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Impact of Low-Dose Ionizing Radiation on Liver Function in Mice: A Systematic Review

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Abstract

Background: Adverse health consequences of exposure to ionizing radiation, especially low-dose radiation (LDR), are highly controversial. Recent studies have shown that ionizing radiation can promote the inflammatory state of the liver. The present study aimed to review the current knowledge of the harmful effects of low-dose ionizing radiation on the liver in mice.

Materials and Methods: A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science (WOS) databases. The PRISMA protocol was employed for systematic literature review, which includes formulation of research questions, systematic review process for selection of articles, quality assessment, data abstraction, and data analysis.

Results: In the first stage of the systematic review process, 1473 articles were retrieved. At last a total of 15 articles were included in the study based on the inclusion and exclusion criteria. LDR from X-rays and gamma rays was utilized for irradiation in these articles. The results revealed that low-dose ionizing radiation can have detrimental effects, including mitochondrial dysfunction, increased oxidative stress, dilation of the central hepatic vein, increased expression of hepatic proteins involved in metabolism, liver inflammation, necrosis, and cancer in the liver.

Conclusion: Given the potentially damaging effects of low-dose ionizing radiation exposure to the liver, early identification of individuals at higher risk of exposure to these radiations can result in better preventive intervention decisions to prevent damage.

Keywords: Ionizing Radiation, Mice, Gamma Rays, X-Rays, Oxidative Stress

Introduction

Ionizing radiation has both natural sources (e.g., radon, cosmic radiation, soil, and food) and artificial sources (e.g., medical applications, the nuclear industry, and power plant accidents) [1]. Humans are constantly exposed to cosmic radiation, as well as radiation from natural radionuclides in the Earth, building materials, food and drink. Moreover, nuclear accident scenarios have led to environmental contamination at unknown levels. Tens of thousands of people, including children, live in contaminated areas and are exposed to ionizing radiation on a daily basis [2].

There has been growing concern about the potential risks of exposure to ionizing radiation. These radiations can cause various of harmful effects, such as direct DNA damage, induction of reactive oxygen species (ROS) as well as malignancies [3, 4]. Many of the ROS that are generated are rapidly suppressed by antioxidants [5]. Oxidative stress occurs when ROS production exceeds the capacity of cells. As a result, lipids, proteins, and DNA are damaged, leading to diminished cellular function, inflammatory responses, and ultimately dysregulation of metabolic processes [6-8].

The adverse health effects of ionizing radiation remain highly debated. More information is needed to gain a more comprehensive understanding of the harmful potential of ionizing radiation at all doses [9]. The

pathological effects of radiation are dose-dependent, with high doses of radiation being most damaging to cells and tissues. Recently, there has been increased interest in examining the biological effects of low-dose ionizing radiation [10].

Low-dose ionizing radiation refers to levels of radiation that deliver relatively small amounts of energy to living tissues per exposure. These doses are typically far lower than the levels that cause acute radiation effects (such as acute radiation sickness). The biological responses to low-dose radiation (LDR) are distinct from those induced by high-dose radiation (HDR). The mechanisms of biological responses to HDR have been extensively studied [11]. Nevertheless, responses to LDR at the molecular, cellular, tissue, or organ levels are not fully understood [12].

Based on studies, the liver is considered a radiation-sensitive organ in high-dose exposures [13, 14], bearing in mind that it is the metabolic center of the body. Major metabolic activities and detoxification are carried out by liver mitochondria through metabolic pathways such as lipid metabolism [2]. Recent studies have indicated that ionizing radiation can augment the inflammatory state of the liver [15, 16]. The presence of an inflammatory environment causes various liver diseases, such as hepatitis and liver cancer [17].

This systematic review aims to inspect existing evidence on the effects of low-dose ionizing radiation on liver function in mice. Given the widespread applications of radiotherapy as well as occupational or environmental exposure to low radiation doses, a precise understanding of its biological effects on vital organs such as the liver is essential. This study ascertains changes in liver function markers (e.g., liver enzymes, oxidative stress, and tissue damage) induced by low-dose ionizing radiation exposure. It also seeks to potential modifying factors (e.g., radiation dose, exposure duration, and genetic characteristics). The findings of this systematic review could contribute to improved radiation protection strategies and health risk assessments associated with low-dose radiation, while providing a foundation for future research in this field.

Materials and Methods

Search strategy: This study followed the PRISMA guidelines to ensure methodological rigor. The literature search was performed to assess all relevant studies on “Impact of Low-Dose Ionizing Radiation on Liver Function in Mice” in both medical subject heading (MeSH) or advance on electronic databases of Web of Science (WOS), PubMed, and Scopus up to August 2024 using the keywords of “low-dose ionizing radiation” OR “LDR” OR “LDI” OR “low-dose ionizing” AND “Mice” OR “Liver” OR “Mouse liver” OR “Mouse” in combination in keywords, title, or abstract. In order to minimize selection bias, manual searches of reference lists from included studies were also conducted. PRISMA’s standardized framework enhances transparency and reproducibility, making it a gold standard for systematic reviews in medical research [18].

Inclusion and exclusion criteria: Inclusion criteria for the screened publications were as follows: (1) Studies involving animal models of low-dose ionizing radiation-induced liver damage in mice; (2) All studies were conducted in vivo; (3) Included animals of all ages; (4) Included studies reporting efficacy outcomes; (5) Conducted over the past 10 years. Exclusion Criteria Applied: (1) Failure to meet all inclusion criteria; (2) Books, book chapters, conference proceedings, case reports, and case series; (3) Reviews or meta-analyses; (4) Duplicate studies; (5) Studies published in languages other than English.

Quality assessment: Two independent reviewers appraised the methodological rigor of the selected studies. In cases of disagreement during data extraction or quality appraisal, a third reviewer was consulted to resolve discrepancies. The risk of bias in all in vivo studies was ascertained using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Risk of Bias Tool [19]. Each study was categorized as having a "high risk," "low risk," or "unclear risk" of bias. The SYRCLE Risk of Bias Tool consists of 10 criteria, grouped into six key domains: Selection bias (Random sequence generation, Baseline characteristics, Allocation concealment), Performance bias (Randomized housing, blinding of caregivers/researchers), Detection bias (Randomized outcome assessment, blinding of outcome assessors), Attrition bias (Incomplete outcome data), Reporting bias (Selective outcome reporting), and Other potential biases (Additional sources of bias).

Research question formulation: The research question was formulated using the PICO framework, which includes Population or Problem, Interest, and Context. In the present study, mice were included as the population, the effect of low-dose ionizing radiation (interest), and, the harmful effects on the liver (Context), which then resulted in the main research question: the harmful effects of low-dose ionizing radiation on the liver in mice.

Systematic review process for selecting articles: The systematic review process for selecting articles includes the steps of identification, screening, and eligibility. Figure 1 displays the flowchart of the article selection process.

Identification: The first step is to identify keywords, followed by a search in the dictionary and encyclopedia to find related and similar meanings. Keywords related to the topic were searched in the databases of interest.

Screening: Along the screening stage, the titles, abstracts, keywords, and publication years of the identified papers were recorded in Excel. The titles and

abstracts of the selected articles were assessed based on several inclusion and exclusion criteria. A 10-year time frame from 2014 to August 2024 was selected for the present research. Relevant full-text articles were downloaded and entered into the eligibility phase.

Eligibility: In this phase, the researchers appraised the eligibility of the articles through carefully scanning the entire collection of articles. The titles, abstracts, and keywords of all articles were reviewed to ensure that they fulfilled the inclusion criteria. In this process, disagreements between researchers were discussed and resolved. The articles obtained following the initial screening were assessed by the first reviewer based on the research topic and inclusion/exclusion criteria. Next, their relevance and accuracy were evaluated by the second and third reviewers. Ultimately, a study entitled "Impact of Low-Dose Ionizing Radiation on Liver Function in Mice: A Systematic Review" was selected.

Results

Background of selected articles: In the initial phase of the systematic review, 1,473 articles were collected from Web of Science (WOS), PubMed, and Scopus. Once inclusion/exclusion criteria were applied and duplicates were removed, 1,337 articles were excluded, leaving 119 for quality assessment. Titles, abstracts, and keywords were thoroughly reviewed to ensure relevance. Of these, 104 were excluded for not focusing on low-dose ionizing radiation's harmful effects on mice livers. Ultimately, 15 articles qualified for evaluation (Fig. 1). Methodologies and findings of selected articles is outlined in Table 1.

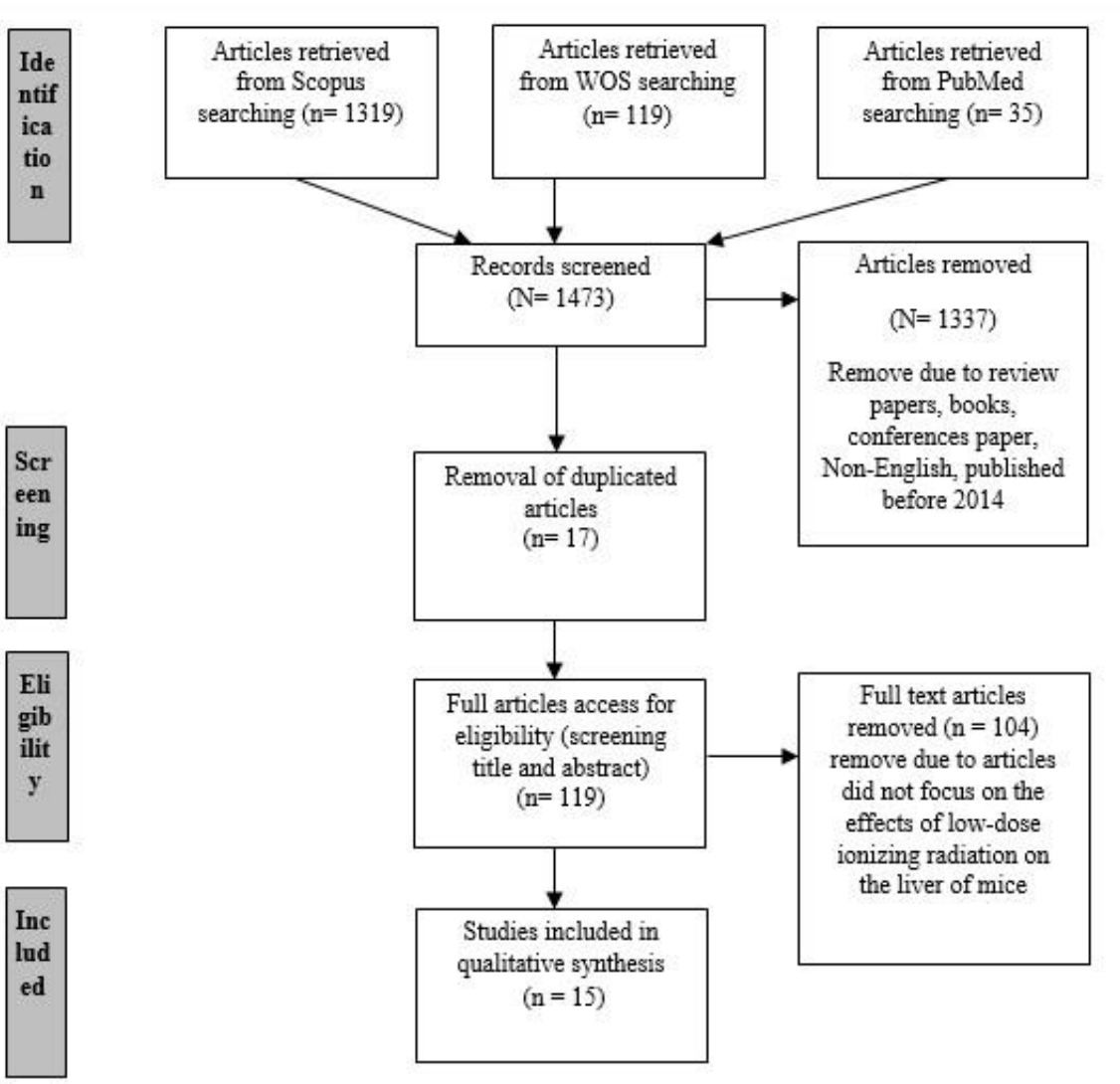

Fig. 1. Flowchart of the study selection process

Table 1. Methodology and findings of selected articles

No.	Citation	Year	Sample size (n)	Radiation type/dose	Data collection time (post irradiation)	Key findings
1	Mayur V. Bakshi [2]	2014	60	Gamma/ 0.02 to 1 Gy	Early (11 days) and late (7 months)	• Immediate inhibition of the glycolytic pathway and diminished pyruvate dehydrogenase availability in the liver. • Inactivation of the transcription factor PPAR-alpha. • Mitochondrial dysfunction and elevated oxidative stress. • Immediate and persistent adverse effects on metabolic pathways (Total body irradiation doses ≥ 0.1 Gy). • Doses as low as 0.1 Gy induced long-term alterations in the liver proteome.
2	Yufeng Zhang [8]	2017	48	X-ray/ -	10 days	• Mitochondrial function initially declined after X-ray exposure but then rapidly recovered. • Mitochondrial function increased ten days post irradiation exposure.
3	V. F. Mikhailov [20]	2021	183	Gamma/ 10 mGy	10 Months	• The activity of tumor suppressors was lower in tumor-bearing mice than in cancer-free mice, whereas oncogene activity (NFkB(p65), IkBα, iNOS, TAL1, CTCF, NEAT1 lncRNA and miR-125b) increased. • These parameters may serve as potential biomarkers for radiation-induced cancer.
4	Xinyue Liang [12]	2018	32	Gamma/ 28 mGy	Every 3 days for 4 months	• At the organ level, the heart was the most affected, followed by the liver and testis. Positive changes in miRs related to DNA damage response were observed in these organs. • Metabolism-related miRs diminished in the liver but increased in the testis. • Both immediate and long-term changes in miR expression profiles were observed in different organs following repeated LDR exposure.
5	Tetsuo Nakajima [21]	2017	-	X-ray/ 4 and 8 Gy Gamma/ 20 mGy	20 mg/day for 400 days, evaluated 3 months after the end of exposure	• Protein expression changes were observed 3 months post-lethal radiation. • Immunohistochemistry revealed increased altered proteins near liver blood vessels. • Chronic and acute radiation induced different protein expression patterns. • Inflammation- and apoptosis-related protein changes persisted 3 months post-chronic exposure. • Protein changes depend on dose, dose rate, and time, influencing long-term liver effects. • MyD88 expression grew in liver endothelial cells 3 months post-acute radiation.
6	Lan Yi [22]	2018	36	Gamma/ 30, 100 or 250 mGy	500 days	• 100 & 250 μGy/h: Significant central vein enlargement vs. control. • 30 μGy/h: Slight central vein dilation, no other liver changes. • 250 μGy/h: Hepatic necrosis, interstitial fibrosis, and steatosis observed.
7	Caitlund Q. Davidson [23]	2020	84	Gamma/ 300 and 1000 mGy	Day 15 of pregnancy	• 300 mGy exposure (16-week offspring, n=84): No effect on mRNA expression of metabolic genes (glucose metabolism, insulin signaling, lipid metabolism). • 1000 mGy exposure: Increased expression of insulin resistance and gluconeogenesis genes. • 4-month female offspring (1000 mGy): Higher liver weight, increased hepatic glucose metabolism proteins, and elevated adipose tissue FDG uptake. • Prenatal radiation ≤300 mGy did not impact metabolic function. • 1000 mGy may be a threshold for sex-specific changes in glucose uptake and liver gene/protein expression. • SLDR altered adipose glucose uptake and hepatic expression, potentially worsening with age.
8	Wan Mazlina Md Saad [24]	2017	10	X-ray/ 100 μGy	1 month	• LDR exposure in Rx group ↑ ROS in liver vs. Cx (P = 0.01). • Rx liver tissues had ↑ AP sites vs. Cx (P = 0.03). • Rx revealed severe nuclear ultrastructure changes vs. Cx.

9	Malgorzata Lysek-Gladysinska [25]	2018	-	X-ray/ 30 and 120 mGy	60 weeks	• Mitochondrial and lipid damage: Irradiated animals showed more hepatocyte mitochondrial damage and lipid buildup than controls. • ApoE$^{-/-}$ sensitivity: Radiation effects were stronger in ApoE$^{-/-}$ mice vs. wild-type. • Lysosomal enzyme changes: Radiation altered hydrolase activities (e.g., acid phosphatase) in wild-type but not ApoE$^{-/-}$ mice. • Liver injury markers: Radiation lowered plasma liver injury markers in wild-type mice but raised hepatic lipase in ApoE$^{-/-}$ mice, suggesting greater hepatocyte resistance in wild-types. • Late radiation effects: Liver disorders linked to disrupted lipid metabolism were reported as a delayed radiation effect.
10	Katsuyoshi Fujikawa [26]	2022	32	Gamma/ 20 mGy	400 days	• Cholesterol biosynthesis and lipogenesis: Increased expression of related genes (Cyp51, Sqle, Fdps) in female mice irradiated at 20 mGy/day for 200–300 days. No significant changes in males. • Adipogenesis regulators: Srebf1 and Pparg expression rose with age and radiation in both sexes. • Dose comparison: Male mice exposed to low (LDR) vs. medium (400 mGy/day) dose radiation indicated distinct gene profiles. • Implications: Findings aligned with higher fatty liver/obesity risk in LDR-exposed females, suggesting metabolism is a key LDR target.
11	I. B. Tanaka III [27]	2017	1129	Gamma/ 20 mGy	700 days	• Irradiated mice showed significant body weight increase within days 200–500. • Higher incidence of adrenal hyperplasia, liver fatty degeneration, ovarian atrophy, and tubulostromal hyperplasia in irradiated mice. • Low-dose gamma radiation caused both earlier cancer onset (induction) and faster progression (early death), varying by the tissue type. • Liver degeneration was significantly higher in irradiated mice from days 300–600 (P=0.001), peaking at day 400 before declining.
12	Roser Esplugas [28]	2018	60	Gamma/ -	10 days	• BPA and 137Cs caused kidney and liver damage by promoting oxidative stress.
13	Fadia Nicolas [29]	2015	-	Gamma/ 100 mGy	-	• Iopamidol alone significantly affected S-nitrosylation in the brain, lung, and liver. • 0.1 Gy (without iopamidol) altered SNO levels in proteins of varying molecular weights in the liver, lung, brain, and plasma. • Liver: ↓ S-nitrosylation at 0.1 Gy (37-kDa proteins). ↑ S-nitrosylation at 4 Gy (in liver and lung).
14	Ayman Jafer [30]	2020	-	X-ray/ 1 Gy	4 hours, 24 hours, 1 and 10 weeks	• Acute X-ray exposure significantly altered the transcriptome in male mice. • BALB/c livers revealed gene expression changes up to 10 weeks post-irradiation. • CBA/Ca livers exhibited only immediate changes (4h post-irradiation).
15	Lan Yi [31]	2017	40	Gamma/ Less than 50, 50 to 500, 500 to 1000 µGy	180 days	• Proteomics analysis indicated 69 proteins with >1.5-fold expression changes in irradiated liver tissues, linked to cytoskeleton, metabolism, defense, mitochondrial damage, detoxification, and tumorigenesis. • RT-PCR and WB suggested low-dose radiation may increase cancer risk. • <50 µGy/h group: Slight central vein dilation; no other liver damage. • 50–500 & 500–1000 µGy/h groups: Significant central vein dilation, necrosis, and inflammation.

Abbreviations: **LDR**: Low-dose radiation, **HDR**: High-dose radiation, **Gy**: Gray, **mGy**: Milligray (10^{-3} Gy), **µGy**: Microgray (10^{-6} Gy), **ROS**: Reactive oxygen species, **miRs**: MicroRNAs, **DDR**: DNA damage response, **PPAR-α**: Peroxisome proliferator-activated receptor alpha, **NFkB**: Nuclear factor kappa B, **iNOS**: Inducible nitric oxide synthase, **TAL1**: T-cell acute lymphocytic leukemia protein 1, **CTCF**: CCCTC-binding factor, **NEAT1**: Nuclear paraspeckle assembly transcript 1, **MyD88**: Myeloid differentiation primary response 88, **AP sites**: Apurinic/apyrimidinic sites, **BPA**: Bisphenol A, **SNO**: S-nitrosylation.

The reviewed studies collectively indicate that low dose ionizing radiation, whether delivered acutely or chronically at varying doses and dose rates, induces significant molecular, metabolic, and histopathological alterations in the liver of exposed mice. These effects manifest both immediately and persist long-term, affecting pathways associated with oxidative stress, mitochondrial dysfunction, lipid metabolism, inflammation, and carcinogenesis.

Metabolic and Mitochondrial Dysfunction: Radiation exposure heavily disrupts hepatic metabolic pathways, with significant alterations in glycolysis, lipid metabolism, and mitochondrial function. Studies by Mayur V. Bakshi et al. [2] indicated that even low-dose acute irradiation (0.1 Gy) in neonatal mice resulted in immediate suppression of glycolysis and diminished pyruvate dehydrogenase availability, impairing the tricarboxylic acid (TCA) cycle. These metabolic disruptions were accompanied by long-term inactivation of PPAR-α, a key regulator of fatty acid oxidation, leading to hepatic lipid accumulation and oxidative stress. Likewise, Katsuyoshi Fujikawa et al. [26] observed sex-specific dysregulation of lipid metabolism genes (Srebf1, Pparg, Cyp51) in mice subjected to chronic low-dose-rate (LDR) radiation (20 mGy/day), with female mice exhibiting pronounced steatosis owing to augmented cholesterol biosynthesis and lipogenesis. Mitochondrial dysfunction was further evidenced by Yufeng Zhang et al. [8], who reported a biphasic response in mitochondrial respiration following X-ray exposure—initial suppression due to ROS-induced damage, followed by compensatory upregulation, suggesting an adaptive but potentially maladaptive stress response. Collectively, these findings suggest that radiation-induced metabolic dysfunction is driven by mitochondrial impairment, PPAR-α suppression, and lipid metabolism dysregulation, contributing to long-term hepatic damage. Moreover, Tetsuo Nakajima et al. [21] reported that chronic low-dose irradiation (20 mGy/day for 400 days) induced persistent changes in proteins linked to inflammation and apoptosis, exacerbating metabolic dysfunction. The study by Malgorzata Lysek-Gladysinska et al. [25] reinforced these observations, revealing that even scatter radiation (secondary exposure from heart irradiation) caused mitochondrial ultrastructural damage and lipid droplet accumulation in hepatocytes, particularly in ApoE-/- mice, exhibiting greater susceptibility owing to impaired lipid clearance. These metabolic perturbations were often accompanied by increased oxidative stress, as witnessed by Wan Mazlina Md Saad et al. [24], where ultra-low-dose X-rays (100 μGy) promoted ROS and oxidative DNA lesions, further impairing mitochondrial efficiency. Thus, radiation-induced metabolic and mitochondrial dysfunction is a multifactorial process, involving energy pathway disruption, oxidative damage, and inflammatory signaling, which may predispose the liver to steatosis, insulin resistance, and fibrosis over time.

Oxidative Stress and DNA Damage: Ionizing radiation consistently induces oxidative stress in the liver, primarily through generating reactive oxygen species (ROS), which subsequently cause DNA damage, lipid peroxidation, and protein modifications. According to studies, even very low-dose radiation (e.g., 100 μGy X-rays) significantly elevates hepatic ROS levels and oxidative DNA damage, as evidenced by elevated apurinic/apyrimidinic (AP) sites and 8-hydroxy-2′-deoxyguanosine (8-OHdG) adducts [24, 28]. Wan Mazlina Md Saad et al. [24] found a marked rise in ROS production (18,154 ± 803 vs. 16,243 ± 997 in controls) and AP site formation (33.37 vs. 27.84 per 10^5 base pairs) in mice exposed to low-dose radiation, accompanied by ultrastructural nuclear damage indicative of apoptosis, such as chromatin condensation and membrane shrinkage (Fig. 2). In the same vein, Esplugas et al. [28] observed that combined exposure to 137Cs and bisphenol-A (BPA) synergistically exacerbated oxidative hepatic injury, underscoring the vulnerability of the liver to environmental radiotoxicants.

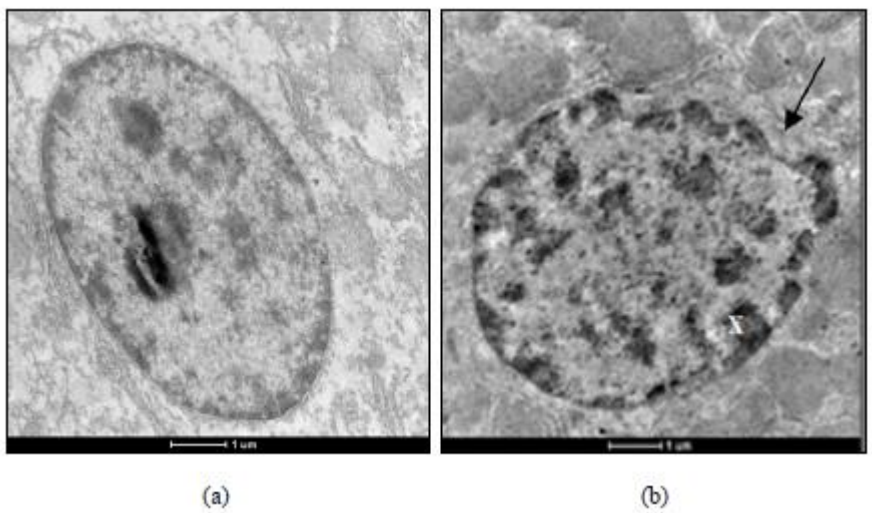

Fig. 2. Nuclear ultrastructural alterations in liver tissue following LDR exposure

At higher doses, oxidative stress disrupts redox-sensitive signaling pathways, including S-nitrosylation of hepatic proteins. Nicolas et al. [29] observed dose-dependent alterations in S-nitrosylated (SNO) proteins following 0.1 Gy and 4 Gy gamma irradiation, with a notable decline in 37-kDa SNO-proteins at low doses—a potential marker of redox imbalance. Persistent oxidative stress also impairs mitochondrial function, as demonstrated by Zhang et al. [8], where X-ray irradiation initially suppressed mitochondrial respiration, coinciding with ROS overproduction, before partial recovery at later stages. These findings collectively highlight oxidative stress as a central mechanism in radiation-induced hepatic injury, with DNA damage and mitochondrial dysfunction serving as critical downstream effectors of long-term pathology.

Inflammation and Fibrosis: Radiation-induced hepatic inflammation and fibrosis emerge as critical long-term outcomes, driven by persistent oxidative stress, pro-inflammatory signaling, and aberrant tissue remodeling. Acute exposure to doses as low as 0.1 Gy triggers immediate inflammatory cascades, as evidenced by elevated MyD88 expression in liver endothelial cells, which persists for months post-irradiation (Fig. 3) [21]. This pattern aligns with chronic models, where protracted low-dose-rate (LDR) exposure (e.g., 20 mGy/day) upregulates proteins linked to NFkB activation and apoptotic pathways, promoting a pro-fibrotic microenvironment [21, 26]. Histopathological analyses reveal dose-dependent central vein dilation, hepatocyte necrosis, and collagen deposition, especially at higher dose rates (≥100 μGy/h) (Fig. 4) [22, 31]. For instance, Lan Yi et al. found that 250 μGy/h gamma radiation induced marked hepatic necrosis, interstitial fibrosis, and steatosis, accompanied by cytoskeletal protein dysregulation—a hallmark of epithelial-to-mesenchymal transition (EMT) (Fig. 5) [22, 31]. These changes correlate with augmented lysosomal hydrolases (e.g., β-glucuronidase) in wild-type mice and exacerbated lipid accumulation in ApoE-/- models, suggesting that metabolic dysfunction amplifies radiation-induced fibrosis [25]. Together, these findings implicate chronic inflammation as a link between initial radiation injury and late-stage fibrotic degeneration, with vascular damage (e.g., central vein dilation) functioning as a key histopathological indicator.

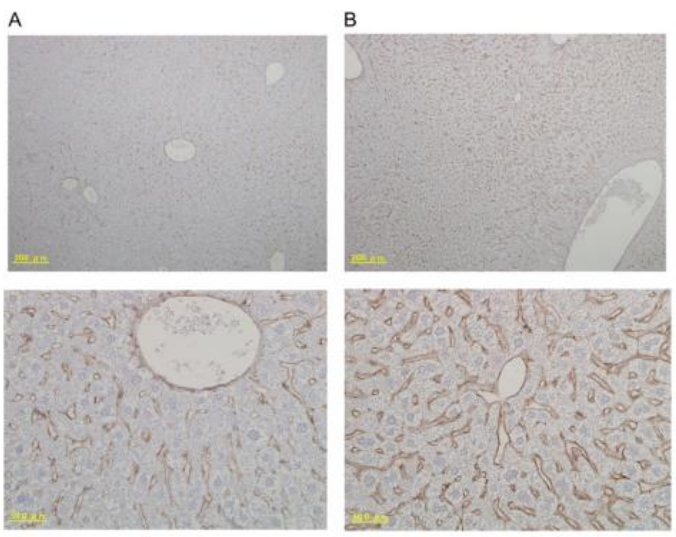

Fig. 3. Immunohistochemically staining analysis of MyD88 in mouse liver 3 months after acute radiation. (A) Control; (B) 3 months after acute radiation. Upper panels are 100× and lower panels are 400×

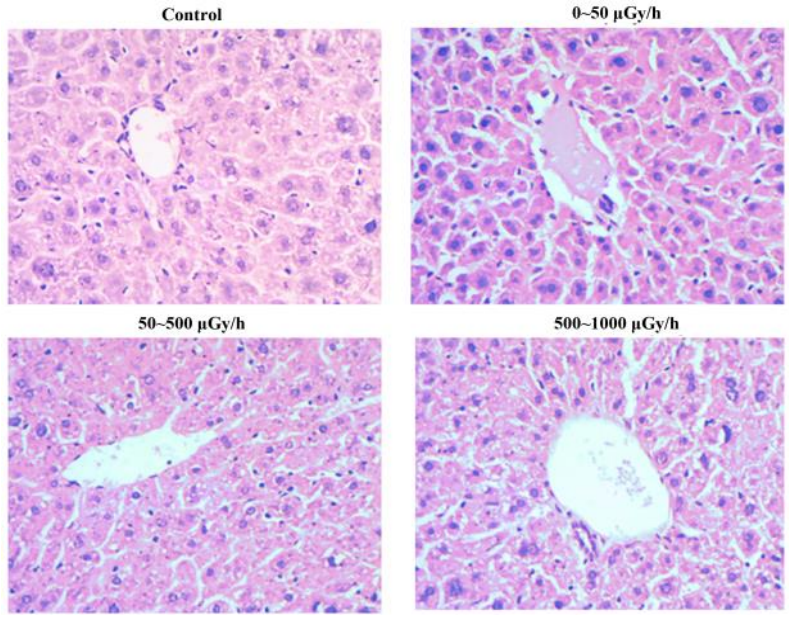

Fig. 4. Morphology of liver tissues of mice receiving different radiation doses (HE×400)

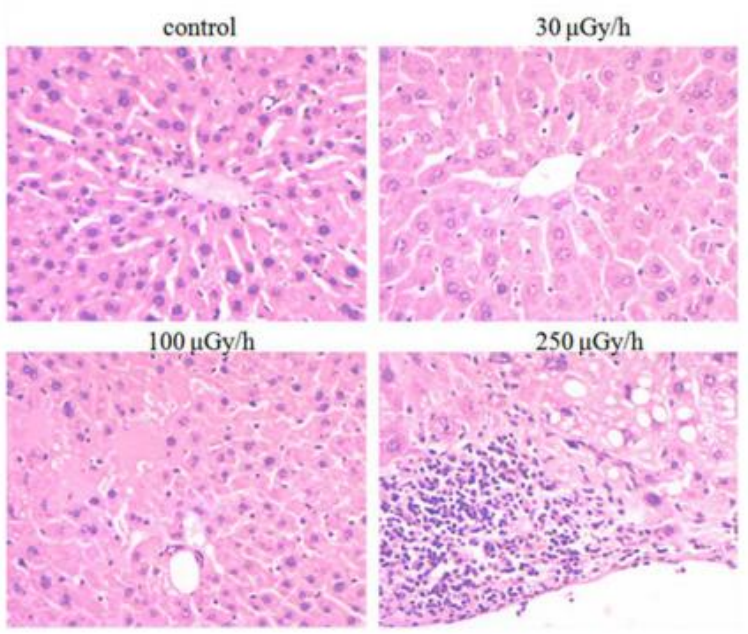

Fig. 5. Morphology of liver tissues obtained from mice chronically exposed to 30, 100, and 250 microGy/h

The fibrotic response is further modulated by time and cumulative dose. Whereas acute high-dose irradiation (8 Gy) elicits rapid inflammatory protein expression (e.g., within 6 days), chronic LDR (8 Gy over 400 days) provokes delayed but sustained upregulation of fibrogenic markers, including collagen-associated proteins [21]. This dichotomy highlights the liver's capacity for adaptive recovery after acute insults but progressive dysfunction under prolonged radiation stress. Notably, the severity of fibrosis correlates with oxidative DNA damage (e.g., AP sites) and ROS overproduction, as observed in ultra-low-dose (100 μGy) exposures [24]. This implies that even minimal radiation can prime the liver for fibrotic remodeling when oxidative defenses are overwhelmed. These insights emphasize inflammation and fibrosis as interconnected endpoints of radiation injury, with implications for late-effect risk assessment in exposed populations.

Carcinogenic and Tumorigenic Effects: The reviewed studies provide compelling evidence that ionizing radiation, even at low or chronic doses, promotes hepatic carcinogenesis via multiple mechanisms, including genomic instability, epigenetic dysregulation, and sustained oxidative stress. V. F. Mikhailov et al. [20] observed that prolonged low-dose irradiation (12.6 Gy at 10 mGy/min) in hybrid mice led to malignant lymphomas in the liver and abdominal tissues, with 14 out of 94 irradiated mice developing tumors by 10 months post-exposure. Molecular analysis indicated a marked suppression of tumor suppressor genes alongside upregulated oncogenic pathways, including NFkB(p65), TAL1, and the long non-coding RNA NEAT1, suggesting their potential as biomarkers for radiation-induced hepatocarcinogenesis. Likewise, Lan Yi et al. [31] found dose-dependent histopathological changes in mice exposed to gamma radiation (50–1000 μGy/h), including hepatic necrosis, inflammation, and altered expression of 69 proteins linked to detoxification, mitochondrial damage, and tumorigenesis. Proteomic and Western blot analyses further identified dysregulated proteins involved in cytoskeletal integrity and cellular defense, reinforcing the notion that chronic low-dose radiation may act as a tumor promoter. In contrast to these findings, Dahl et al. reported no significant changes in global DNA methylation, indicating no observable alteration in epigenetic regulation in their study [9]. Moreover, I. B. Tanaka III et al. [27] reported a significant rise in fatty liver degeneration and neoplastic lesions in female B6C3F1 mice subjected to continuous low-dose-rate gamma radiation (20 mGy/day), with severity peaking at 400 days post-exposure. The elevated incidence of moderate-to-severe hepatic lesions correlated with prolonged oxidative stress and metabolic dysfunction, especially in lipid metabolism genes (Srebf1, Pparg). These findings align with the broader hypothesis that radiation-induced persistent oxidative DNA damage (e.g., 8-OHdG) and chronic inflammation establish a permissive microenvironment for malignant transformation. Collectively, these studies emphasize that even sub-lethal radiation exposures can promote hepatic carcinogenesis through synergistic effects on genomic stability, redox balance, and oncogenic signaling, with dose-rate and cumulative dose playing critical roles in determining long-term outcomes.

Dose- and Time-Dependent Responses: The hepatic response to ionizing radiation is heavily dependent on both the dose as well as the temporal pattern of exposure. Acute exposure to low doses (≤0.1 Gy) induces subtle but persistent metabolic disruptions, such as inhibition of glycolysis and PPAR-α inactivation, which may not cause immediate histopathological. damage but result in long-term metabolic dysfunction and oxidative stress [2, 24]. In contrast, moderate doses (0.5–1 Gy) trigger acute inflammatory responses,

mitochondrial impairment, and transient suppression of respiratory function, followed by partial recovery [8, 21]. At higher doses (≥1 Gy), significant cellular damage occurs, including necrosis, fibrosis, and vascular abnormalities, particularly when exposure is prolonged [22, 31].

Chronic low-dose-rate (LDR) exposure (e.g., 20 mGy/day over months) yields distinct effects compared to acute irradiation. According to studies, prolonged LDR disrupts lipid metabolism, upregulates genes involved in cholesterol biosynthesis (Cyp51, Srebf1), and promotes hepatic steatosis, especially in female mice [26, 27]. Moreover, the timing of analysis post-exposure is critical; while some metabolic changes (e.g., ROS elevation) appear within hours or days, others (e.g., fibrosis, oncogenic activation) manifest months later [20, 21]. Notably, prenatal exposure to sub-lethal doses (1000 mGy) alters fetal programming, leading to sex-specific metabolic dysfunction in adulthood, suggesting that developmental stages influence radiation susceptibility [23]. Collectively, these findings indicate that dose rate, cumulative dose, and post-exposure interval critically determine the spectrum of hepatic injury, ranging from reversible metabolic shifts to irreversible structural and carcinogenic damage.

The liver exhibits a spectrum of radiation-induced pathologies, ranging from transient metabolic disturbances to irreversible fibrosis and cancer. Key mechanisms include PPAR-α inactivation, ROS overproduction, and oncogenic signaling, with outcomes modulated by dose rate, sex, and genetic background. These findings emphasize the need for further research into organ-specific thresholds and countermeasures against chronic radiation effects.

Discussion

Ionizing radiation has become an indispensable therapeutic modality in modern medicine, especially for the treatment of various diseases and malignancies [32]. Despite its widespread clinical applications, a growing body of evidence demonstrates that exposure to ionizing radiation may induce detrimental biological effects, posing significant risks to human health [33]. Even though substantial progress has been made in elucidating the mechanisms of biological response to ionizing radiation in mammalian systems, critical knowledge gaps still persist in this field. Notably, the precise molecular and cellular pathways responsible for the long-term adverse effects of in vivo radiation exposure remain incompletely understood. Among the potential consequences, radiation-induced damage to vital organs and tissues—especially the liver—has emerged as a major concern owing to its essential physiological functions. Given the susceptibility of hepatic tissue to oxidative stress and genomic instability following radiation exposure, a thorough examination of its pathological alterations is warranted. Accordingly, this study aimed to systematically review and critically ascertain the existing literature about the detrimental effects of low-dose ionizing radiation on hepatic tissue in murine models, with special emphasis on underlying mechanisms, histopathological changes, and long-term clinical implications.

Cesium-137 (Cs-137) remains one of the most prevalent gamma-ray sources in radiation studies owing to its well-characterized emission properties [34]. A growing body of evidence suggests that even low-dose gamma radiation can induce significant hepatic injury, primarily mediated through oxidative stress pathways. For example, Roser Esplugas et al. demonstrated that low-dose gamma radiation triggers liver damage by exacerbating oxidative stress, a finding consistent with broader literature linking radiation to redox imbalance [28]. Mechanistically, such exposure has proved to disrupt hepatic glycolysis and impair pyruvate dehydrogenase activity shortly after irradiation, suggesting acute metabolic dysfunction [2]. Over the long term, these impacts may evolve into persistent alterations in lipid metabolism, exacerbated hepatic inflammation, and suppression of peroxisome proliferator-activated receptor alpha (PPARα), a key regulator of mitochondrial function and oxidative stress mitigation.

The metabolic consequences of low-dose radiation are further underscored by studies exploring microRNA (miRNA) regulation. Liang et al. observed a marked reduction in metabolism-related miRNAs in mice livers following low-dose exposure, implicating post-transcriptional dysregulation in radiation-induced metabolic disturbances [12]. Likewise, Katsuyoshi Fujikawa et al. reported that low-dose ionizing radiation promoted fatty liver development and obesity in female mice, reinforcing the liver's metabolic vulnerability to radiation [26]. Nevertheless, the dose-dependency of these effects remains a critical consideration. Davidson et al. noted that while a 300 mGy dose had negligible impact on glucose and lipid metabolism, sublethal exposure (1000 mGy) significantly augmented liver weight, altered glucose-metabolizing enzymes, and enhanced FDG uptake in adipose tissue, highlighting a threshold for metabolic disruption [23]. These discrepancies may arise from variations in experimental models, exposure duration, or species-specific responses, warranting further investigation.

Beyond metabolic dysfunction, low-dose radiation has been linked to severe hepatic pathologies, including necrosis, fibrosis, and carcinogenesis. Real-time PCR and Western blot analyses have indicated upregulated inflammatory and oncogenic markers following irradiation, suggesting elevated risks of tissue damage and malignancy [31]. This is in line with findings by I. B. Tanaka III et al., who demonstrated that ionizing

radiation not only initiates but also accelerates hepatic carcinogenesis, resulting in premature mortality in mice models [27]. The oncogenic potential of chronic low-dose exposure was further corroborated by V. F. Mikhailov, who documented radiation-induced malignant lymphomas in the liver and surrounding tissues after ten months of exposure, albeit with a relatively low incidence (14/94 mice) [20]. Such studies highlight the latent yet serious risks of prolonged low-dose radiation. Notably, the severity of hepatic damage appears to be dose-dependent, as outlined by Lan Yi in a study utilizing uranium tailings (UT)-derived gamma radiation. While very low doses (30 μGy) caused only mild central vein dilation without statistical significance, higher doses (100–250 μGy) induced pronounced histopathological changes, including necrosis, steatosis, and fibrosis [22]. This dose-response relationship suggests that hepatic tolerance to radiation may be overcome beyond a critical threshold, highlighting the need for stringent safety limits in occupational and environmental settings. Collectively, these studies demonstrate the dual role of low-dose gamma radiation as both a metabolic disruptor and a carcinogenic agent in the liver. While oxidative stress and PPARα inactivation emerge as common mechanistic threads, the variability in outcomes across studies well indicate the influence of dose, exposure duration, and model specificity.

X-rays represent one of the most extensively studied forms of radiation in mice models, with significant implications for mitochondrial and cellular integrity. Yufeng Zhang et al. reported that low-dose X-ray irradiation initially induces a severe decline in mitochondrial function in domestic mice, followed by a subsequent recovery days later [8]. This biphasic response suggests a potential adaptive mechanism, though the underlying processes remain to be fully elucidated. Notably, comparative analyses across studies reveal that irradiated animals exhibit pronounced mitochondrial ultrastructural damage and heightened lipid deposition in hepatocytes compared to controls [24, 25], underscoring the disruptive impact of X-rays on metabolic and cellular homeostasis.

Further inspections into the long-term consequences of radiation exposure have uncovered persistent alterations in hepatic protein expression. Tetsuo Nakajima et al. observed significant changes in the expression of proteins associated with liver inflammation and apoptosis even three months post-chronic irradiation, suggesting that radiation-induced perturbations may extend well beyond the initial exposure period [21]. Complementing these findings, Ayman Jafer et al. reported that acute X-ray exposure induces substantial transcriptomic modifications in mice [30], underscoring the broad genomic and proteomic disruptions triggered by irradiation.

A critical mediator of radiation-induced damage is oxidative stress, which arises from an imbalance between reactive oxygen species (ROS) production and the biological system's capacity to detoxify these reactive intermediates or repair resultant damage. ROS interact with cellular macromolecules - including lipids, nucleic acids, proteins, and enzymes - leading to widespread oxidative damage. Wan Mazlina Md Saad et al. provided compelling evidence that irradiated mice exhibited a marked growth in ROS generation compared to non-irradiated controls, accompanied by extreme nuclear ultrastructural alterations [24]. These findings are in accordance with the broader literature, reinforcing the central role of oxidative stress in radiation pathology and suggesting that antioxidant-based therapeutic strategies may alleviate some of these deleterious effects.

The greatest influence of gamma radiation has been reported to disrupt metabolism and induce oxidative stress. Although low doses do not cause significant clinical changes, they may result in dilation of the central hepatic vein. These rays affect metabolism through inhibiting the glycolysis pathway, reducing pyruvate dehydrogenase availability, impairing lipid metabolism, promoting hepatic inflammation, and downregulating metabolism-regulating microRNAs. Some studies have also indicated that even low-dose ionizing radiation (LDIR) can both initiate and accelerate liver cancer. Meanwhile, X-rays induce transient effects on mitochondria, ultrastructural damage, persistent changes in protein expression, as well as alterations in hepatic gene transcripts. In general, various types of low-dose ionizing radiation (LDR) can harm the liver through the generation of reactive oxygen species (ROS), though the severity and pattern of damage may differ.

While mice models provide invaluable insights into the hepatic effects of ionizing radiation (IR), extrapolating these findings to humans requires caution owing to interspecies differences in metabolism, lifespan, radiation sensitivity, and environmental exposures. According to studies, mice exhibit dose-dependent metabolic dysfunction (e.g., PPAR-α inactivation, oxidative stress) and carcinogenic risks similar to those observed in human epidemiological data (e.g., atomic bomb survivors and radiation workers). However, key limitations include: (1) mice studies often use controlled, single-exposure paradigms, while humans confront cumulative, low-dose environmental or medical exposures; (2) mice have higher basal metabolic rates and shorter lifespans, potentially accelerating pathology manifestation; and (3) genetic diversity in humans may modulate radiation susceptibility, unlike inbred mice strains.

Although ionizing radiation can have therapeutic properties and be employed to treat diseases such as

cancer, the results of the present study revealed that low-dose ionizing radiation can cause destructive effects in the liver. In the present study, although only the literature related to the harmful effects of these rays on the liver was reviewed, it is suggested that in future studies, the harmful effects of these radiations on other vital organs in other animals should also be examined for summary and conclusion.

Given the limitations of current studies, which have primarily focused on animal models (e.g., mice), future research should systematically explore the effects of these rays on other vital organs and across different animal species. Such studies could result in a more comprehensive understanding of the biological consequences of ionizing radiation and pave the way for developing safer protocols in clinical applications. Finally, early detection of at-risk individuals and adoption of preventive strategies could help mitigate the harmful effects of this radiation.

Conclusion

The present study demonstrated that exposure of the liver to ionizing radiation, even at low doses, can result in detrimental consequences, including mitochondrial dysfunction, increased oxidative stress, inflammation, necrosis, and even cancer. These adverse effects primarily take place through mechanisms such as oxidative stress and disruption of cellular metabolism. Although ionizing radiation is used in the treatment of diseases such as cancer, the findings caution that even low doses can be harmful to the liver.

Conflict of interest

None declared.

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Ethical Considerations

Since this review was conducted using previously published data, formal ethical approval was not required. All included studies were performed in accordance with recognized ethical guidelines.

Authors' Contributions

Behzad Fouladi Dehaghi: Supervision of data collection, analysis, and methodology validation; Sara Tabanfar and Seyvan Sobhani: Conception of the research idea, data collection and analysis, and writing and editing the initial draft of the manuscript. All authors have read and approved the final manuscript for publication.

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