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MAPPING THE RESEARCH LANDSCAPE: IONIZING RADIATION-INDUCED OXIDATIVE STRESS AND INFLAMMATION IN THE BRAIN – A BIBLIOMETRIC ANALYSIS

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Abstract

Introduction: Ionizing radiation (IR) - induced oxidative stress and inflammation in the brain represent a significant global challenge, contributing to the molecular mechanisms underlying brain tissue damage and neurovascular disruption.

Objective: This bibliometric analysis aims to evaluate the findings of studies investigating IR-induced oxidative stress and inflammation in the brain.

Search Strategy: Utilizing the Scopus and Web of Science (WOS) databases, we analyzed 524 articles, including 404 research articles and 120 review articles.

Results: Our results reveal a notable rise in research activity, reflecting increased awareness of this critical issue. The "International Journal of Radiation Biology" and the "International Journal of Molecular Sciences" emerged as the most prolific journals, playing pivotal roles in disseminating relevant findings. The United States, China, Egypt and India were identified as leading contributors, with institutions in Egypt and United States making significant impacts through high publication volumes. Kim J. and Tang F. emerged as notable authors in the field. **Conclusions:** Insights from this work are essential for shaping future research directions and enhancing our understanding of the underlying mechanisms, which are vital for developing protective and therapeutic strategies to mitigate radiation exposure's effects.

Keywords: *ionizing radiation; brain; oxidative stress; inflammation.*

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Резюме

КАРТИРОВАНИЕ ИССЛЕДОВАТЕЛЬСКОГО ЛАНДШАФТА: ОКИСЛИТЕЛЬНЫЙ СТРЕСС И ВОСПАЛЕНИЕ В ГОЛОВНОМ МОЗГЕ, ВЫЗВАННЫЕ ИОНИЗИРУЮЩИМ ИЗЛУЧЕНИЕМ – БИБЛИОМЕТРИЧЕСКИЙ АНАЛИЗ

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Введение: Ионизирующее излучение (ИИ), индуцирующее окислительный стресс и воспаление в головном мозге, представляет собой значительную глобальную проблему, способствующую молекулярным механизмам повреждения мозговой ткани и нарушению нейроваскулярной функции.

Цель: Данный библиометрический анализ направлен на оценку результатов исследований, посвящённых влиянию ИИ на развитие окислительного стресса и воспаления в мозге.

Стратегия поиска: С использованием баз данных Scopus и Web of Science (WOS) было проанализировано 524 статьи, включая 404 оригинальных исследования и 120 обзорных статей.

Результаты: Наши результаты выявили заметный рост исследовательской активности, что отражает возрастающее внимание к данной проблеме. Журналы International Journal of Radiation Biology и International Journal of Molecular Sciences оказались наиболее продуктивными и играют ключевую роль в распространении соответствующих научных данных. Соединённые Штаты, Китай, Египет и Индия определены как ведущие страны-участники, при этом учреждения Египта и США внесли значительный вклад благодаря высокому количеству публикаций. Среди авторов выделяются Kim J. и Tang F.

Выводы: Полученные выводы имеют важное значение для формирования будущих направлений исследований и углубления понимания основных механизмов, что критически важно для разработки защитных и терапевтических стратегий по снижению последствий воздействия радиации.

Ключевые слова: *ионизирующее излучение; мозг; окислительный стресс; воспаление.*

Для цитирования:

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Түйіндеме

ЗЕРТТЕУ ЛАНДШАФТЫНЫҢ КАРТАСЫ: ИОНДАУШЫ СӘУЛЕЛЕНУДІҢ МИДАҒЫ ТОТЫҒУ КҮЙЗЕЛІСІ МЕН ҚАБЫНУҒА ӘСЕРІ – БИБЛИОМЕТРИЯЛЫҚ ТАЛДАУ

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Кіріспе: Иондаушы сәулелену (ИС) - мида тотығу күйзелісі мен қабынуды тудырады, ми тінінің зақымдануы мен нейроваскулярлық бұзылыстардың молекулалық механизмдеріне ықпал ететін елеулі жаһандық мәселе болып табылады.

Зерттеу мақсаты: Бұл библиометриялық талдау мида сәулеленудің әсерінен дамитын тотығу күйзелісі мен қабыну туралы зерттеген жұмыстардың нәтижелерін бағалауға бағытталған.

Зерттеу әдістері: Scopus және Web of Science (WOS) деректер қорларын пайдалана отырып, барлығы 524 мақала талданды, оның ішінде 404 түпнұсқа зерттеу және 120 шолу мақалалары.

Нәтижелері: Нәтижелер зерттеулер белсенділігінің айтарлықтай өскенін көрсетті, бұл мәселенің маңыздылығына деген назардың артқанын білдіреді. *International Journal of Radiation Biology* және *International Journal of Molecular Sciences* журналдары ең өнімді басылымдар ретінде анықталды және маңызды ғылыми деректерді таратуда жетекші рөл атқарады. АҚШ, Қытай, Египет және Үндістан жетекші елдер ретінде ерекшеленді, олардың ішінде Египет пен АҚШ мекемелері жоғары жарияланымдарымен айтарлықтай үлес қосты. Авторлар арасында Kim J. және Tang F. ең белсенді зерттеушілер ретінде аталды.

Қорытынды: Бұл жұмыстың нәтижелері болашақ зерттеу бағыттарын айқындау және негізгі механизмдерді тереңірек түсінуді қамтамасыз ету үшін маңызды, ал бұл радиация әсерін азайтуға арналған қорғаныш және терапиялық стратегияларды әзірлеуде шешуші мәнге ие.

Түйінді сөздер: *иондаушы сәулелену; ми; оксидативті стресс; қабыну.*

Дәйексөз үшін:

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Introduction

Ionizing radiation (IR) is a type of radiation with energy sufficient to overcome the bonding forces holding tightly bound electrons in their respective orbitals around the nuclei of atoms and molecules, causing the atoms to lose or gain electrons, thus becoming charged ions or free radicals. In biological organisms, ionization exerts its effects through two primary mechanisms: direct and indirect [44]. Direct ionization damages cellular molecules by breaking chemical bonds, leading to DNA strand breaks [5]. Indirect effects arise when radiation interacts with water molecules within cells, producing reactive oxygen species (ROS) via water radiolysis, which can damage DNA, proteins, and lipids [67], ultimately leading to cellular dysfunction, DNA mutations, and cell death [36]. The biological consequences of radiation exposure depend on several factors, including radiation type, dose rate, exposure duration, and tissue radiosensitivity [28].

The discovery of X-rays by Wilhelm Conrad Röntgen (November 8, 1895), radioactivity by Antoine Henri Becquerel (1896) and the free electron by Joseph John Thomson (1897) were pivotal events that revolutionized science at the end 19th century, profoundly influencing the development of physics, chemistry and medicine, while laying the groundwork for future scientific discoveries and advances. These breakthroughs significantly expanded scientific and medical knowledge, marking a milestone in the progress of their respective fields [45]. However, the advent of nuclear technology has also been associated with catastrophic events, including the bombings of Hiroshima and Nagasaki (Japan, 1945), accidents at Kyshtym (Russia, then USSR, 1957), Windscale Piles (United Kingdom, 1957), Three Mile Island (USA, 1979), Chernobyl (Ukraine, then USSR, 1986), and Fukushima (Japan, 2011) [23].In Kazakhstan, the Semipalatinsk nuclear test site saw 456 nuclear explosions, including 111 atmospheric tests (86 in the air and 25 on the surface), between 1949 and 1962 [6]. These events have had profound consequences, including genomic instability, increased incidence of cancers and non-cancerous diseases, and population decline [35, 24, 22]. Currently, there are 411 nuclear power plants operating worldwide to meet growing energy demands, which does not exclude the possibility of future nuclear incidents [30].

The use of IR in industry (sterilization, materials testing), medical procedures (X-rays, computed tomography), and oncology (radiation therapy) has expanded significantly over the last decade [21, 55]. The International Commission on Radiological Protection (ICRP) has established a threshold dose of 0,5 Gy for cardiovascular and cerebrovascular diseases. However, clinical studies in neuroradiology and radiotherapy indicate that this threshold is frequently exceeded during medical interventions, Highlighting the need for research on the cumulative effects of repeated radiation exposure on patients and healthcare workers [52]. Research indicates that radiation doses exceeding > 0.5 Gy cause brain damage, while doses between 0 and 0.5 Gy do not exclude the possibility of developing neurocognitive and neurodegenerative diseases [48], necessitating further detailed investigation.

Under normal physiological conditions, ROS are primarily generated in cells by the mitochondrial electron transport chain and NADPH oxidases, playing critical roles in energy metabolism and immune defense, maintaining vital cellular functions [7]. Cells have endogenous antioxidant systems, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), which effectively neutralize ROS, maintaining their levels within physiological norms and preventing cellular and tissue damage [31]. In pathological conditions, oxidative stress is defined as an imbalance between the excessive production of ROS and the cell's ability to neutralize them through its antioxidant defense mechanisms. As a result, oxidative stress disrupts redox signaling processes [9], which contributes to the development of diseases such as atherosclerosis [66] and neurodegenerative disorders, including Parkinson's disease and Alzheimer's disease [33]. Oxidative stress also triggers lipid peroxidation, damaging polyunsaturated fatty acids (PUFAs) in cell membranes, leading to compromised cellular integrity and function [69].

The body’s protection is supported not only by endogenous antioxidants but also by the inflammatory response. Inflammation is a defensive reaction of the immune system aimed at eliminating the cause of damage, clearing away damaged cells, and initiating the healing process. However, an excessive inflammatory response, despite its protective and beneficial role, can lead to increased ROS production, tissue damage, and the progression of disease. Oxidative stress, lipid peroxidation, and neuroinflammation are central to the development of neurodegenerative diseases. Globally, the incidence of neurological disorders ranges from 10 to 15 cases per 100,000 people annually [53]. Furthermore, oxidative stress stimulates the production of pro-inflammatory cytokines, such as interleukins, interferons, and growth factors [1].

The brain, in turn, consumes 20% of the body's total oxygen and 25% of its glucose supply [19], while PUFAs account for approximately 35% of the brain's total lipids [49]. Compared to other organs, the brain is unique due to its high PUFA content, low levels of endogenous antioxidants, and increased sensitivity to oxygen deprivation, making it particularly vulnerable to oxidative stress [50]. Modern radiology does not plase sufficient emphasis on the cerebrovascular network, despite its crucial role in oxygen transport and brain metabolism. Secondary damage caused by oxidative stress is directly linked to the inflammatory process, which leads to neurovascular network. [4]. Radiation induces neuropathological changes in the brain [26], leading to subsequent neurological and neuropsychological disorders [8], including neuroinflammation [59], neurovascular dysfunction, blood-brain barrier (BBB) disruption, synaptic impairment, neuronal death [43], and impaired neurogenesis. These effects ultimately contribute to cognitive decline [61] and neurodegenerative diseases [56].

In academic literature, numerous bibliometric analyses cover various aspects, including radiotherapy, diagnostics, treatment methods, primary and metastatic brain cancer, and radionecrosis [65]; studies examining the relationship between oxidative stress and cognitive impairments (chemobrain) associated with cancer treatment, particularly chemotherapy [40]; and the biological effects of radiation exposure below 100 mSv [46]. Unlike previous bibliometric analyses, which primarily focus on cancer treatment and cognitive impairments, our study provides a more targeted and in-depth investigation of specific processes. Specifically, our analysis examines publications

from various countries and journals, exploring how IR induces oxidative stress and subsequent neuroinflammation, while detailing the molecular and cellular mechanisms involved. Additionally, we evaluate global publication trends, collaboration networks, and influential contributors in this field.

The aim of our analysis is to comprehensive assess the impact of IR on oxidative stress and inflammation in the brain, exploring their roles in cognitive and cerebrovascular impairments and neurodegenerative diseases. By identifying current trends and knowledge gaps, this study seeks to guide future research and advance understanding of these critical processes.

Search Strategy. On December 30, 2024, we conducted a bibliometric analysis examining the effects of IR on oxidative processes and neuroinflammation in the brain. This analysis involved a comprehensive search of the Scopus and Web of Science (WOS) databases. Inclusion criteria were restricted to original and review articles primarily available in English, while proceeding papers, book chapters, and editorial materials were excluded. Using advanced search parameters, we conducted an exhaustive query of both databases and downloaded all relevant bibliographic metadata in BibTeX and text formats. The collected data were then exported into RStudio as an Excel file. Figure 1 presents a flowchart depicting the complete search strategy employed for data collection. Articles deemed irrelevant based on their titles, abstracts, and full-text content were systematically excluded.

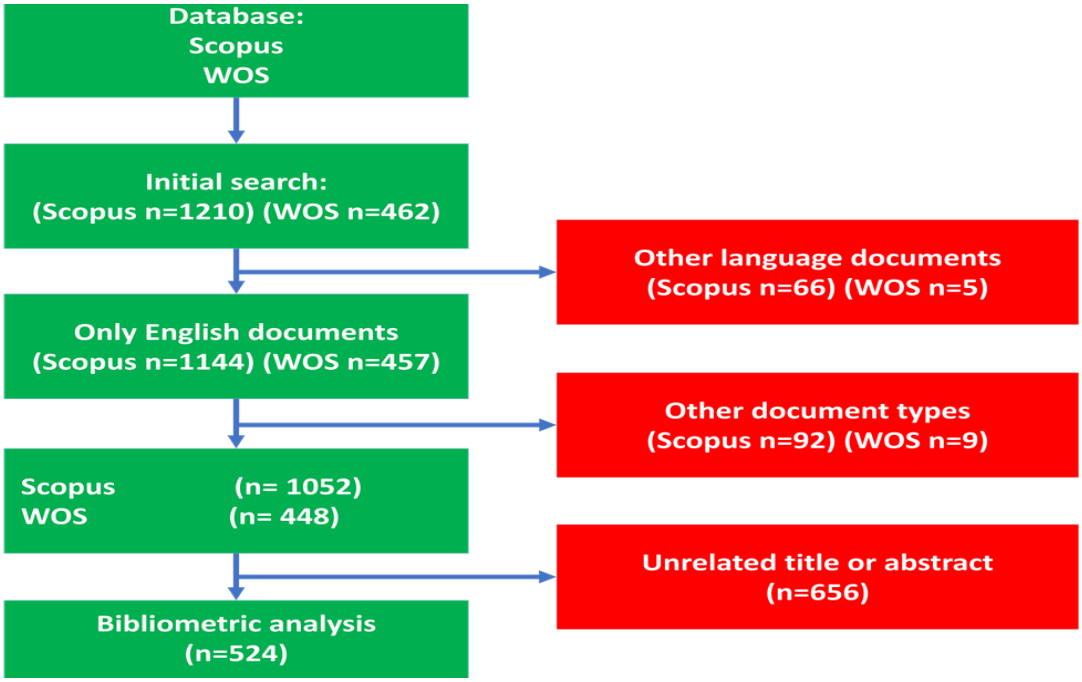

Figure 1. The flow chart depicting the selection process of research and review articles for a bibliometric analysis on the effects of IR on oxidative stress and neuroinflammation in the brain.

Bibliometric Analyses

In this investigation, we conducted performance analysis and science mapping utilizing the bibliometric package (version 4.1.3) and Biblioshiny web applications within RStudio (RStudio 2023.09.1+494, PBC, Boston, MA). The analysis covered a period of 58 years for English-language research articles and 43 years for English-language review articles, focusing on key bibliometric indicators such as citation and publication counts, prolific institutions and authors, and international collaborations.

Results

Search results

Initially, 1210 papers from Scopus and 462 from WOS were collected for a comprehensive examination of the impact of IR on oxidative stress and neuroinflammation in the brain. After applying eligibility criteria and excluding 656 unsuitable studies, a total of 524 papers were deemed suitable for this bibliometric analysis (Figure 1).

Key attributes of the encompassed studies

This bibliometric analysis aims to examine global research findings on IR-induced oxidative stress and neuroinflammation in the brain. In total, 524 research and review articles were identified and analyzed. The dataset included 404 research articles, involving 2008 authors, sourced from 246 documents. Similarly, the 120 review articles featured contributions from 536 authors, originating from 94 sources. On average, these research articles received 31.32 citations per document, while the review articles had a higher citation impact, averaging 81.5 citations per document. Table 1, "Most Globally Cited Documents," presents the 10 most frequently cited research and review articles. The publication growth rate over the study period was calculated using the annual growth rate. In this research domain, the growth rate for research articles was determined to be 6.04%, while review articles exhibited a notably lower growth rate of 3.28%. Additionally, an analysis of research articles revealed a total of 10617 references and 956 author keywords. In contrast, review articles contained 6062 references and 386 author keywords.

Trend of publication and citation

Interest in studying IR, oxidative stress, and neuroinflammation in the brain emerged at the end of the 20th century. Between 1966 and 1986, the number of English language research publications on this topic was at its lowest, with only 8 studies conducted. However, with the advancement of innovative technologies in the 21st century, the demand for research on the effects of IR has increased

Table 1. **Ranking of the Top 10 most cited research and review publications worldwide on the effects of IR on oxidative processes and neuroinflammation in the brain.**

Ranking	Study references	Title of the document	Journal name	DOI	Total citations
Research articles					
1	Monje M.L. et al. (2003) [42]	Inflammatory blockade restores adult hippocampal neurogenesis	Science	10.1126/science.1088417	2081
2	Hong J.H. et al. (1995) [29]	Induction of acute phase gene expression by brain irradiation	International Journal of Radiation Oncology*	10.1016/0360-3016(95)00279-8	317
3	Cronk J.C. et al. (2018) [12]	Peripherally derived macrophages can engraft the brain independent of irradiation and maintain an identity distinct from microglia	Journal of Experimental Medicine	10.1084/jem.20180247 10.1038/srep42928	275
4	Wood K.A. et al. (1995) [64]	The role of free radicals and p53 in neuron apoptosis in vivo	Journal of Neuroscience	10.1523/JNEUROSCI.15-08-05851.1995	218
5	Clark P.J. et al. (2008) [11]	Intact neurogenesis is required for benefits of exercise on spatial memory but not motor performance or contextual fear conditioning in C57BL/6J mice	Neuroscience	10.1016/j.neuroscience.2008.06.051	202
6	Hwang S.Y. et al. (2006) [32]	Ionizing radiation induces astrocyte gliosis through microglia activation	Neurobiology of disease	10.1016/j.nbd.2005.08.006	186
7	Lee W.H., Wood K.A. et al. (2010) [39]	Irradiation induces regionally specific alterations in pro-inflammatory environments in rat brain	International journal of radiation biology	10.3109/09553000903419346	153
8	Kyrkanides S. et al. (1999) [37]	TNFα and IL-1β mediate intercellular adhesion molecule-1 induction via microglia–astrocyte interaction in CNS radiation injury	Journal of neuroimmunology	10.1016/S0165-5728(98)00270-7	142
9	Kyrkanides S. et al. (2002) [38]	Cyclooxygenase-2 modulates brain inflammation-related gene expression in central nervous system radiation injury	Molecular Brain Research	10.1016/S0169-328X(02)00353-4	140
10	Daroczi, B. et al. (2006) [13]	In vivo radioprotection by the fullerene nanoparticle DF-1 as assessed in a zebrafish model	Clinical Cancer Research	10.1158/1078-0432.CCR-06-0514	135
Review articles					
1	Galano A. et al. (2011) [17]	Melatonin as a natural ally against oxidative stress: a physicochemical examination	Journal of pineal research	10.1111/j.1600-079X.2011.00916.x	1040
2	Stewart F.A. et al. (2012) [58]	ICRP publication 118: ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs–threshold doses for tissue reactions in a radiation protection context	Annals of the ICRP	10.1016/j.icrp.2012.02.001	1025
3	Chen X. et al. (2012) [10]	Oxidative stress in neurodegenerative diseases	Neural regeneration research	10.3969/j.issn.1673-5374.2012.05.009	515
4	Tofilon P.J. et al. (2000) [60]	The radioresponse of the central nervous system: a dynamic process	Radiation research	10.1667/0033-7587(2000)153[0357:TROTCN]2.0.CO;2	459
5	García J.J. et al. (2014) [18]	Protective effects of melatonin in reducing oxidative stress and in preserving the fluidity of biological membranes: a review	Journal of pineal research	10.1111/jpi.12128	424
6	Shiloh Y. et al. (1997) [54]	Ataxia-telangiectasia and the Nijmegen breakage syndrome: related disorders but genes apart	Annual review of genetics	10.1146/annurev.genet.31.1.635	409
7	Wells P.G. et al. (2009) [63]	Oxidative stress in developmental origins of disease: teratogenesis, neurodevelopmental deficits, and cancer	Toxicological sciences	10.1093/toxsci/kfn263	363
8	Hajam Y.A. et al. (2022) [20]	Oxidative stress in human pathology and aging: molecular mechanisms and perspectives	Cells	10.3390/cells11030552	351
9	McKinnon P.J. et al. (2009) [41]	DNA repair deficiency and neurological disease Johnson K. J. et al. (2014)	Nature Reviews Neuroscience	10.1038/nrn2559	248
10	Holley A.K. et al. (2011) [27]	Manganese superoxide dismutase: guardian of the powerhouse	International journal of molecular sciences	10.3390/ijms12107114	240

significantly. Notably, the highest number of publications was recorded in 2024 (n = 30) and in 2020 (n = 28) (Figure 2A). When examining the trend in average annual citations, a significant increase in total citations per article was observed in 2003, peaking at 10.17 citations per study (Figure 2B).

From 1981 to 2024, there was a steady increase in the number of review articles exploring the effects of IR on oxidative stress and neuroinflammation in the brain. The period between 1981 and 2001 had the lowest rate of scientific publications, with only 5 studies released. Conversely, the highest number of publications was observed in 2022 (n=15) and 2021 (n=14), as depicted in Figure 2C. When analyzing trends in average annual citations within the same timeframe, the total number of citations peaked in 2012 at 24.66 and has since declined (Figure 2D).

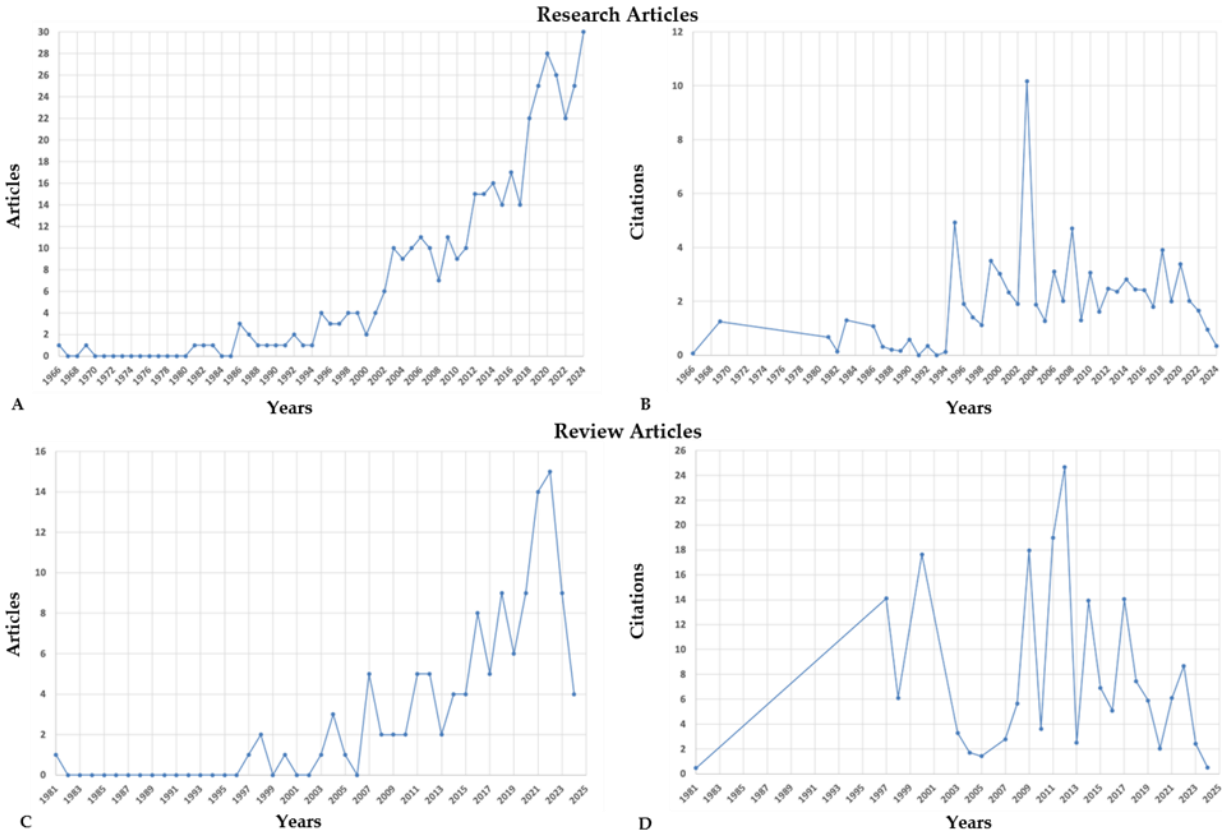

Figure 2. Global annual trends in (A) research article publications and (B) citations, as well as (C) review article publications and (D) citations, in the field of IR's impact on oxidative processes and neuroinflammation in the brain.

Most relevant affiliations

The Egyptian Atomic Energy Authority (EAEA) and the National Center for Radiation Research and Technology secured the top position among the leading ten institutions publishing the highest number of research articles on the effects of IR on oxidative stress and neuroinflammation in the brain, each contributing 33 articles. Closely following are the Egyptian Atomic Energy Authority (EAEA) and University of California System, ranking second and third, with 24 and 19 articles, respectively.

In our examination of review articles within this research domain, University of California System stands out as the most prolific institution, contributing 9 articles. Additionally, National University of Singapore and Stanford University each contributed significantly, publishing five articles respectively, demonstrating notable research productivity.

Most Productive Authors and Their Collaboration Network

During our examination of the effects of IR on oxidative stress and neuroinflammation in the brain, we analyzed the number of publications authored by various researchers.

Among the top contributing researchers in terms of published research articles, *Kim J., Li Y., Limoli C. and Zhang Y.* rank as the most prolific authors, each demonstrating a stable research trajectory with eight articles published consistently from 2004 to 2024. Similarly, *Deng Y., Fike J., Kim S., Ma H., and Wang X.* have each published seven articles, sustaining high productivity. *Tang F.* ranks first among the most influential authors of review articles, having published five articles between 2017 and 2022. Following closely behind, Marazziti D. has authored four review articles from 2012 to 2020, placing them in second place in terms of publication volume. *Baroni S., Costes S., Fike J., Loganovsky K., and Ren B.* have each published three articles, placing them third among the leading authors. The ongoing contributions of these authors highlight their significant impact and continued engagement in advancing research within their respective fields.

Most Productive Journals

Among the leading journals contributing a significant portion of the total publications in this research domain, the "International Journal of Radiation Biology" has the highest

number of research articles, with 22 publications. It is followed by "Radiation Research" and "International Journal of Molecular sciences", which have published 15 and 14 research articles.

Regarding review articles, the "International Journal of Molecular Sciences" is the most prolific journal, with seven published review articles. Following this, "Cells", “Frontiers in Oncology”, “International Journal of Radiation Biology”, “Medical Hypotheses”, “Neuroscience and Biobehavioral Reviews” and “Radiation Research” are the second most productive journals, each with three review articles. Additionally, “Cancers”, “Clinical Neuropsychiatry” and “CNS and Neurological Disorders – Drug Targets” have each published two review articles, making them the third most productive journals.

World Research Production and Collaborations

Figure 3A illustrates the most significant scholarly contributions from 76 known international collaborations, focusing on published research articles examining the impact of IR on oxidative processes and neuroinflammation in the brain. In terms of international cooperation and leading contributions, the United States (n=29), China (n=13), and Germany (n=9) rank first, second, and third among the top 10 countries. Figure 6A also presents that collaborative efforts between China and United States, as well as between Canada and United States, each occurred five times. In contrast, the highest collaboration was observed between the China and Singapore, as well as between the Egypt and Saudi Arabia, with three instances in each case.

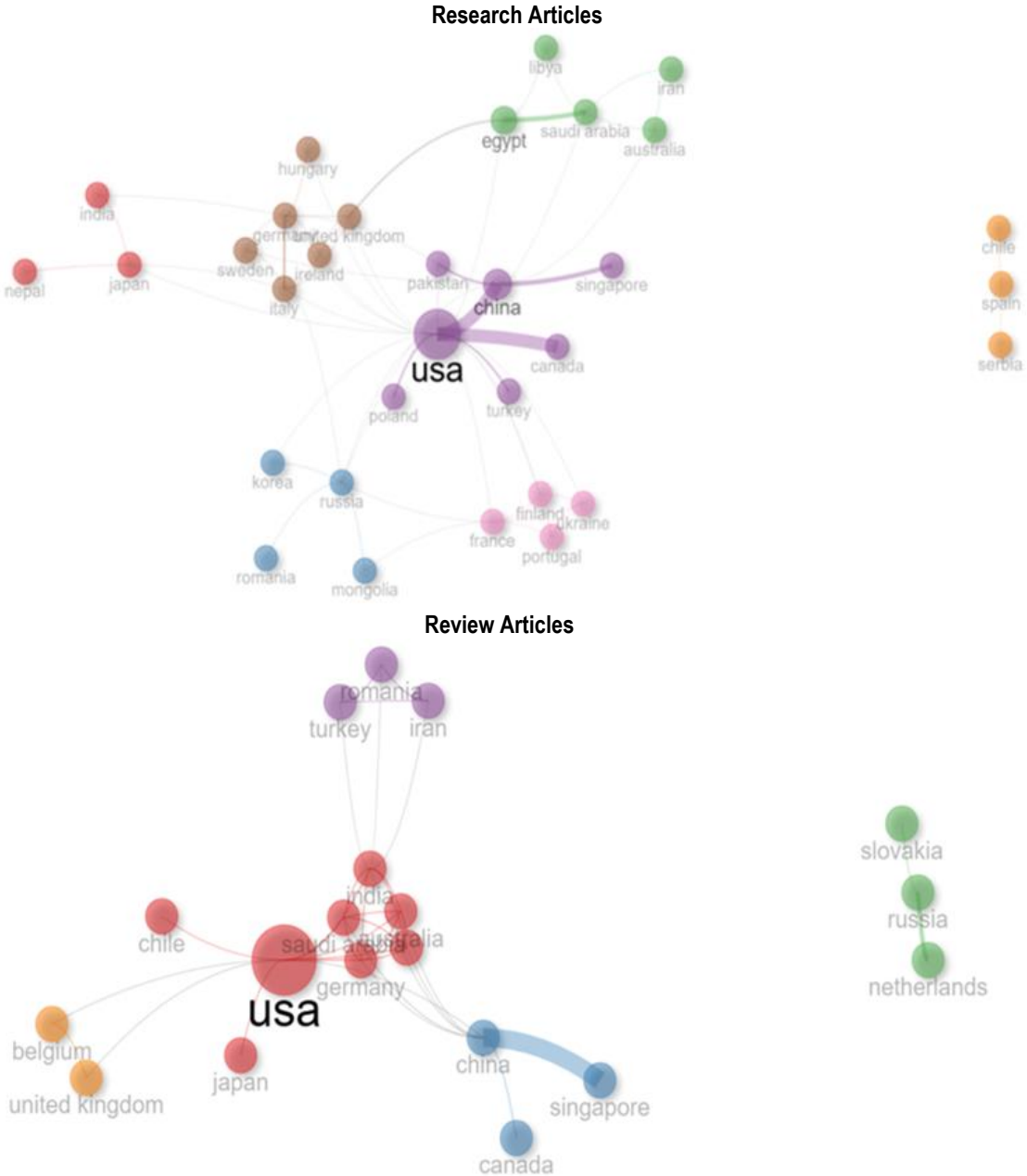

Figure 3. (A) World collaboration map provides a visual representation of international collaborations in publishing research articles, highlighting the global scope of studies on the effects of IR on oxidative stress and neuroinflammation in the brain. Figure 3. (B) World collaboration map illustrates collaboration networks between countries in publishing review articles, summarizing research on the same topic. The thickness of the connecting arrows indicates the strength of collaboration between countries.

Figure 3B highlights 39 notable international collaborations related to review articles on the influence of IR on oxidative stress and neuroinflammation in the brain. Our analysis identified USA (n=10), China (n=10) and India (n=9) as the leading contributors in terms of scholarly output. Figure 6B emphasizes that the strongest collaboration occurred between China and Singapore, with 4 instances of joint publications.

Upon analyzing the most cited countries in research and review articles, our findings indicate that the United States holds the top position, with articles authored by US-based researchers receiving the highest average citation counts - 6318 citations for research articles and 2521 citations for review articles. Furthermore, China ranks second, with 829 citations for research articles, followed by India with 726 citations. For review articles, Mexico and Canada are among the most highly cited, with 1040 and 974 citations, respectively, highlighting their significant contributions to the academic discourse on the effects of IR on oxidative processes and neuroinflammation. These results underscore extensive global collaboration and notable expertise, fostering a deeper understanding of the interplay between IR, oxidative stress and neuroinflammation.

A bibliometric analysis further reveals the scientific productivity of various countries. The USA leads in both research and review articles, with 233 and 68 publications, respectively, demonstrating its significant contributions to the field. It is followed by China, which has published 130 research articles and 25 review articles, indicating its active research engagement. Egypt ranks third with 90 research articles, while India has published 16 review articles, showcasing strong academic performance. These findings highlight the prominence of these countries in scientific research on IR-related oxidative stress and neuroinflammation.

TreeMap

Figure 4A presents a TreeMap visualization depiction the top 20 author keywords most frequently used in research articles on IR-induced oxidative stress and neuroinflammation in the brain. The analysis revealed that the keywords “ionizing radiation” (30%) and “oxidative stress” (13%) were the most commonly applied in this research domain.

Similarly, Figure 4B provides a TreeMap visualization illustrating the top 20 author keywords frequently encountered in review articles within this field. The most recurrent keywords were “ionizing radiation” (21%) and “neuroinflammation” (13%).

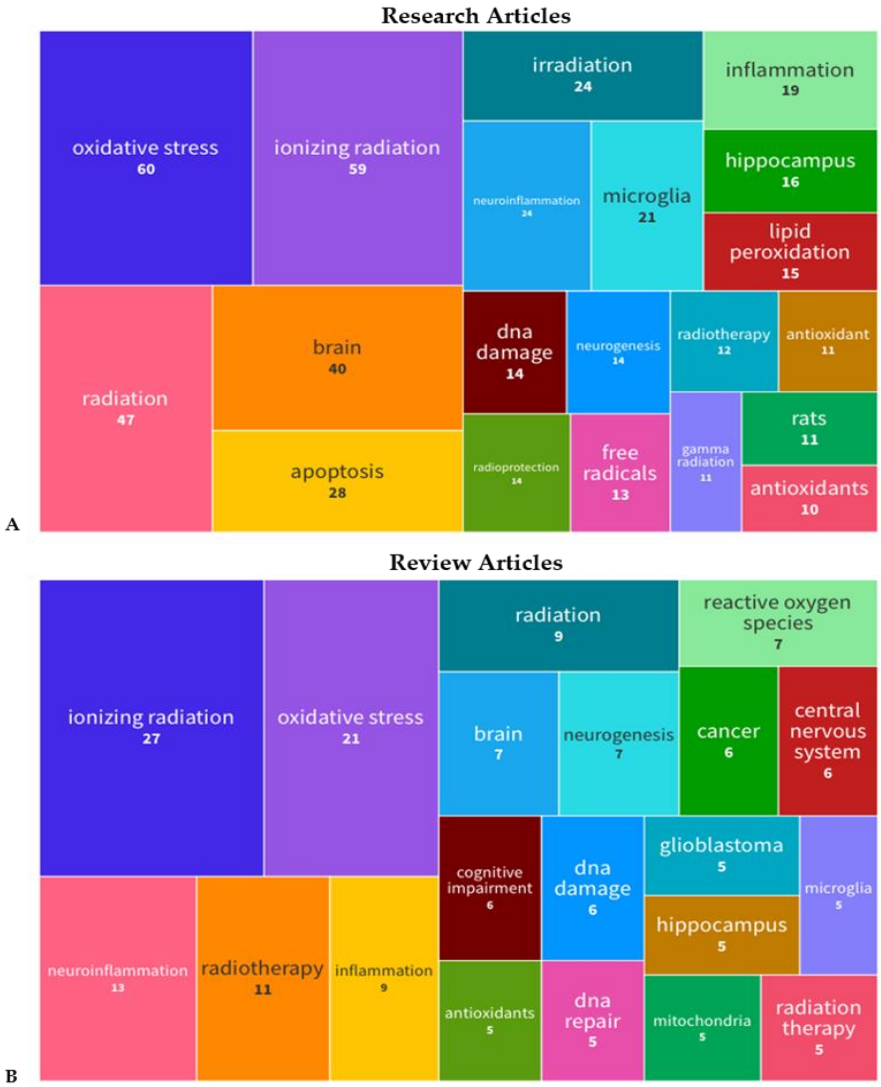

Figure 4. TreeMap representing the top twenty authors' keywords commonly found in research (A) and review articles (B) related to the influence of IR on oxidative stress and neuroinflammation in the brain.

Discussion

Given the growing publication trend on the effects of IR in inducing oxidative stress and neuroinflammation in the brain since 1966, it is evident that this topic remains a critical issue in scientific research, yet to be fully resolved. Of the total 524 review and research articles analyzed, 239 research papers and 87 review articles were published in the last decade, accounting for 62,2% of all publications. This trend suggests that the effects of IR on oxidative stress and neuroinflammation in the brain will remain a subject of interest, with the number of related studies likely to increase in the coming years.

Among the contributing countries, the United States holds the leading position, having published 301 articles in this field. These findings highlight the significant scientific contribution of American researchers, reaffirming the country's role as a major source of scientific literature, particularly in peer-reviewed scientific journals. China follows with 155 articles, demonstrating its active participation in this area of study. This surge in radiology-related publications reflects the country's growing investment in nuclear energy for peaceful purposes.

Egypt ranks third, contributing 90 research articles. Notably, institutions such as the Egyptian Atomic Energy Authority (EAEA), the National Center for Radiation Research and Technology and the Egyptian Knowledge Bank (EKB) have collectively published 90 research papers, securing the first, second and third positions in terms of institutional contributions. This highlights Egypt's significant commitment to scientific progress in this field.

Based on the publications included in the bibliometric analysis, a positive correlation has been identified between exposure to IR at various doses and the risk of developing neurological disorders. Despite extensive research efforts, the molecular mechanisms underlying this association remain insufficiently understood. The INWORKS study demonstrated a increased risk of mortality from "mental disorders" following radiation exposure, while data from Mayak workers indicated a statistically significant elevation in the risk of Parkinson's disease. Additionally, there is a documented link between low to moderate doses of chronic radiation exposure and an elevated risk of dementia, Alzheimer's disease, and Parkinson's disease. Alzheimer's disease is characterized by intracellular accumulation of beta-amyloid and neurofibrillary tangles, accompanied by oxidative stress, inflammation, apoptosis and neuronal necrosis. In contrast, the pathogenesis of Parkinson's disease involves the degeneration of dopaminergic neurons in the substantia nigra and other neuronal structures, as well as the formation of cytoplasmic inclusions containing ubiquitinated proteins (Lewy bodies) within neurons [57]. A synthesis of study results, based on 13 relevant studies involving over 276 000 participants, has provided limited evidence of a decline in overall cognitive functions worldwide after exposure to low to moderate doses of IR [47]. Ahmad's studies indicate that radiation-exposed workers exhibited elevated levels of superoxide ($O_2\bullet^-$), IL-6, interleukin-1a (IL-1a) and macrophage inflammatory protein 1α (MIP-1α) in the moderate and high dose groups (as classified by ICRP data) compared to both the control group and low dose group. The biological effects of IR are induced either directly through DNA damage or indirectly through the generation of ROS, which account for approximately 70% of all radiation-induced biological effects. Based on the assessment of ROS levels in the blood under conditions of increased $O_2\bullet^-$, it was hypothesized that lymphocytes and erythrocytes could be the primary sources of the elevated superoxide levels [2]. The meta-analysis results emphasize the significant impact of low doses of IR on the dynamics of antioxidant-oxidative stress, particularly on catalase (CAT) and superoxide dismutase (SOD), which account for 55% of all assessed markers. This highlights the need for continued research to elucidate the underlying mechanisms and to inform targeted interventions aimed at mitigating the adverse effects of low-dose IR exposure on human health [14]. Despite credible causal interpretations and evidence of potential dose-response relationships suggesting the occurrence of neurological changes after radiation exposure, uncertainty remains regarding random or confounding factors.

Our bibliometric study analyzes research on alterations in particularly vulnerable regions of the brain following radiation exposure. Exposure to IR has been shown to induce the generation of reactive oxygen and nitrogen species (ROS/RNS), leading to a decreased in Na, K-ATPase activity in the cerebral cortex, while the cerebellum demonstrates relative resistance to radiation-induced alterations in this enzyme. Consequently, the radiation-induced reduction in a2 and a3 isoforms results in the relative predominance of the a1 isoform, enhancing Na^+ binding efficiency by the enzyme. Contemporary theories of primary brain dysfunction suggest that the impaired functionality of a2 and a3 Na, K-ATPase subunits may increase susceptibility to neurodegenerative disorders following radiation exposure [34]. Studies on animal models have demonstrated that exposure to a 9 Gy dose significantly decreased the activities of SOD, CAT, and glutathione reductase, and also increased the levels of malondialdehyde (MDA) and carbonyl proteins in the tissues of the cerebellum and cerebral cortex, indicating pronounced oxidative stress. Additionally, changes in neurotransmitter levels, enhanced inflammatory and apoptotic responses, accumulation of amyloid plaques, and reduced brain electrical activity were observed [3].

The keyword "hippocampus" appears multiple times, highlighting its relevance as a key area for further research. The study demonstrated that the hippocampal response to IR suggests a neuroprotective effect at the lowest whole-body exposure dose (0.063 Gy), as it activated the CREB pathway and exhibited anti-inflammatory properties by reducing the number of activated microglia. In contrast, after two years, exposure to 0.5 Gy led to an increase in inflammation and oxidative stress markers, along with CREB deactivation, indicating a shift toward neurodegeneration [25]. Radiation-induced oxidative stress, inflammation and apoptosis in the brain are hypothesized to be associated with the dysregulation of the Nrf2/HO-1/NF-κB signaling pathway. As evidence of oxidative and inflammatory damage, results of study demonstrated that post-irradiation, the activity of key antioxidant enzymes, including CAT, SOD, glutathione peroxidase (GSH-Px), glutathione (GSH), and glutathione reductase (GSR), as well as the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1), were significantly reduced and levels of MDA, nitric

oxide (NO), interleukin-1β (IL-1β), IL-6, transforming growth factor-β1 (TGF-β1), and nuclear factor-kB (NF-kB) protein were markedly elevated. Furthermore, B-cell lymphoma 2 (Bcl-2) expression was downregulated, while Bcl-2-associated X protein (Bax) and tumor necrosis factor-alpha (TNF-α) expression were significantly upregulated, along with an increase in caspase-3-positive cells in the hippocampus, confirming the activation of apoptotic pathways. These findings suggest that radiation disrupts the Nrf2/HO-1/NF-kB axis, leading to impaired antioxidant defense, sustained neuroinflammation, and apoptotic neuronal loss, highlighting the potential of targeting this pathway for neuroprotection in radiation-induced brain injury [70]. Studies have also shown that excessive oxidative stress activates NF-κB, a key regulator of inflammatory and immune responses, as well as the Nrf2/heme oxygenase-1 (Nrf2/HO-1) signaling pathway, which plays a crucial role as an endogenous antioxidant defense mechanism. These pathways play a crucial role in modulating inflammatory, antioxidant, and anti-apoptotic processes, making them potential therapeutic targets for diseases associated with oxidative stress and inflammation. In response to γ-radiation exposure, the study results demonstrated a significant increase in the levels of neuroinflammatory mediators IL-6, NF-κB, and GFAP ($p \leq 0.001$), along with a marked reduction in the anti-inflammatory marker IL-10. Radiation exposure inhibited the expression of Nrf2 and HO-1 proteins and genes by promoting ROS activation—key mediators of radiation-induced damage—thereby inducing apoptosis and triggering multiple inflammatory factors. Apoptosis is regulated by the caspase signaling cascade, and this study revealed a significant upregulation of caspase-3 expression, whereas the expression of the anti-apoptotic marker Bcl-2 was markedly decreased in the IR group compared to the control group. Histological analysis confirmed these findings: γ-radiation exposure in rats led to severe degeneration of cortical neurons, neuronal apoptosis, pronounced perivascular edema, and vascular congestion in the brain. Additionally, the hippocampus exhibited signs of cellular disorganization, shrinkage of large pyramidal neurons with hyperchromatic nuclei, and prominent vacuolation in the granular cell layers [15].

The results also show that both single (5 Gy) and fractionated (10 Gy) exposure to ionizing radiation lead to impairments in spatial memory, reduced motor activity, and cognitive dysfunction. It is suggested that radiation-induced damage, manifested as edema and necrosis of the dentate gyrus (DG) in the hippocampus, may contribute to cognitive decline. Post-irradiation, a significant decrease in BDNF and Tau gene expression was observed, potentially promoting neurodegenerative processes. Under normal conditions, Tau protein plays a crucial role in the formation and stabilization of microtubules; however, its abnormal phosphorylation disrupts tubulin binding, leading to cognitive impairment. The results demonstrated a substantial downregulation of genes associated with neuronal function, including calcium ion transport regulation, neurotransmitter secretion, and neuronal differentiation, which may further exacerbate cognitive deficits. Concurrently, an upregulation of genes involved in inflammatory and immune responses, such as monocyte and lymphocyte chemotaxis, angiogenesis, and chemokine-mediated signaling pathways, highlights the pivotal role of neuroinflammation in the pathogenesis of radiation-induced cognitive dysfunction. Furthermore, the results of the study confirms that ionizing radiation-induced brain damage is driven by oxidative stress, DNA strand breaks, and apoptosis, as evidenced by the downregulation of key antioxidant genes (Nrf2, HO-1, Keap1) and the upregulation of p21. The regulation of genes associated with p53-dependent apoptosis (bax, bcl2, caspase3) underscores the critical role of programmed cell death in radiation-induced neurotoxicity [51].

Exposure to 7 Gy of brain irradiation resulted in significant cognitive and emotional dysfunctions, including impaired contextual fear memory and depression-like behavior in mice. A reduction in the number of immature neurons, indicating impaired proliferation of neural stem cells and adult hippocampal neurogenesis, may contribute to the cognitive and emotional disturbances observed after irradiation. Further analysis revealed that cranial irradiation disrupted the hippocampal neurogenic microenvironment, characterized by increased oxidative stress and neuroinflammation. Antioxidant defense markers, including SOD, GSH-Px and CAT, were significantly decreased, while GSH levels declined and MDA levels increased, indicating oxidative damage. Additionally, hippocampal levels of pro-inflammatory cytokines IL-6, TNF-α, and IL-17A were significantly elevated, whereas the anti-inflammatory cytokine IL-4 was markedly reduced. These findings suggest that radiation-induced cognitive and emotional dysfunctions may be linked to disruptions in hippocampal neurogenesis and a pro-inflammatory shift in the neurogenic microenvironment [62]. There is also evidence suggesting that whole-body irradiation of rats at a dose of 4 Gy induces oxidative stress, inflammation, and apoptosis. This is demonstrated by a significant increase in pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and C-reactive protein, accompanied by a concurrent decrease in IL-10 levels. Additionally, elevated MDA levels, along with reduced activity of SOD, CAT, GSH-Px and GSH, indicate impaired antioxidant defense mechanisms. Immunohistochemical analysis further revealed a marked upregulation of caspase-3 and p53, highlighting enhanced apoptotic activity in the brains of irradiated rats [16].

In rats exposed to 15 Gy of radiation, the expression levels of NOX2, NOX4, and caspase-3 were significantly increased compared to the control group ($p < 0.001$). The key mediators of the oxidative system include NADPH oxidases (NOX), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), mitochondria, and antioxidant defense enzymes. Among the NADPH oxidase subgroups, NOX2 and NOX4 play a critical role in radiation-induced oxidative stress. Ionizing radiation-induced oxidative stress, DNA damage, and genomic instability trigger the activation and upregulation of these enzymes. The release of pro-inflammatory and pro-fibrotic cytokines, along with the activation of endothelial cells, fibroblasts, macrophages, neutrophils, and lymphocytes, can enhance the expression and activity of NOX2 and NOX4, leading to excessive ROS production and the development of oxidative stress. Excessive ROS production can suppress antioxidant defense enzymes, compromise vascular integrity, and disrupt the cerebral microcirculation, leading to hypoxia and necrosis of normal brain tissue. MDA and NO levels were significantly increased in the brains of rats exposed to

radiation compared to the control ($p < 0.001$), whereas CAT, SOD, and GSH-Px levels were markedly reduced in the irradiated group ($p < 0.01$). These findings highlight the role of NOX-mediated oxidative stress in radiation-induced brain damage and emphasize the need for further investigation into potential neuroprotective strategies [68].

In our bibliometric study, we explored various aspects of radiology, oxidative stress and neuroinflammation of the brain. Our analysis covered topics such as radiation-induced brain damage across different dose levels, alterations in neurogenesis due to prenatal and postnatal radiation exposure, oxidative stress mechanisms in the brain and the roles of pro-inflammatory and anti-inflammatory cytokines. All data were sourced from the WOS and Scopus databases. Despite our comprehensive analysis, several unresolved challenges persist in this field. One of the primary obstacles is the transition from experimental studies to clinical applications, which is complicated by factors such as environmental influences, dietary habits and physical and psychological conditions. These variables can lead to inconsistencies and hinder the accuracy of research findings. Our bibliometric approach, based on empirical data from published articles, focused on metadata analysis, including information about authors, institutions and countries, to evaluate research productivity and collaboration. However, we did not perform a textual content analysis. Additionally, only full-text articles in English were included in our study, while publications with abstracts in English and those published in other languages were excluded.

Conclusions

International collaboration in research on the effects of IR on oxidative stress and neuroinflammation in the brain is essential for develop advanced strategies to prevent and treat radiation-induced health complications. This bibliometric analysis offers comprehensive qualitative and quantitative insights into key contributing countries, leading authors, institutions, scientific journals and global collaboration trends in radiology. Our results highlight the substantial contributions of the United States, Egypt, China and India, underscoring their leading roles in this research field. Furthermore, the involvement of regions with prior radiation exposure further emphasizes the global significance of this issue.

Over the past decade, there has been a notable surge in research on IR-induced oxidative stress and neuroinflammation, reflecting its growing importance in understanding the broader implications of radiation exposure. Despite persistent knowledge gaps regarding the effects of IR, our analysis provides valuable insights that can help shape future research directions. Given the increasing evidence of IR's detrimental impact on brain health, it is crucial for future studies to adopts a multidisciplinary approach, integrating radiology, neuroscience and molecular biology. This integration will be key to developing targeted therapeutic strategies and protective measures. This comprehensive review serves as a foundation for advancing our understanding of IR's effects on brain health, guiding future research priorities and informing clinical practice to mitigate radiation-induced neurotoxicity.

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