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Biochemical and Hepatological Effects of Low Dose Radiation Exposure in Animal Models: Implications for Human Health

Aliyu Yakubu[1], Mohammed Dauda Goni[1,*], Abdul-Azeez Ibrahim Okene[2]

[1] Department of clinical Sciemces, Faculty of Veterinary Medicine, Universiti Malaysia Kelantan Malaysia
[2] Faculty of Health Science, Higher College of Technology, Men Campus, Sharjah, United Arab Emirates

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ABSTRACT

Exposure to low-dose ionizing radiation (LDIR) is an increasing public health concern due to its potential to induce chronic biochemical and hepatological consequences. This review examines the mechanisms and implications of LDIR exposure in animal models, focusing on its impact on the liver, low-dose radiation exposure (LDIR) triggers oxidative stress, DNA damage, and inflammatory responses, resulting in alterations in liver enzyme activities, lipid metabolism, and cellular signaling pathways. These biochemical changes contribute to the growth of hepatic steatosis, fibrosis, and an increased risk of hepatocellular carcinoma. Hepatological consequences of LDIR include impaired liver regeneration, chronic inflammation, and the development of liver disorders, including non-alcoholic fatty liver disease and cirrhosis. The review highlights the importance for further research to clarify the long-term impacts of LDIR on human health, including the development of sensitive biomarkers, refined dose-response relationships, and personalized approaches to radiation protection. Interdisciplinary collaboration and the integration of advanced molecular and computational tools are crucial for enhancing our understanding of LDIR effects and creating effective interventions to mitigate radiation-induced liver damage. The findings highlight the significance of optimizing public health policies and radiation exposure guidelines to minimize the hazard of chronic liver diseases in people exposed to occupational or environmental radiation.

1. Introduction

Low-dose ionizing radiation (LDIR) is increasingly recognized as a significant health concern, with widespread implications due to its pervasive presence in various environments [132]. As a form of radiation with sufficient enough energy to ionize molecules and atoms, LDIR is generated from both natural sources like cosmic rays and radon, as well as artificial sources such as medical diagnostics, nuclear power plants, and some activities from industries. ("Ionizing Radiation," 2024). Although the impacts of exposure to high-dose radiation have been well recognized, the health implications of

* *Corresponding author.*
E-mail address: dauda.g@umk.edu.my

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chronic, low-dose exposures are less understood, particularly regarding their potential to induce long-term biochemical, cellular, and organ-specific damage [78].

Among the organs susceptible to radiation, the liver stands out owing to its vital role in metabolism, detoxification, and immune modulation, making it highly vulnerable to even low levels of oxidative and inflammatory stress induced by radiation [89]. In the liver, ionizing radiation exposure has been shown to disrupt biochemical pathways, alter metabolic processes, and affect the regulation of liver enzymes. These disturbances can result in various hepatological issues, such as inflammation, malignancy and in severe cases, fibrosis [80]. The liver's sensitivity to radiation-induced oxidative stress is a major factor in driving this damage, as low-dose radiation can increase reactive oxygen species (ROS), which subsequently trigger oxidative damage to cellular macromolecules, such as lipids, proteins, and DNA [89]. Moreover, radiation-induced oxidative stress can disrupt lipid metabolism and modulate liver enzyme activity, leading to alterations in liver function and increasing susceptibility to conditions such as liver fibrosis, hepatocellular carcinoma, nonalcoholic fatty liver disease (NAFLD) [9]. These liver-specific effects underscore the importance for targeted research to explore the molecular mechanisms underlying radiation-induced hepatic dysfunction and identify potential interventions to mitigate this damage [100].

While most research on radiation's effects has focused on high-dose exposure, mounting evidence suggests that low-dose exposure defined as doses less than 100 millisieverts (mSv) can also have significant biological effects, especially with chronic exposure [107]. According to epidemiological studies on people exposed to radiation low-dose, such as atomic bomb survivors, workers in radiation-intensive industries, and patients undergoing frequent radiological diagnostics, reveal an increased danger of cancer and other chronic diseases linked to exposure to low-dose radiation [118]. However, these epidemiological findings are often difficult to interpret due to confounding factors, such as lifestyle, genetic predisposition, and other environmental exposures [50]. Therefore, animal models are essential for disentangling the specific biological processes by which low-dose radiation affects the liver, allowing for controlled investigations that reveal radiation's direct impacts on biochemical and hepatological health [153].

Animal research have revealed that low-dose radiation can cause oxidative stress, induce DNA damage in liver cells and disrupt antioxidant defenses, contributing to the onset of hepatic inflammation, fibrosis, and further pathologies [89]. For instance, in rodents, chronic exposure to low-dose radiation has been demonstrated to activate proinflammatory pathways and upregulate cytokines like tumor necrosis factoralpha (TNFα) and interleukin6 (IL6), which are known to mediate liver damage and promote fibrogenesis [102]. Similarly, lipid peroxidation, a process triggered by radiation-induced ROS, has been observed to compromise liver cell membranes and increase the susceptibility to metabolic disorders and nonalcoholic fatty liver disease [38]. These findings align with an increasing amount of data connecting oxidative stress and inflammation to radiation-induced liver toxicity and highlight the need for further research into the biochemical pathways involved in radiation-induced hepatic injury [142].

The World Health Organization (WHO) and the World Organisation for Animal Health (OIE) have emphasized the importance of understanding radiation's impact on both human and animal health, given that environmental radiation exposure can affect ecosystems and food safety, with indirect impacts on human health [136]. WHO's guidelines on radiation safety underscore the necessity of limiting radiation exposure to prevent chronic health conditions and advocate for a greater focus on low-dose radiation risks due to the cumulative exposure in medical, environmental, and occupational settings [143]. The OIE also recognizes the implications of radiation exposure in veterinary health and zoonotic disease control, stressing that animal models can offer important perspectives on the impact of radiation on biological systems and help refine human safety standards [135]. These

perspectives highlight a need for more robust research frameworks to assess the chronic health impacts of low-dose radiation and establish comprehensive guidelines for exposure limits [109].

This review aims to fill existing gaps in present knowledge by examining the biochemical and hepatological effects of radiation exposure at low doses in animal models and drawing implications for human health. By exploring mechanisms such as oxidative stress, inflammation, lipid metabolism disruption, and antioxidant depletion, this review aims to elucidate how low-dose radiation contributes to liver disease progression and metabolic disturbances. Additionally, the potential for translating these findings into human health contexts is discussed, with a focus on developing protective strategies, improving risk assessment, and informing public health policies. Given the liver's significant role in systemic homeostasis and the increasing prevalence of low-dose radiation exposure, understanding the biochemical underpinnings of radiation-induced liver injury is crucial for advancing preventive and therapeutic measures.

Mechanisms of Effects of Low-Dose Radiation in Animal Models

Understanding the mechanisms underlying the impacts of exposure to low-dose radiation is essential for understanding its impact on biological systems and its extrapolation to human health. Low-dose radiation, typically defined as exposure to ionizing radiation levels below 100 mSv, elicits a range of molecular and cellular responses distinct from those triggered by high-dose radiation [19]. While high-dose radiation often results in immediate cell death and severe tissue damage, low-dose radiation causes subtle but chronic effects that cumulatively alter cellular homeostasis and organ function [3].

A key mechanism of low-dose radiation involves the production of reactive oxygen species (ROS) through water molecules radiolysis [79]. The ROS produced comprise hydrogen peroxide, superoxide anion and hydroxyl radicals, which can directly harm cellular macromolecules like proteins, lipids and DNA [37]. Unlike high-dose radiation, which causes extensive DNA double-strand breaks, low-dose radiation tends to induce more single-strand breaks and oxidative modifications to the DNA, leading to mutations and genomic instability over time [70]. These modifications activate the DNA damage response (DDR) pathways, such as p53 signaling, which orchestrates cell cycle arrest, apoptosis or DNA repair based on the level of damage. Prolong DDR signaling at low doses can result in inefficient repair, increasing the likelihood of mutagenesis [80].

The amplification of the effects of radiation low-dose is largely dependent on mitochondria. Oxidative stress caused by radiation disrupts mitochondrial membrane integrity, leading to further ROS production in a vicious cycle known as ROS-induced ROS release [7]. This exacerbation of oxidative damage not only impairs mitochondrial function but also disrupts cellular energy homeostasis and signaling pathways [164]. Additionally, the discharge of mitochondrial DNA and other damage-associated molecular patterns (DAMPs) into the cytosol activates inflammatory reactions through pattern recognition receptors like Toll-like receptors (TLRs) and the inflammasome [22].

Epigenetic modifications are another hallmark of exposure to low-dose radiation. These include alterations in DNA methylation, histone modifications, and non-coding RNA expression, which collectively reprogram gene expression without modifying the DNA sequence [13]. Epigenetic changes affect pathways regulating oxidative stress, inflammation, and proliferation of cell, potentially assisting in long-term consequences such as carcinogenesis and tissue dysfunction [120]. Importantly, these epigenetic effects can be heritable, raising concerns about the transgenerational impact of low-dose exposure to radiation [66].

Radiation Low-dose also activates complex intercellular communication networks, including bystander effects, in which cells that are not exposed to radiation display radiation-like responses owing to signals received from exposed neighboring cells [29]. Mediators of this response include cytokines, ROS, and microRNAs, which propagate inflammatory and stress responses throughout the tissue [137]. This phenomenon underscores the systemic nature of low-dose radiation effects, where localized exposure can influence distant, unexposed tissues [94].

Inflammation is a significant outcome of exposure to low-dose radiation and a driver of subsequent tissue remodeling and fibrosis [94]. Radiation triggers nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling and other pro-inflammatory pathways, resulting in the generation of cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) [57]. These cytokines amplify the attraction of immune cells to the radiation exposure site, perpetuating a chronic inflammatory state. Over time, persistent inflammation promotes tissue fibrosis through the stimulation of hepatic stellate cells and the accumulation of extracellular matrix components, which disrupt normal liver architecture and function [113].

Low-dose Radiation's Biochemical Effects in Animal Models

Low-dose ionizing radiation, although generally associated with subtler effects compared to high-dose exposure, still induces significant biochemical alterations within cells and tissues [94]. In animal models, particularly rodent models, these alterations are most apparent in the liver, a vital organ for detoxification and metabolism, but they extend to other organ systems as well [28]. The biochemical consequences of exposure to low-dose radiation manifest through oxidative stress, altered enzyme activities, perturbation of metabolic pathways, lipid and protein damage, and changes in cellular signaling cascades [39]. These effects eventually lead to liver dysfunction, metabolic disturbances, and an elevated risk of chronic diseases, such as cancer and fibrosis [56].

Reactive Oxygen Species (ROS) Generation and Oxidative Stress

The most significant biochemical consequence of exposure to low-dose radiation is the production of reactive oxygen species (ROS) [90]. Even at low concentrations, ionizing radiation ionizes water molecules in tissues, resulting in the production of ROS like superoxide anion (O_2^-), hydroxyl radicals (OH^-) and hydrogen peroxide (H_2O_2) [130]. These ROS are extremely reactive and can harm cellular macromolecules, including lipids, nucleic acids and proteins [55]. The liver is particularly vulnerable to ROS-induced injury due to its role in detoxification and its high metabolic activity [20].

Researches in animal models have shown that low-dose radiation results in the generation of ROS in liver cells, where it overwhelms the liver's antioxidant defenses [129]. Antioxidant enzymes such as glutathione peroxidase , superoxide dismutase (SOD) and catalase are crucial for neutralizing ROS [126]. However, in irradiated animals, a significant depletion of these antioxidants has been observed, leading to increased oxidative damage [66]. This oxidative imbalance is responsible for the initiation of lipid peroxidation, which not only damages cellular membranes but also produces reactive aldehydes like malondialdehyde (MDA) that further propagate cellular injury [67].

The oxidative stress caused by low-dose radiation exposure is connected with changes in liver enzyme activities. For instance, reduced levels of glutathione (GSH) and an increased GSH/GSSG ratio have been noted in rodents following chronic low-dose radiation exposure, indicating an impaired antioxidant defense system and increased oxidative burden [86]. This biochemical disruption at the

molecular level contributes significantly to liver inflammation, fibrosis, and, eventually, carcinogenesis [85].

Mechanisms of DNA Damage and Repair

Low-dose radiation causes DNA damage, including base modifications single-strand breaks (SSBs) and double-strand breaks (DSBs), and [106]. These DNA injuries are typically repaired by cellular DNA repair mechanisms, but persistent low-dose exposure can overcome these repair processes, resulting in the accumulation of genetic mutations and genomic instability [71]. In animal models, DNA damage markers such as γH2AX foci (a marker for DSBs) and 8oxoguanine (a marker for oxidative DNA damage) are routinely observed after low-dose radiation exposure in liver cells [112].

The liver cells, which have high rates of cell turnover, are vulnerable to the mutagenic impacts of low-dose radiation [10]. The DNA damage caused by radiation is primarily repaired via two processes: nonhomologous end joining (NHEJ) and homologous recombination (HR) [158]. In low-dose radiation scenarios, NHEJ is the predominant repair mechanism, but it is error-prone, often leading to mutations and chromosomal aberrations [131]. Moreover, current studies in animal models propose that the low-dose radiation-induced DNA damage also affects epigenetic regulators, potentially altering gene expression patterns associated with cancer and fibrosis [108].

Failure to repair DNA damage or mutations may lead to cell cycle arrest or apoptosis in severely damaged cells. However, certain cells may evade these processes and enter a state of senescence. Senescent cells release proinflammatory cytokines and other molecules that exacerbate liver tissue damage, ultimately leading to liver fibrosis and chronic inflammation [40].

Changes in Enzyme Activity and Protein Expression

Low-dose radiation can alter the activity of numerous enzymes involved in metabolism, detoxification, and signal transduction [148]. One of the most significant biochemical alterations observed in animal models is the change in cytochrome P450 (CYP450) enzymes, which are engaged in the metabolism of xenobiotics and endogenous compounds in the liver. Studies in rodents have demonstrated that exposure to low-dose radiation leads to changes in the expression of various CYP450 isoforms, potentially impairing drug metabolism and increasing susceptibility to toxic metabolites [159].

Apart from CYP450 enzymes, radiation-induced oxidative stress and inflammation can result in the modification of liver enzymes engaged in lipid metabolism and glucose [88]. Animal researches have shown that exposure to low-dose radiation induces insulin resistance and glucose intolerance, likely due to altered hepatic glucose metabolism [8]. For instance, increased expression of gluconeogenesis-related enzymes such as glucose6phosphatase has been observed in the livers of irradiated animals, leading to elevated blood glucose levels [63]. Simultaneously, radiation-induced disruptions in lipid metabolism are common, with increased hepatic triglyceride accumulation and lipid peroxidation, which are markers of radiation-induced nonalcoholic fatty liver disease (NAFLD) or fatty liver [11].

These enzyme changes reflect the compromised metabolic capacity of the liver following radiation exposure and may have lasting effects on energy homeostasis, contributing to systemic metabolic disturbances and a higher chance for cardiovascular diseases and liver dysfunction [99].

Inflammatory Pathways and Cytokine Production

One of the most notable biochemical effects of exposure to low-dose radiation is the induction of an inflammatory response [102]. Ionizing radiation activates multiple proinflammatory signaling pathways in the liver, including the NFκB and MAPK pathways, leading to the generation of proinflammatory cytokines like TNFα, IL6, and IL1β [110].These cytokines promote liver inflammation, which, if chronic, can lead to fibrosis and cirrhosis [62].

Animal researches have revealed that even low doses of radiation results in significant infiltration of the liver immune cells, including Kupffer cells, the local macrophages (Hauptmann et al., 2020). Activated Kupffer cells release additional inflammatory mediators, which further exacerbate liver tissue damage and promote fibrosis. In the perspective of long-term low-dose exposure, this inflammation-driven fibrogenesis can impair liver architecture and function, contributing to long-term liver disease [62].

Moreover, inflammatory cytokines can alter the balance of tissue remodeling and repair, shifting it toward pathological fibrosis [125]. This phenomenon is reinforced by elevated expression of collagen and other extracellular matrix proteins, which ultimately results in liver scarring and fibrosis [93]. The biochemical feedback loop of inflammation, oxidative stress and fibrotic remodeling underscores the persistent nature of liver damage caused by radiation [9].

Metabolic Disturbances and Hepatic Steatosis

Metabolic disturbances induced by low-dose radiation exposure are most evident in hepatic lipid metabolism [89]. Studies in rodent models reveal that low-dose radiation exposure results in disparity between lipid synthesis and degradation pathways in the liver, leading to hepatic steatosis or fatty liver [96]. Radiation-induced oxidative stress and the inflammatory response contribute to impaired fatty acid oxidation and altered lipid transport, leading to the accumulation of triglycerides in hepatocytes [37].

Animal studies also show a decrease in the activity of enzymes that play a role in fatty acid oxidation, like carnitine palmitoyltransferase 1 (CPT1), and an increase in lipid biosynthesis enzymes like acetylCoA carboxylase (ACC), which further promotes fat increase in the liver [153]. The liver's inability to properly handle lipids due to radiation-induced metabolic alterations leads to increased lipid peroxidation and the formation of toxic lipid aldehydes, which harm hepatocyte membranes and support further inflammation [74].

Epigenetic Modifications and Gene Expression

Exposure to low-dose radiation has been revealed to induce epigenetic modifications in liver cells, which can results in long-term modifications in gene expression [13]. These modifications comprise histone modification, DNA methylation and changes in microRNA expression. Studies on animal have shown that low-dose radiation can influence the expression of genes related to oxidative stress responses, inflammation, and fibrogenesis [24]. For instance, the downregulation of antioxidant genes like NRF2 and upregulation of proinflammatory genes such as NFκB have been observed in the livers of irradiated rodents [105].

Moreover, radiation-induced changes in the expression of specific microRNAs, which regulate gene expression post transcriptionally, have been implicated in liver fibrosis and cancer. MicroRNAs such as miR21 and miR34a have been identified as key regulators of liver injury and fibrosis following radiation exposure. These epigenetic changes can have lasting effects on hepatic function and may contribute to the chronic health risks linked to exposure to low-dose radiation.

Hepatological Effects of Low-dose Radiation in Animal Models

The liver is an essential organ responsible for metabolic processes, immune functions and detoxification. It is exposed to a variety of toxic insults, including ionizing radiation [83]. Exposure to low-dose radiation, while typically considered to be nonlethal, induces a variety of hepatological consequences [102]. These include inflammation, oxidative stress, changes in cell proliferation, and alterations in hepatic architecture, all of which contribute to long-term liver dysfunction and increase the possibility of chronic liver diseases, such as fibrosis, liver cancer and cirrhosis [114].

Hepatic inflammation caused by radiation

One of the earliest and most prominent hepatological impacts of exposure to low-dose radiation is the induction of hepatic inflammation [126]. Animal models, particularly rodents, have been widely used to study the pathophysiological mechanisms behind liver damage caused by radiation [28]. Low-dose radiation triggers several inflammatory pathways in the liver, notably the NFκB and MAPK signaling pathways, which play central roles in the recruitment of immune cells and the generation of proinflammatory cytokines like TNFα, IL6, and IL1β [141].

Researches using rodent models irradiated to low-dose radiation (12 Gy) have shown an increase in proinflammatory cytokines levels and the infiltration of Kupffer cells (The liver's resident macrophages) and neutrophils [26]. The activation of these immune cells results in the secretion of additional inflammatory mediators such as chemokines and prostaglandins, which further amplify the inflammatory reaction and caused damage to the hepatic tissue [33].

Chronic inflammation resulting from repeated low-dose radiation exposure can shift the immune system toward a profibrogenic environment [5]. Activated Kupffer cells and infiltrating immune cells produce transforming growth factor beta (TGFβ), an important mediator of hepatic fibrosis [62]. This cytokine promotes the activation of hepatic stellate cells (HSCs), which differentiate into myofibroblasts and release extracellular matrix proteins, including collagen (Kim & Kim, 2024). This process is a hallmark of radiation-induced liver fibrosis, a disorder that can progress to cirrhosis and increase vulnerability to liver cancer [32].

Oxidative Stress and Peroxidation of Lipid in the Liver

Oxidative stress is another significant hepatological consequence of low-dose radiation exposure [79]. Reactive oxygen species (ROS) are produced when radiation interacts with tissue water, leading to the production of highly reactive free radicals like hydrogen peroxide (H_2O_2), superoxide anion (O_2^-) and hydroxyl radicals (OH^-) [37]. These radicals are capable of damaging cellular components, comprising proteins, lipids, and DNA. In the liver, this oxidative impairment leads to lipid peroxidation, a process in which ROS attack the unsaturated fatty acids in cell membranes, resulting in the generation of toxic aldehydes like malondialdehyde (MDA) [154}.

Lipid peroxidation products, such as MDA, can further exacerbate liver injury by inducing inflammation and fibrosis [97]. In rodent models, exposure to low-dose radiation has been demonstrated to elevate MDA levels in hepatic tissues, indicative of increased lipid damage [138]. The resulting hepatic steatosis, or fatty liver, is a well-documented consequence of radiation-induced oxidative stress [157]. This steatosis may occur owing to an inequality between lipid synthesis and lipid oxidation in the liver, resulting in the accumulation of triglycerides and other lipids [68].

Moreover, the liver's antioxidant defense mechanisms, comprising glutathione peroxidase and superoxide dismutase (SOD), are often overwhelmed by the persistent oxidative stress caused by exposure to low-dose radiation [81]. This depletion of antioxidant enzymes exacerbates the oxidative damage and contributes to further hepatocellular injury, inflammation, and fibrosis [9].

Hepatic Fibrosis and Cirrhosis

As low-dose radiation exposure persists, the liver responds with fibrosis, a pathological increase of extracellular matrix components, primarily collagen [89]. This fibrosis is driven by the stimulation of hepatic stellate cells (HSCs), Which are key players in the fibro genic response [162]. HSCs, when activated by inflammatory cytokines like TGFβ and TNFα, transdifferentiate into contractile myofibroblasts that secrete collagen and other fibro genic proteins [77]. In rodents exposed to low-dose radiation, significant activation of HSCs has been noted, and this leads to the progressive increase of collagen fibers in the liver, leading to fibrosis [129].

The early phases of radiation-induced fibrosis are distinguished by pericentral and periportal collagen deposition, which interrupts the normal architecture of the liver and impairs hepatic function [152]. As fibrosis progresses to more advanced stages, it can lead to cirrhosis, a disorder marked by the extensive scarring of the liver tissue and the development of regenerative nodules [15]. Cirrhosis significantly damages liver function, resulting in portal hypertension, ascites, and liver failure [128]. In animal models, low-dose radiation-induced liver fibrosis can progress to cirrhosis over time, particularly when combined with additional risk factors like viral hepatitis or alcohol consumption [89]. Cirrhosis is also a Hepatocellular carcinoma (HCC) significant risk factor, underscoring the long-term risk of cancer development following chronic radiation exposure [92].

Changes in Hepatic Regeneration and Cell Proliferation

The liver has a significant ability for regeneration, but radiation-induced DNA damage can impair this regenerative ability [89]. Hepatocytes in the liver typically undergo cell division in reaction to injury, and low-dose radiation-induced liver injury triggers a compensatory proliferative response [119]. However, repeated or prolonged radiation exposure can impair hepatocyte proliferation due to DNA damage and genomic instability [162]. In rodent models, the regenerative response to radiation injury often involves the activation of progenitor cells in the liver [144]. However, low-dose radiation has been demonstrated to lead to aberrant regeneration, where hepatocytes fail to properly regenerate, or senescent hepatocytes accumulate [52]. This disrupted regenerative process contributes to the growth of fibrosis and cirrhosis, as hepatocytes are unable to replace damaged cells, and the liver is unable to return to normal function [15].

In addition, the epigenetic alterations induced by low-dose radiation exposure can permanently alter the liver's regenerative capacity [94]. Changes in histone modification and DNA methylation profiles affect the expression of genes critical for cell cycle regulation, resulting in abnormal hepatocyte turnover and progression to fibrosis [2].

Liver Cancer (Hepatocellular Carcinoma)

The long-term effects of prolonged low-dose radiation exposure to the liver is an increased risk for the development of hepatocellular carcinoma (HCC), a primary cause of global cancer-related mortality [140]. The growth of HCC after radiation exposure is primarily due to the accumulation of

genomic mutations, particularly those in oncogenes and tumor suppressor genes, as well as the continuous inflammatory environment that supports tumor growth [122].

In animal models, exposure to low-dose radiation leads to a rising incidence of HCC after prolonged exposure, especially in animals with preexisting liver fibrosis [42]. The inflammatory mediators released by activated Kupffer cells and the altered gene expressions induced by radiation promote cell existence, proliferation, and invasion, they are all signs of malignancy [147].

In rodent studies, radiation-induced chromosomal aberrations and epigenetic modifications have been linked to the transformation of hepatocytes into malignant cells, increasing the liver's vulnerability to carcinogenesis [13]. Furthermore, radiation exposure also reduces the liver's capacity to to undergo normal apoptosis, allowing damaged cells to survive and proliferate, a key process in tumorigenesis [89].

Effects of Chronic Exposure to Low-Dose Radiation on Human Health

It is becoming more widely acknowledged how long-term exposure to low-dose radiation affects human health as a significant public health concern, particularly in contexts where individuals are chronically exposed to low-dose of radiation, such as occupational settings, environmental contamination, or medical diagnostics [118]. Although the immediate consequences of exposure to high-dose radiation are extensively documented, the health effects of sustained exposure to low-dose often manifest subtly over time, complicating their assessment and management [69]. These effects can lead to chronic health issues, particularly affecting the liver and associated metabolic systems [61].

One of the most concerning implications of prolonged radiation exposure to low-dose is its potential to induce carcinogenesis [53]. Chronic exposure to radiation low-dose has been linked to a higher incidence of liver cancer, primarily by processes involving chronic inflammation, epigenetic changes, and genomic instability [26]. Radiation-induced oxidative stress is essential in these processes by causing persistent damage to DNA and activating inflammatory pathways [44]. Prolonged inflammatory states, mediated by cytokines comprising tumor necrosis factor-alpha (TNF-α) and interleukins, leading to a microenvironment conducive to tumorigenesis [124]. Furthermore, epigenetic changes, such as alterations in DNA methylation and histone variations, may reprogram gene expression in ways that favor oncogenic transformation [73].

Non-alcoholic fatty liver disease (NAFLD) is another possible consequence of prolonged exposure to low-dose radiation [139]. Ionizing radiation has been implicated in altering lipid metabolism, resulting in the accumulation of lipids in hepatocytes [111]. This disruption may occur due to radiation-induced oxidative stress and mitochondrial malfunction, which damage lipid oxidation and rise the synthesis of fatty acids [37]. Over time, these changes can progress to more serious illnesses, like non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis [45]. The interaction between radiation caused metabolic dysregulation and chronic inflammation exacerbates the progression of these diseases, highlighting a significant area of concern for populations exposed to chronic low-dose radiation [7].

Radiation-induced chronic inflammation and immune dysregulation also have implications for hepatitis [57]. The immune system's capacity to eradicate infections may be compromised by prolonged low-dose radiation exposure., increasing susceptibility to viral hepatitis [94]. Additionally, radiation-induced damage to hepatocytes and the stimulation of hepatic stellate cells can perpetuate a cycle of liver injury, inflammation, and fibrosis [162]. This cycle not only contributes to the progression of hepatitis but also creates a predisposing environment for the progress of secondary complications, including cirrhosis and hepatocellular carcinoma [34].

Furthermore, low-dose radiation exposure is linked to broader metabolic disorders, comprising insulin resistance, dyslipidemia, and metabolic syndrome [133]. Radiation-induced mitochondrial dysfunction and chronic oxidative stress disrupt normal cellular energy metabolism, contributing to systemic metabolic abnormalities [41].These effects are compounded by inflammation-driven insulin resistance, which can exacerbate the possibility of developing type 2 diabetes and cardiovascular diseases [145]. Evidence from animal studies suggests that the liver, being a key organ in glucose and lipid metabolism, is especially susceptible to these radiation-induced metabolic disturbances, emphasizing the importance of additional research to better understand these mechanisms and their impact on human health [36].

Collectively, the long-term implications of exposure to low-dose radiation on human health are multifaceted, with significant impacts on liver function, inflammation, and metabolic processes. These effects underscore the need for robust epidemiological studies to delineate dose-response relationships and identify vulnerable populations. Additionally, the creation of biomarkers for monitoring and early detection of radiation-induced health effects could provide valuable tools for mitigating risks and improving outcomes. As our knowledge of these mechanisms advances, translating findings from animal models to human health contexts remains a critical priority for public health and radiation protection efforts.

2. Future Directions and Research

The study of exposure to low-dose radiation remains in development, with a pressing need to bridge critical knowledge gaps to better understand its health implications, especially in the context of chronic, low-dose exposures [118]. Future studies should concentrate on unraveling the complex biological processes associated with low-dose radiation effects, leveraging advanced molecular and computational tools to achieve greater precision in understanding its mechanisms and outcomes [161]. These efforts will be instrumental in guiding public health policies, therapeutic interventions, and radiological protection frameworks [18].

One of the primary future directions is the development of robust, high-resolution biomarkers to assess low-dose radiation exposure and its biological consequences [160]. Current biomarkers, such as DNA damage markers and oxidative stress indicators, offer a foundation, but they lack specificity and sensitivity for detecting low-dose effects [16]. Progresses in omics technologies including genomics, proteomics, metabolomics, and epigenomics provide opportunities to identify novel biomarkers that capture the systemic and long-term consequences of exposure to radiation [117]. For example, profiling microRNAs or circulating extracellular vesicles has shown promise in reflecting radiation-induced cellular and molecular changes [148].

Additional research is required to better refine the dose-response association for low-dose radiation. The linear no-threshold (LNT) model, commonly applied in radiation protection, assumes that even the smallest dose has the potential of harmful effects [17]. However, emerging proof from both epidemiological studies and animal models proposes that low-dose radiation may elicit non-linear effects, including adaptive responses and hormesis under certain conditions [40]. A more refined knowledge of these dynamics could reshape radiation safety standards and therapeutic approaches, especially in the context of radiation therapy and medical imaging [12].

Animal models remain an indispensable tool for exploring the long-term consequences of low-dose radiation, but there is a growing need for models that better mimic human biology [6]. Traditional animal studies often fall short in capturing the complexity of human responses to radiation exposure [116]. Advances in humanized animal models, organoid systems, and in vitro 3D culture models offer potential pathways to improve translational relevance [103]. These models can

help elucidate the interplay between radiation-induced molecular changes and tissue-level outcomes, including inflammation, fibrosis, and carcinogenesis [60].

The combination of computational modeling and artificial intelligence (AI) presents another hopeful avenue for advancing low-dose radiation research. Computational approaches can simulate radiation interactions at multiple scales from atomic to organismal levels providing insights into dose distribution, molecular damage, and biological outcomes [54]. AI can further enhance these models by identifying patterns in large datasets, such as those generated by omics studies or epidemiological surveillance [150]. These tools can accelerate hypothesis generation, optimize experimental designs, and improve risk assessment methodologies [87].

Given the growing recognition of individual variability in radiation responses, future research should also prioritize personalized approaches to radiation protection and therapy [25]. Factors such as genetic predisposition, age, sex, and co-morbidities influence how individuals respond to low-dose radiation [151]. Precision medicine frameworks, which consider these variables, could enable tailored interventions to mitigate radiation-induced health risks while maximizing therapeutic benefits in clinical settings [22].

Finally, interdisciplinary collaboration is essential to advance the field. Low-dose radiation research intersects with numerous disciplines, including radiation biology, toxicology, epidemiology, oncology, and public health. Collaborative efforts among these fields can facilitate a holistic knowledge of the effects of radiation and drive the development of integrated policies for prevention, diagnosis, and treatment [4]. Additionally, increased engagement with regulatory bodies and policymakers can ensure that emerging scientific insights inform practical guidelines and societal decision-making.

3. Conclusion

The increasing recognition of low-dose ionizing radiation as a significant environmental and occupational hazard necessitates a deeper understanding of its long-term impacts on liver function and overall health. This review has highlighted the biochemical and hepatological effects of exposure to low-dose radiation in animal models, shedding light on the complex interactions between oxidative stress, inflammatory cytokines, lipid metabolism, and antioxidant defenses in the liver. Moreover, the review has emphasized the potential human health implications, particularly in the context of liver diseases comprising cancer, nonalcoholic fatty liver disease (NAFLD), hepatitis, and metabolic disorders.

From a biochemical perspective, low-dose radiation has been demonstrated to cause cellular oxidative stress, alter liver enzyme activities, provoke inflammatory responses, and disrupt metabolic pathways, leading to long-term hepatic cells dysfunction. The liver, being a critical organ for detoxification, metabolism, and immune modulation, is particularly vulnerable to the cumulative impacts of radiation exposure. The resulting liver injury can appear as fibrosis, hepatocellular carcinoma, and metabolic abnormalities, which may persist even after the cessation of radiation exposure.

Given the multifaceted nature of radiation-induced liver damage, future studies should aim to enhance our knowledge of the molecular mechanisms driving radiation related liver diseases. In particular, the role of epigenetic modifications, gene environment interactions, and long-term cumulative exposure needs to be further explored. Advances in animal models, such as the use of humanized mice and single cell technologies, will likely provide more precise insights into the impacts of low-dose radiation at a cellular and molecular level.

Furthermore, the development of effective interventions to mitigate the biochemical and hepatological effects of exposure to low-dose radiation is of paramount importance. Investigating

radioprotective agents, anti-inflammatory therapies, and antifibrotic drugs could provide novel strategies for preventing or treating radiation-induced liver damage. Additionally, gene therapy and biological methods, like the use of stem cells or epigenetic modification techniques, may offer promising solutions for restoring liver function after radiation-induced injury.

Optimizing public health policies and radiation exposure guidelines is equally critical, especially for populations at higher risk due to occupational or medical radiation exposure. Establishing safe radiation dose thresholds, as well as radiation safety protocols, could minimize the risk of liver damage across various sectors, from healthcare to environmental settings. Moreover, improving the monitoring systems to track cumulative radiation exposure and implementing educational programs for employees and the general community will help mitigate the long-term burden of radiation-induced liver diseases.

Table 1
Summary of biochemical effects of exposure to low-dose radiation in animal models

Biochemical Consequence	Description	Key Findings	References
Oxidative Stress	Increased reactive oxygen species (ROS) production damaging lipids, proteins, and DNA	ROS production triggers lipid peroxidation, leading to cell membrane damage	[82,142]
Antioxidant Depletion	Decrease in antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH)	Antioxidant enzyme depletion reduces cellular defense, enhancing vulnerability to oxidative damage	[31,72]
Inflammatory Cytokine Release	Activation of cytokines, like TNF-α and IL-6	Elevated cytokine levels lead to inflammation, promoting fibrosis and cellular injury	[5,113]
Lipid Metabolism Disruption	Changes in lipid storage and metabolism pathways	Increases in hepatic lipids and triglycerides contribute to non-alcoholic fatty liver disease (NAFLD)	[49,104]
DNA Damage	Damage to DNA molecules in hepatocytes	DNA damage can results mutations and carcinogenesis	[43,149]

Table 2
Hepatological consequences of exposure to low-dose radiation in animal models

Hepatological Consequence	Description	Observations in Animal Models	Implications for Human Health	References
Fibrosis	Excessive deposition of extracellular matrix proteins	Observed collagen accumulation and fibrotic changes	Increased risk of liver fibrosis and cirrhosis	[32,46,121]
Inflammation	Chronic inflammatory response within liver tissues	Raised inflammatory markers (e.g., IL-6, TNF-α)	May lead to chronic inflammation and hepatitis	[14,27, 134]
Hepatic Steatosis	Accumulation of fat in liver cells	Increased hepatic triglyceride levels and lipid droplet accumulation	Risk of non-alcoholic fatty liver disease (NAFLD)	[47,123]

Carcinogenesis	Development of liver cancer	Increased DNA damage and mutations in hepatocytes	Elevated risk of hepatocellular carcinoma (HCC)	[1,51, 65]
Metabolic Dysregulation	Alterations in glucose and lipid metabolism pathways	Observed insulin resistance and glucose intolerance	Potential for metabolic syndrome and diabetes	[21,98, 101]

Table 3
Future directions for research on low-dose radiation and liver health

Research Area	Objective	Expected Impact	References
Mechanistic Studies	Identify molecular pathways involved in radiation-induced liver injury, focusing on oxidative stress and DNA repair mechanisms	Improved understanding of liver-specific mechanisms underlying radiation damage	[89,162]
Epigenetic Research	Examine radiation's epigenetic effects on liver cells, like DNA methylation and histone modifications	Insight into long-term effects of radiation exposure on gene expression and disease risk	[66,76]
Radioprotective Agents	Explore potential drugs or natural compounds (e.g., antioxidants) that mitigate radiation effects	Development of preventive therapies to reduce liver damage from low-dose radiation exposure	[48,91]
Humanized Animal Models	Utilize humanized liver models in animals for translational studies on radiation-induced liver disease	Better translation of findings from animal studies to human health implications	[115,156]
Public Health and Policy Studies	Assess epidemiological data and recommend exposure guidelines for occupational and environmental settings	Establishment of evidence-based policies to minimize radiation exposure and protect liver health	[30,143]

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