissue regeneration, vascular damage, and genomic instability [1-4]. The nervous system is particularly vulnerable to ionizing radiation, and radiation-induced neural injury may develop through multiple interconnected pathways. These include excessive generation of reactive oxygen species, DNA damage, mitochondrial impairment, vascular dysfunction, impaired neurogenesis, synaptic injury, and sustained neuroinflammatory activation. Collectively, these processes contribute to both early and delayed neurological complications. Radiation-induced brain injury is therefore considered a multifactorial pathological condition involving endothelial dysfunction, disruption of the blood-brain barrier, demyelination, reduced neurogenic capacity, synaptic dysfunction, mitochondrial damage, and persistent inflammatory responses within neural tissue [5-7].

The hippocampus represents one of the most radiosensitive brain regions because of its central role in learning, memory formation, and adult neurogenesis. Radiation exposure may compromise hippocampal function by reducing the survival and proliferative capacity of neuronal precursor cells, altering the local neurogenic microenvironment, promoting glial differentiation, and suppressing the generation of new neurons. These structural and cellular alterations are regarded as key mechanisms underlying radiation-associated cognitive impairment [8,9]. Given that oxidative stress, inflammation, and genotoxic damage are central contributors to radiation-induced tissue injury, increasing attention has been directed toward natural bioactive compounds with antioxidant, anti-inflammatory, and DNA-protective properties. In this context, Herniarin is a naturally occurring simple coumarin derivative with potential pharmacological relevance as an antioxidant, antigenotoxic, anti-inflammatory, and cytoprotective compound. Its radioprotective potential is supported by experimental evidence indicating that herniarin can reduce oxidative stress, DNA damage, apoptosis, and radiation-associated cellular injury across various biological models.

Direct evidence for the radioprotective activity of herniarin has been demonstrated in human lymphocytes exposed to X-rays. In this model, herniarin reduced radiation-induced cytotoxicity, genotoxicity, apoptosis, micronucleus formation, and intracellular reactive oxygen species accumulation [10]. These findings indicate that herniarin may exert direct radioprotective effects by limiting oxidative stress and protecting DNA from radiation-induced damage (Figure 1).

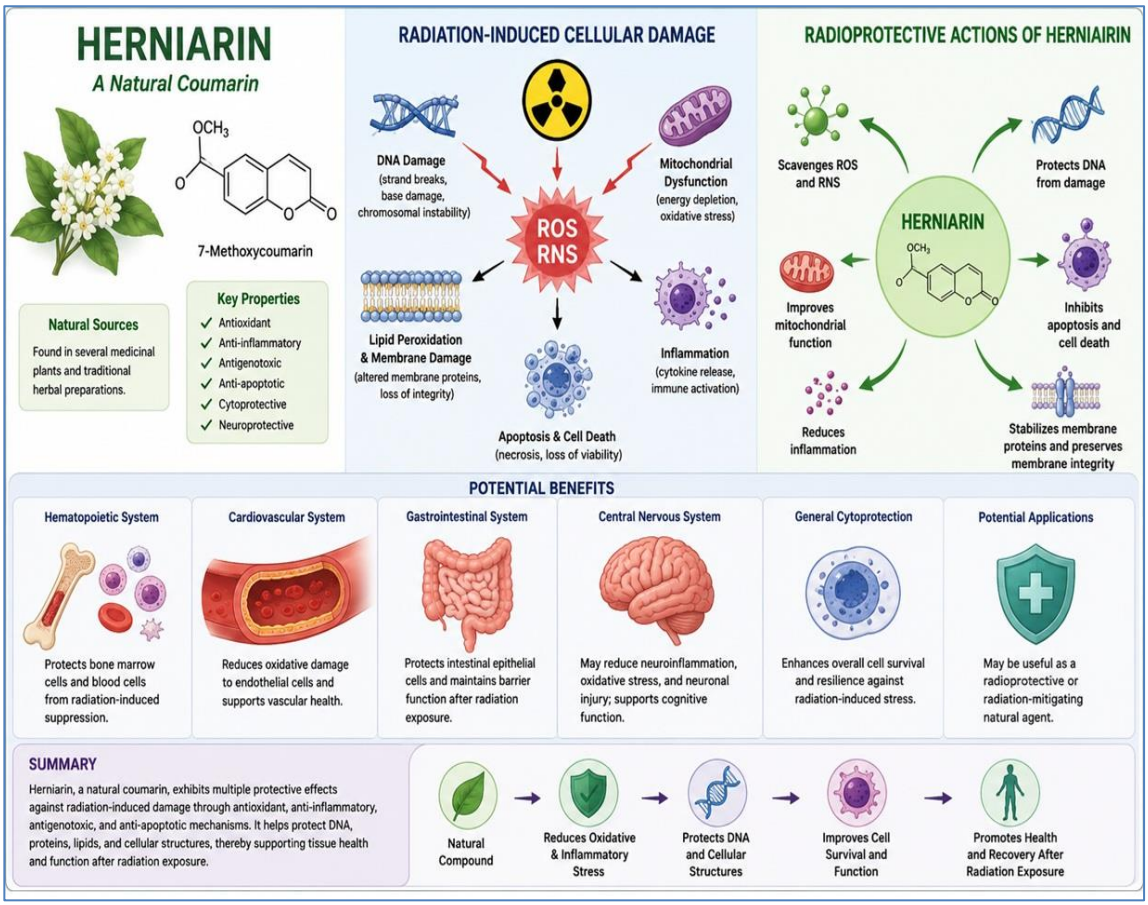


Fig. 1. Radioprotective Actions of Herniarin in Radiation-Induced Cellular Injury

Additional in vivo evidence suggests that herniarin may protect cellular membrane structures after irradiation. In gamma-irradiated mice, herniarin improved radiation-induced alterations in erythrocyte membrane proteins during the post-irradiation period [11]. This effect may reflect membrane-stabilizing and antioxidant activity, since radiation-induced oxidative stress can damage membrane lipids and proteins, leading to impaired cellular integrity and function. The antigenotoxic and cytoprotective potential of herniarin is also supported by studies using non-radiation oxidative injury models. In rat bone marrow cells exposed to cisplatin, herniarin reduced genotoxicity, apoptosis, necrosis, and oxidative stress [12]. Although cisplatin and ionizing radiation are different damaging agents, they share several common mechanisms of toxicity, including reactive oxygen species generation, DNA damage, mitochondrial dysfunction, and activation of cell death pathways. Therefore, these findings support the possible protective relevance of herniarin in rapidly dividing and radiosensitive tissues such as bone marrow. Herniarin-containing plant fractions have shown anti-inflammatory and neuroprotective effects in neuroinflammatory models, including regulation of inflammatory cytokines and antioxidant enzymes [13]. These effects suggest possible relevance for radiation-induced neuroinflammation, particularly in the central nervous system, where oxidative stress and microglial activation contribute to delayed brain injury and cognitive impairment (Table 1).

Table 1. Radioprotective and Cytoprotective Effects of Herniarin in Experimental Models

Herniarin research model	Main findings	Results
Human lymphocytes exposed to X-rays	Herniarin reduced radiation-induced cytotoxicity, genotoxicity, apoptosis, micronucleus formation, and ROS accumulation.	Demonstrates direct radioprotective, antioxidant, and antigenotoxic effects [10].
Gamma-irradiated mice	Herniarin improved radiation-induced alterations in erythrocyte membrane proteins during the post-irradiation period.	Suggests membrane-stabilizing and antioxidant protection in vivo [11].
Rat bone marrow cells exposed to cisplatin	Herniarin reduced genotoxicity, apoptosis, necrosis, and oxidative stress.	Supports protection of rapidly dividing hematopoietic cells from oxidative/genotoxic injury [12].
Human lymphocytes exposed to hydrogen peroxide	Herniarin reduced oxidative DNA damage.	Supports protection against ROS-mediated DNA injury [14].
Herniarin-containing plant fractions in neuroinflammatory models	Reported anti-inflammatory and neuroprotective effects, including modulation of inflammatory cytokines and antioxidant enzymes.	Suggests possible relevance for radiation-induced neuroinflammation and cognitive impairment [13].

CONCLUSION

Ionizing radiation-induced injury is mediated by oxidative stress, DNA damage, mitochondrial dysfunction, inflammation, vascular injury, and impaired cellular repair. Herniarin, a natural simple coumarin, has promising antioxidant, antigenotoxic, anti-inflammatory, and cytoprotective properties that may be relevant to radioprotection. Available evidence suggests that it may reduce ROS-mediated DNA damage, preserve cellular integrity, and modulate inflammatory responses. However, further mechanistic and preclinical studies are necessary to confirm its efficacy and establish its translational potential as a radioprotective agent.

REFERENCES

[1]. Wei J, Wang B, Wang H, Meng L, Zhao Q, Li X, Xin Y, Jiang X. Radiation-Induced Normal Tissue Damage: Oxidative Stress and Epigenetic Mechanisms. Oxid Med Cell Longev. 2019;2019:3010342.

[2]. Zhou L, Zhu J, Liu Y, Zhou PK, Gu Y. Mechanisms of radiation-induced tissue damage and response. MedComm (2020). 2024;5(10):e725.

[3]. Azzam EI, Jay-Gerin JP, Pain D. Ionizing radiation-induced metabolic oxidative stress and prolonged cell injury. Cancer Lett. 2012;327(1-2):48-60.

[4]. Vignard J, Mirey G, Salles B. Ionizing-radiation induced DNA double-strand breaks: a direct and indirect lighting up. Radiother Oncol. 2013;108(3):362-369

[5]. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: A review. Front Oncol. 2012; 2:73.

[6]. Rola R, Sarkissian V, Obenaus A, Nelson GA, Otsuka S, Limoli CL, Fike JR; New Collective Author. High-LET radiation induces inflammation and persistent changes in markers of hippocampal neurogenesis. Radiat Res. 2005;164(4 Pt 2):556-60.

[7]. Raber J, Rola R, LeFevour A, Morhardt D, Curley J, Mizumatsu S, VandenBerg SR, Fike JR. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. Radiat Res. 2004;162(1):39-47.

[8]. Kalmakhelidze S, Museridze D, Sanikidze T, Gogebashvili M, Tophuria D, Ivanishvili, N, Ormotsadze G. Study of Cognitive Parameters in Postradiation Period in White Mice. Radiobiology and Radiation Safety. 2021; 1(1): 57–62.

[9]. Kalmakhelidze S, Museridze D, Gogebashvili M, Lomauri K, Gabunia T, Sanikidze T. Effects of ionizing radiation on cognitive parameters in white mice. Georgian Med News. 2022;(324):187-192. Al Fares E, Sanikidze T, Kalmakhelidze S, Topuria D, Mansi L, Kitson S, Molazadeh M. The Alleviating Effect of Herniarin Against Ionizing Radiation-Induced Genotoxicity and Cytotoxicity in Human Peripheral Blood Lymphocytes. Curr Radiopharm. 2022;15(2):141-147.

[10]. Kalmakhelidze S, Shekiladze E, Ormotsadze G, Gvilava I, Tsimakuridze M, Sanikidze T, Kipiani N. Ionizing Radiation-induced Changes In The Absorption Spectrum Of Erythrocyte Membrane Proteins. Radiobiology and Radiation Safety. 2022; 2(3).

[11]. Salehcheh M, Safari O, Khodayar MJ, Mojiri-Forushani H, Cheki M. The protective effect of herniarin on genotoxicity and apoptosis induced by cisplatin in bone marrow cells of rats. Drug Chem Toxicol. 2022;45(4):1470-1475.

[12]. Liliana Porras-Dávila S, Zamilpa A, Jiménez-Ferrer E, Jiménez-Aparicio A, Alejandra Santillan-Urquiza M, Díaz-Patricio F, Herrera-Ruiz M. Anti-Inflammatory and Neuroprotective Effects of Standardized Fractions in Herniarin and Daphnoretin from Distictis buccinatoria. Chem Biodivers. 2023;20(5):e202200969.

[13]. Salehi AM, Rezaei R, Sadeghi A et al. Diagnostic value of neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and systemic immune-inflammation index for predicting the severity of acute pancreatitis. BMC Gastroenterol 2025; 25: 751

Requirements for Authors

- The article should be submitted to the A4 format in the text editor Microsoft Office Word;
- Areas: upper - 20 mm; Left - 30 mm; Right -20 mm; Bottom - 20 mm
- Font: Times New Roman. Interval -1,0
- In the article formulas must be typed in the formula's editor Equation
- Drawings and illustrative materials should be inserted in the JPEG or TIFF format
- Write the article title (14 Pt, Bold) on the first line
- Bypassing the line - the surname and first name of the author(s) (11 Pt, Bold)
- One of the authors will need to be identified as the corresponding author (*), with their full name and email address displayed.
- Full name of the organization on the next line, with indicating the country or residence (11 Pt, Bold, in case of participation of different organizations in the article should be used "[1]")
- Skipping of two lines - abstract (11 Pt, Italics, not more than 500 words)
- Maximum 5 Key words (11Pt)
- Contents of the article (11Pt) by skipping the line
- Bypassing two lines – references (10 Pt). Used literature should be numbered according the sequence it is used in the main text (when citing inside the text, the number of the source should be written in square brackets). Use the following example while creating the reference list:

  [1] Author(s') surname(s) and initial(s). (Year of publication). Article name. *Journal in which the article is published*, *issue*, pages.

  [1] Derwing, T. M., Rossiter, M. J., & Munro, M. J. (2002). Teaching native speakers to listen to foreign-accented speech. *Journal of Multilingual and Multicultural Development*, *23*(4), 245-259.

- Electronic version of the article must be sent to the e-mail: radiobiologia2020@gmail.com
- The file must be named by the last name of the author

The editorial board is responsible for the topics of the materials submitted for publication in the journal, and the authors' responsibility relies on the content of the article, the results and conclusions. The publisher is not responsible for possible damages, which could be a result of content derived from this publication and any liabilities arising from them remain the responsibility of the authors. Articles incompatible with the above-mentioned requirements or incompatible with the theme of the article are not considered for publication. Materials are published by the author's editorship.

Editorial office: 14 Levan Gotua St, Rooms-913; 931, Tbilisi, Georgia, 0160

Tel: (+995) 032 237-03-00/911, **Mob**. (+99532)555-10-17-90
E-mail: radiobiologia2020@gmail.com

Website:https://radiobiology.ge