Acupuncture and Herbal Medicine

Ferulic acid reduces inflammatory response induced by radiation through Sirt1-NLRP3 pathway

Yao Nie[1,2], Mingyue Huang[1], Tingyu Yang[3], Yu Mei[1], Huiting Zhang[1,4], Xue Wei[1,4], Yue Gao[1,*], Zengchun Ma[1,*]

[1]Beijing Institute of Radiation Medicine, Beijing, China; [2]Anhui Zhifei Longcom Biopharmaceutical Co., Ltd., Hefei, China; [3]Tianjin University of Traditional Chinese Medicine, Tianjin, China; [4]School of Traditional Chinese Medicine, Guangdong Pharmaceutical University, Guangzhou, China

Abstract

Objective: A model of inflammatory damage was induced by radiation to investigate whether ferulic acid (FA) can reduce the inflammatory response through the Sirt1-NLRP3 inflammatory pathway. This will help discover radiation-protective drugs and elucidate the molecular mechanisms related to radiation-induced inflammatory damage.

Methods: A mouse model of radiation-induced immunoinflammatory injury was established to verify the anti-inflammatory effects of FA *in vivo*. C57BL/6J mice were randomly divided into six groups, and 5 Gy whole-body irradiation was used for modeling. Mice were administered a gastric solvent, amifostine, or 25, 50, or 100 mg/kg FA daily for 12 days, consecutively, before irradiation. The serum of mice was collected 24 hour after irradiation to observe the content of inflammatory factors interleukin (IL)-1β, IL-18, IL-6, and tumor necrosis factor (TNF)-α. The spleen and thymus tissues of mice were weighed and the organ index was calculated for pathological testing and immunofluorescence detection.

Results: FA reduced the radiation-induced decrease in the spleen and thymus indices. FA significantly reduced the secretion of inflammatory factors in the serum and reversed the radiation-induced reduction in lymphocytes in the spleen and thymus of mice. FA activated Sirt1 and inhibited the expression of the NLRP3 inflammasome to alleviate the inflammatory response.

Conclusions: FA reduced radiation-induced inflammation in animals, possibly by activating Sirt1 and reducing nucleotide oligomerization domain (NOD)-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome expression, thereby reducing the secretion of inflammatory factors.

Keywords: Ferulic acid, NLRP3 inflammasome, Radiation inflammation, Sirt1

Graphical abstract: http://links.lww.com/AHM/A110

Introduction

With the development of science and technology as well as the nuclear industry, ionizing radiation has been widely used in the fields of scientific research, medicine, military, and industry. Along with its application, the number of individuals involved in radiation-related work has increased significantly, and various biological effects of ionizing radiation have gradually attracted public attention[1]. Individuals are widely exposed to low-dose radiation from natural sources, medical radiation diagnosis and treatment, aerospace navigation, and high-background environments, whereas exposure to high-dose radiation accidents such as nuclear leakages and nuclear weapon explosions are rare; both pose a serious threat to human health[2]. When killing tumor cells, radiation damages normal cells, including circulating cells in the peripheral blood, especially immune cells, leading to tumor progression and recurrence[3–4]. Radiation interacts with the immune system in various ways, affecting the homeostasis and functional integrity of immune cells, thereby inducing tissue damage and inflammation[5–7].

Therefore, immunomodulators that improve immunity may reverse or prevent radiation-induced immune damage. Ferulic acid (FA, 4-hydroxy-3-methoxycinnamic acid) is a phenolic acid widely found in plants. It is an effective component of traditional Chinese medicine (TCM), such as Angelicae Sinensis Radix and Chuanxiong Rhizoma. It is also found in food such as coffee, wheat bran, and corn husks[8]. FA has a variety of physiological functions, among which the widely used ones are: (1) anti-thrombotic function: inhibition of platelet aggregation, inhibition of tryptamine, and thromboxane-like substance release. Currently, marketed

Yao Nie, Mingyue Huang, and Tingyu Yang contributed equally to this work.

**Corresponding author. Zengchun Ma, E-mail: mazchun@139.com; Yue Gao, E-mail: gaoyue@bmi.ac.cn.*

Received 20 November 2023 / Accepted 4 May 2024

How to cite this article: *Nie Y, Huang M, Yang T, Mei Y, Zhang H, Wei X, Gao Y, Ma Z. Ferulic acid reduces inflammatory response induced by radiation through Sirt1-NLRP3 pathway. Acupunct Herb Med 2024;4(3):367–374. DOI: 10.1097/HM9.0000000000000109*

sodium ferulate is primarily used for the treatment of cardiovascular and cerebrovascular diseases and leukopenia. (2) Antioxidant function: scavenging free radicals, and inhibiting and scavenging enzymes that produce free radicals. Its application in food, healthcare products, cosmetics, and other industries is increasing[9]. In addition, FA has a strong anti-radiation effect that improves the survival rate of irradiated mice[10], increases peripheral blood counts[11], and promotes the recovery of bone marrow hematopoietic function[12]. However, few studies have analyzed the signaling pathways and target mechanisms of FA in terms of its radioprotective effects.

In recent years, studies have reported that the up-regulation of nucleotide oligomerization domain (NOD)-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome expression plays a key role in radiation immune injury[13–15], which can promote the maturation and secretion of inflammatory cytokines interleukin (IL)-1β and IL-18[13,16]. The question remains whether FA can alleviate radiation-induced immune damage by inhibiting inflammatory responses. Therefore, in the present study, we evaluated the role and mechanism of action of FA in attenuating radiation-induced immune-mediated inflammatory injury in animals.

Materials and methods

Drugs and materials

IL-1β, IL-18, IL-6, and tumor necrosis factor (TNF)-α mouse enzyme-linked immunosorbent assay (ELISA) Kits were purchased from Nanjing Jiancheng Bioengineering Institute. Rabbit anti-IL-1β, anti-IL-18, anti-NLRP3, and anti-Sirt1 antibodies were purchased from Abcam (USA). FA was purchased from Shanghai Yuanye Biotechnology Co., Ltd. and amifostine for injection was purchased from Ark Pharm, USA.

Animals and radiation

One hundred and twenty 6-week-old single pathogen-free (SPF) C57BL/6J mice (half male and half female) were purchased from Beijing Weitong Lihua Laboratory Animal Technology Co., Ltd. The mice were housed in the SPF animal room of the Animal Center of the Academy of Military Medical Sciences. The feeding conditions were as follows: the temperature was 26 ± 0.5°C, the relative humidity was 50% ± 5%, the light was a 12-hour day/night cycle, each room had an independent air purification system, and the mice were provided with sterile distilled water.

Mice were randomly divided into six groups. Group I was administered 1% sodium carboxymethyl cellulose as the normal control group. Group II received 5 Gy radiation and 1% sodium carboxymethyl cellulose as radiation model group. In Group III, 1% sodium carboxymethyl cellulose was administered orally for 12 days. On the 12th day, amifostine (0.1 mg/10 g) was injected intraperitoneally 30 to 40 minutes before 5 Gy radiation[17–18]. Group IV received 5 Gy radiation and low-dose FA (25 mg/kg + 5 Gy) as the low-dose FA group. Group V received 5 Gy radiation and a medium dose of FA (50 mg/kg + 5 Gy), and was the medium-dose FA group. Group VI received 5 Gy radiation and a high dose of FA (100 mg/kg + 5 Gy)[19].

Thirty to 40 minutes after the last administration, the mice were transferred to the radiation center and subjected to a single whole-body irradiation at a dose of 5 Gy[20–21]. The single irradiation dose rate was 68.34 cGy/min; this was provided by the Institute of Radiation Medicine, Academy of Military Medical Sciences.

Organ index analysis

The mice in each group were euthanized 24 hours after irradiation. The spleen and thymus tissues were weighed and the corresponding organ indices were calculated using the following equation[22]:

Organ index = organ weight (mg)/mg/animal weight (g).

Hematoxylin & eosin (H&E) staining

Spleen and thymus tissues were fixed in neutral formalin (10%) buffer for 24 hours, dehydrated, and embedded in paraffin after routine dehydration, sectioned at 5 μm, deparaffinized, and stained with H&E. Then, pathological changes in tissues were observed using a light microscope.

Quantification of IL-1β, IL-6, IL-18, and TNF-α levels

The IL-1β, IL-6, IL-18, and TNF-α levels in the serum of mice were detected using the corresponding ELISA kits according to the manufacturer's instructions. Briefly, the corresponding serum samples were added to a 96-well plate and the blank wells were left untreated. Except for the blank wells, 100 μL horseradish peroxidase (HRP)-labeled antibody was added to the rest of the wells, incubated for 1 hour, then the liquid was discarded, 350 μL washing solution was added to the detection wells, the plate was left to stand for 60 seconds, the washing solution was removed, and this process was repeated five times. Fifty microliters of each substrate (A and B) were added to each well and incubated at 37°C in the dark for 15 minutes. Termination solution was added to each well and proteins were detected within 15 minutes at a wavelength of 450 nm.

Immunofluorescence analysis

Paraffin sections of the spleen and thymus were removed, deparaffinized in water before antigen repair, and blocked with serum. Primary anti-sirtuin 1 (SIRT1) or NLRP3 antibody was added and incubated at 4°C overnight, then HRP-labeled secondary antibody was added. The sections were washed thrice with phosphate-buffered saline (PBS) for 5 minutes each time, ReadiUse Tyramide (TSA) was added, and the tissues were incubated at room temperature in the dark for 10 minutes. Next, the samples were washed thrice with tris-buffered saline with Tween (TBST) for 5 minutes each time before the second primary antibody, nuclear factor-kappa B (NF-κB), was added and incubated at 4°C overnight. After incubation with secondary antibodies, the sections were stained with 4',6-diamidino-2-phenylindole (DAPI), observed using a fluorescence microscope, and images were captured.

Statistical analysis

All experiments were repeated at thrice for statistical analyses. The data were expressed as mean ± standard deviation (SD) and plotted using GraphPad software. Statistical analysis of data between multiple groups was performed using one-way way analysis of variance (ANOVA), and statistical analysis of data between two groups was performed using the *t* test.

Results

Effect of FA on organ index in mice after radiation

Compared to the control group, the organ index of each group of mice in the irradiation model group was significantly reduced (Figure 1), indicating successful establishment of the model. Compared to the irradiation group, the spleen indices of male mice in the 25 and 50 mg/kg FA groups and female mice in the 100 mg/kg FA group were significantly increased (Figure 1A), indicating that FA had a significant protective effect on the spleens of mice 24 hours after irradiation. Simultaneously, compared to the irradiation group, the thymus index of the positive drug group and the 50 and 100 mg/kg FA groups was significantly increased (Figure 1B), indicating that FA had an obvious protective effect on the thymus of the irradiated mice. Collectively, 50 mg/kg FA exhibited a better protective effect on the spleen and thymus than the other two doses.

Effect of FA on the histopathological changes of spleen and thymus in mice after radiation

In the control group, the boundary between the red and white pulps of the spleen was explicit, the shape of splenic bodies in the white pulp was regular, the number of lymphocytes was abundant, and a large area of extramedullary hematopoiesis was observed in the red pulp. In the thymus, the structure of the thymic lobules and the boundary between the cortex and medulla were clearly visible and the number of lymphocytes in the cortex was high. In the spleen tissues of the radiation group, the volume of splenic bodies in the white pulp decreased significantly, as did the number of lymphocytes showing apoptosis and nuclear fragmentation. Simultaneously, the number of neutrophils and multinucleated giant cells in the red pulp dramatically increased. The thymus tissue was replaced by a large area of proliferative connective tissue with numerous local calcium foci. Large tracts of lymphocyte necrosis, nuclear fragmentation, or lysis, accompanied by a small amount of neutrophil infiltration, were observed. In the positive drug group, the boundary between the red and white pulps was sharp, and the number of splenic corpuscle lymphocytes increased. In the 50 mg/kg FA group, the degree of radiation damage was reduced compared to that in the radiation group, the boundary between the red pulp and white pulp was clearly visible, the volume of the white pulp spleen body was reduced, the number of lymphocytes was reduced, and the number of neutrophils was increased in the red pulp, indicating that 50 mg/kg FA played a favorable protective role. In the positive control group and the FA low- and high-dose groups, the degree of radiation damage was also reduced (Figures 2 and 3).

Effect of FA on the secretion of inflammatory factors in serum

Radiation significantly increased IL-1β, IL-18, IL-6, and TNF-α levels in the serum of mice (Figure 4). Amifostine injected 40 minutes before irradiation significantly reduced IL-18 and TNF-α levels in the serum of mice and IL-1β levels specifically in male mice. FA showed

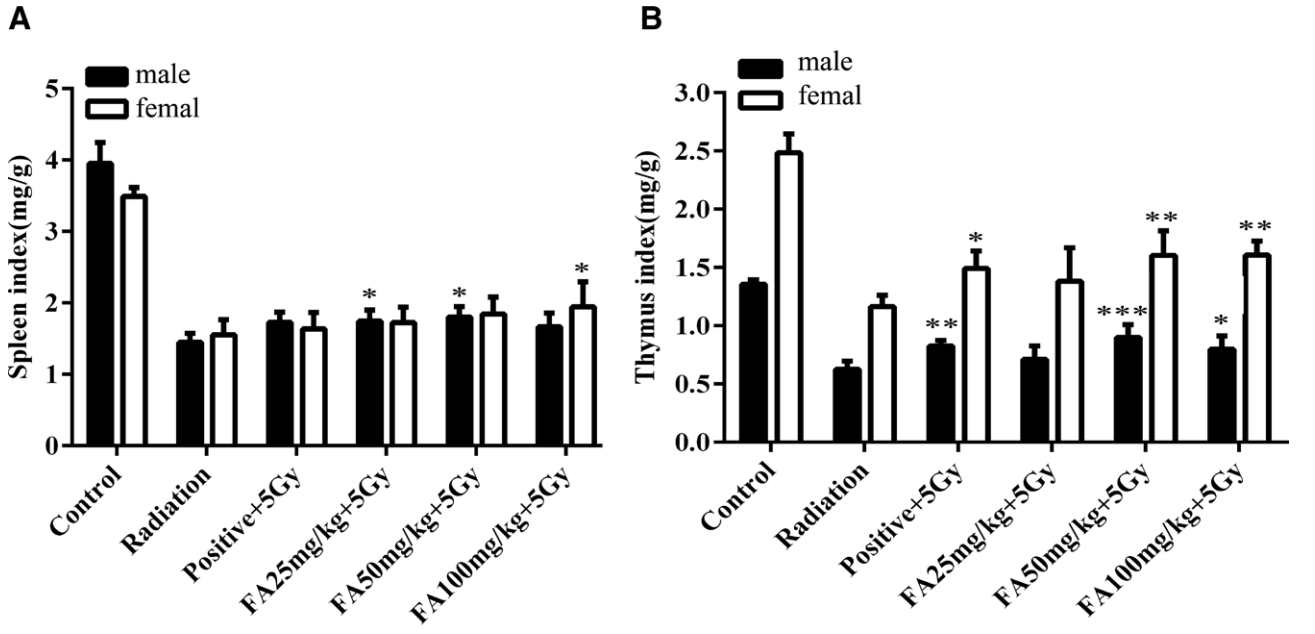

Figure 1. Effects of FA on organ indexes of spleen and thymus in mice after radiation. Organ index = organ weight (mg)/mg/animal weight (g). (A) Spleen index of mice 24 h after irradiation. (B) Thymus index of mice 24 h after irradiation ($\bar{x} \pm s$, $n = 10$). Statistical analysis of data between multiple groups was performed using one-way way ANOVA. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ *vs*. radiation. ANOVA: Analysis of variance; FA: Ferulic acid.

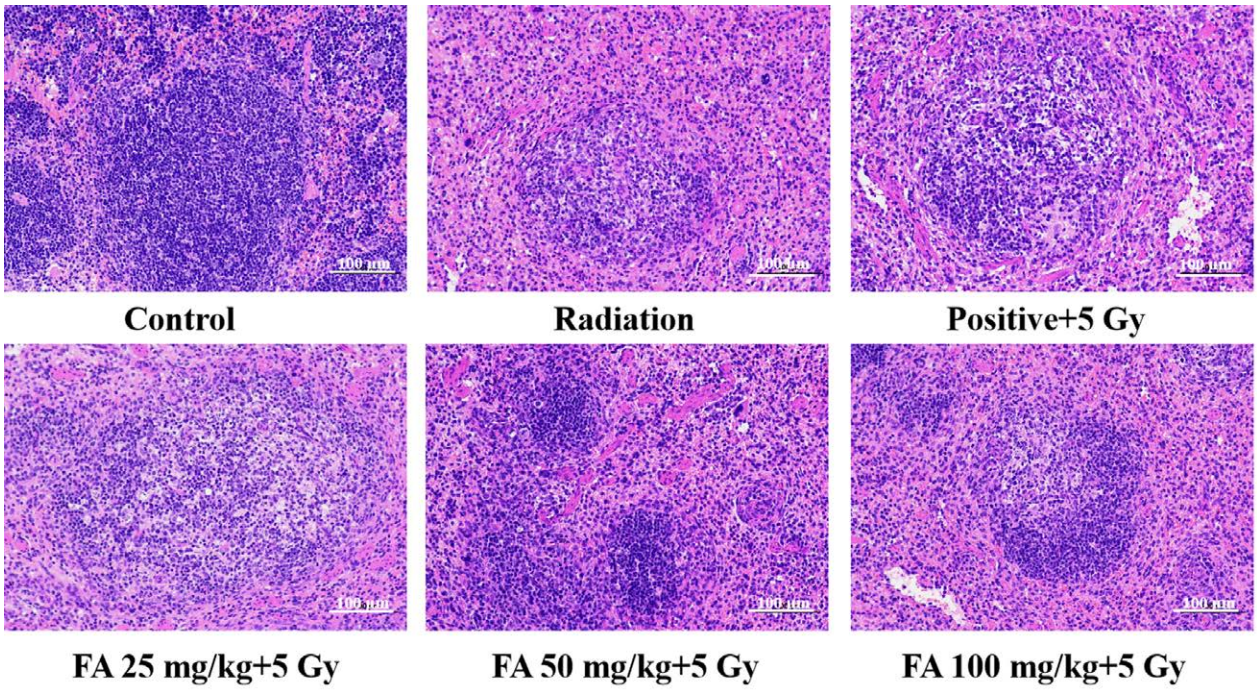

Figure 2. Representative pictures of H&E staining of spleen tissues. Spleen sections were stained with H&E 24 h after irradiation to analyze for changes in morphology and inflammatory cell infiltration. Scale bar, 100 μm. FA: Ferulic acid; H&E: Hematoxylin & eosin.

a strong anti-inflammatory effect on mice (especially 50 mg/kg), which significantly reduced the content of inflammatory factors in serum except IL-1β in female mice. With regard to these inflammatory factors alone, FA appeared to be more effective in male mice; however, further confirmation is needed.

FA increased Sirt1 expression in the spleen

To determine the potential mechanism underlying the protective effect of FA on radiation-induced immune damage, Sirt1 protein expression in the spleens of male mice was measured using fluorescent immunolabeling. Sirt1 was labeled with fluorescein isothiocyanate (FITC) and was shown by red fluorescence using a fluorescence microscope. The nucleus was blue under DAPI staining. As shown in Figure 5, fluorescein was expressed in the marginal zone and white pulp area of the spleen tissue. The superposition of the two figures showed the expression of Sirt1. Compared with the radiation group, Sirt1 expression in the spleen of the positive drug group and the low- and medium-dose FA groups was significantly increased, indicating that FA can activate the expression of Sirt1 *in vivo*, which may produce anti-inflammatory and anti-radiation effects through the Sirt1-NLRP3 pathway. However, no significant activation was Sirt1 in the high-dose FA group was observed.

FA inhibited NF-κB and NLRP3 activation in irradiated mice

To further test whether FA could achieve anti-inflammatory and anti-radiation effects by regulating the Sirt1-NF-κB-NLRP3 inflammasome pathway, we detected the expression of NF-κB and NLRP3 in the spleens of male mice again using immunofluorescence. The nuclei were stained blue, NF-κB appeared red and NLRP3 appeared green using a fluorescence microscope (Figure 6). In the control group, NF-κB expression occurred primarily in the cytoplasm, which was not highly activated. NLRP3 was also expressed at low levels, primarily distributed at the edge of the spleen tissue, and rarely expressed in the middle white pulp area. In irradiated mice, NF-κB was activated and flood into the nucleus; the expression of NLRP3 was significantly increased and was primarily distributed in the marginal area of the spleen, as well as in the middle section of the white pulp area of the spleen. Low and medium doses of FA decreased NLRP3 expression Green fluorescence was significantly weaker in the medium-dose FA group, indicating that the expression of NLRP3 was notably inhibited. These results were consistent with those of Sirt1 fluorescence expression, indicating that FA can produce anti-inflammatory and anti-radiation effects through the Sirt1-NF-κB-NLRP3 inflammasome pathway at the cellular level.

Discussion

In this study, 5 Gy ^{60}Co γ-ray irradiation was used to establish a mouse model of immune inflammation. Changes in the levels of inflammatory factors were detected in the peripheral blood of C57BL/6J mice. Organ index, pathological changes, and the expression of inflammasome-related proteins were observed in the spleen and thymus tissues. The spleen and thymus are important immune organs, and their organ indices reflect the immune function of the body to a certain extent. FA reduced the radiation-induced decrease in the spleen and thymus indices. Simultaneously, the H&E staining

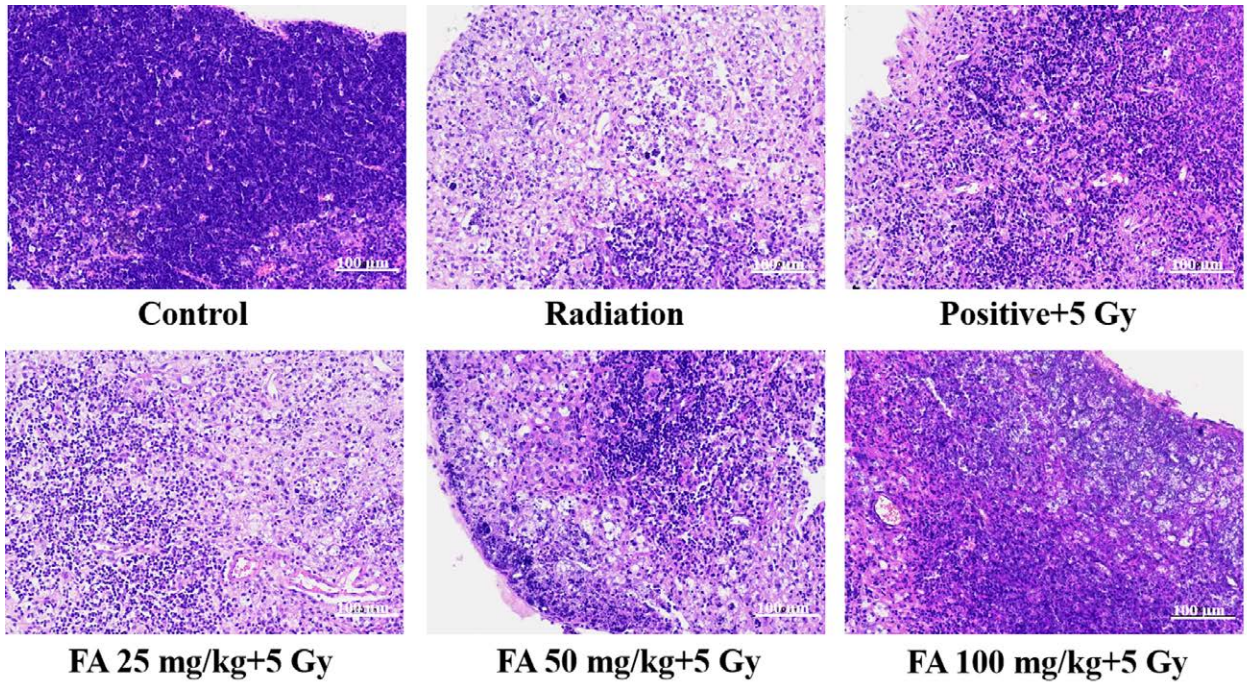

Figure 3. Representative pictures of H&E staining of thymus tissues. Thymus sections were stained with H&E 24 h after irradiation to check changes in morphology and inflammatory cell infiltration. Scale bar, 100 μm. FA: Ferulic acid; H&E: Hematoxylin & eosin.

results of the pathological sections of the spleen and thymus tissues showed that the intragastric administration of FA before irradiation had a protective effect similar to that of amifostine, as it increased the number of lymphocytes in the spleen and thymus tissues and exhibited an immuno-protective effect. By measuring the expression levels of inflammatory factors IL-1β, IL-18, IL-6, and TNF-α in the serum of mice, it was shown that FA showed satisfied anti-inflammatory effect on the irradiated mice, which significantly reduced IL-1β, IL-18, and TNF-α secretion. However, notably, that there were differences in the secretion of inflammatory factors in the sera of female and male mice, which might be related to sex and individual differences in mice.

Inflammasomes are a complex of proteins containing members of the NLR family, including NLRP1, NLRP3, and other inflammasomes[23]. After the NLRP3 inflammasome is activated, it recruits apoptosis-associated speck-like protein (ASC) and caspase-1 to oligomer itself and close the spatial distance of procaspase-1, and then clears itself to mature caspase-1, which further promotes the secretion of IL-1β and IL-18. It is involved in the inflammatory and innate immune responses[13]. Ionizing radiation increases the reactive oxygen species (ROS) level *in vivo*, activates the NLRP3 protein complex pathway, which activates the inactive precursor of Caspase-1, clefts it to the bioactive Caspase-1, and enhances the production of pro-inflammatory cytokines IL-1β and IL-18. This results in the production of chemokines, TNF-α, and high mobility group histone 1 (HMGB-1)[14,24–25]. NF-κB is a transcription factor[26] that also acts as a key mediator of inflammatory response and can regulate several aspects of innate and adaptive immune function[27]. After cells are exposed to ionizing radiation, proteasomal degradation of inhibitor of nuclear factor kappa B (IκB) is phosphorylated, leading to abnormal activation and nuclear translocation of NF-κB[28]. Simultaneously, NF-κB signaling pathway, as a typical immune-inflammatory pathway, participates in the regulation of TNF-α and IL-1β expression after activation, promotes the production of pro-IL-1β and pro-IL-18, and leads to inflammatory response[29]. Sirt1 is the mammalian homolog of yeast silent information regulator 2 (Sir2), which belongs to class III histone deacetylases[30]. In addition to histone deacetylation, Sirt1 regulates the activity of NF-κB, p53, poly(ADP-ribose) polymerase 1 (PARP-1), and other transcription factors[31]. Sirt1 plays a central role in regulating inflammatory responses. In *in vitro* experiments, Sirt1 gene silencing has been shown to increase the levels of inflammatory factors such as TNF-α, IL-1β, and IL-6, and Sirt1 knockout *in vivo* can promote the infiltration of macrophages in adipose tissue[32]. Sirt1 inhibits the expression of NLRP3 by deacetylating inflammation-related transcription factors to achieve anti-inflammatory and anti-apoptosis effects[32].

To further study the role of Sirt1-NLRP3 inflammasome pathway in the anti-radiation function of FA *in vivo*, the expression of Sirt1, NF-κB, and NLRP3 proteins in the spleen of mice was detected using immunofluorescence. These results further confirm the activation of Sirt1 by FA. Moreover, the expression of NLRP3 dramatically decreased, while that of Sirt1 increased. At the cellular level, FA significantly reduced the expression of NLRP3 and Caspase-1 proteins, as well as the expression of inflammatory factors IL-1β and IL-18, indicating that FA could inhibit the activation of NLRP3 inflammasome in AHH-1 cells induced by radiation[33]. Collectively, these results suggest that FA activates Sirt1 and inhibits NLRP3 inflammasome expression to alleviate the inflammatory response.

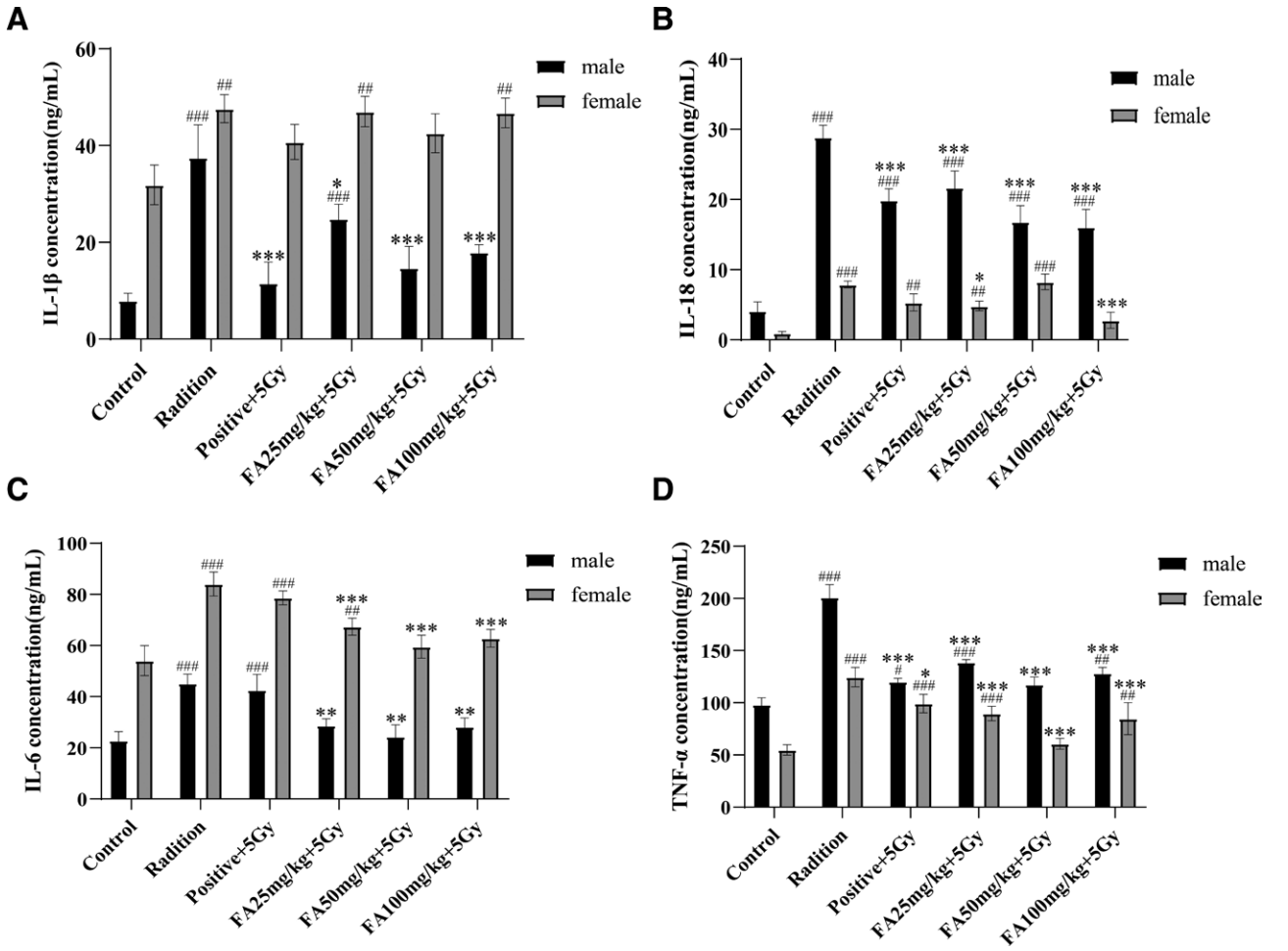

Figure 4. FA had a protective effect on radiation-induced immune inflammation in mice. The mice were administered amifostine or FA by gavage for 12 days and then irradiated with 5 Gy on the 12th day. Mice were euthanized 24 h after irradiation, and serum was collected. The content of (A) IL-1β; (B) IL-18; (C) IL-6; and (D) TNF-α in serum ($\bar{x} \pm s$, $n = 3$). Statistical analysis of data between multiple groups was performed using one-way way ANOVA. $^{###}P < 0.001$ *vs.* control. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ *vs*. radiation. ANOVA: Analysis of variance; FA: Ferulic acid; IL: Interleukin; TNF: Tumor necrosis factor.

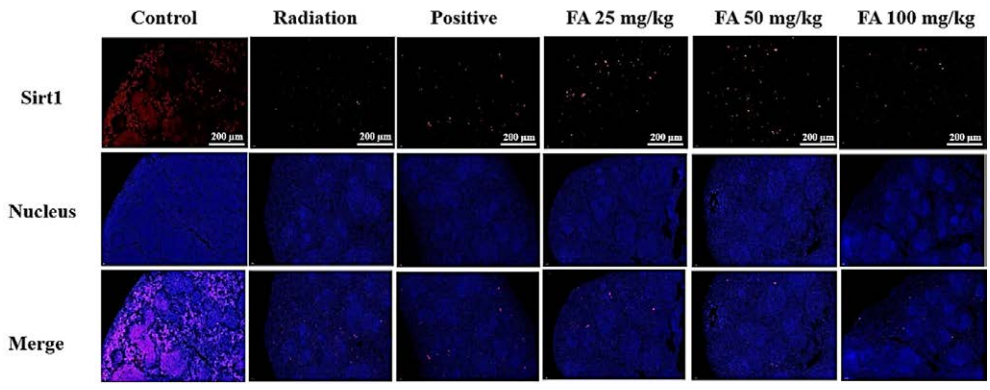

Figure 5. FA could increase the expression of Sirt1 in the spleen of mice. The mice were administered amifostine or FA by gavage for 12 days and then irradiated with 5 Gy on the 12th day. The protein expression of Sirt1 in the spleen and thymus of male mice 24 h after irradiation was detected using immunofluorescence. The red fluorescence represented Sirt1 and the blue fluorescence represented nucleus (2.6×).

FA inhibited the NLRP3 inflammasome by activating Sirt1 and regulating NF-κB to achieve anti-inflammatory and anti-radiation effects. Sirt1 protein inhibits the transcriptional activity of NF-κB by deacetylation[34–35], and the transcriptional expression of NLRP3 is dependent on NF-κB[36]. This suggests that activation of Sirt1 may effectively regulate the NLRP3 inflammatory complex, thereby reducing inflammation by interfering with Sirt1-NF-κB-NLRP3 inflammasome pathway[37]. However, gender-specific differences in inflammatory responses, the use of a single mouse strain (C57BL/6J), and a focus on only the spleen and thymus limit the generalizability of the findings. Additionally, the study's reliance on a single radiation dose and in vitro validation necessitates

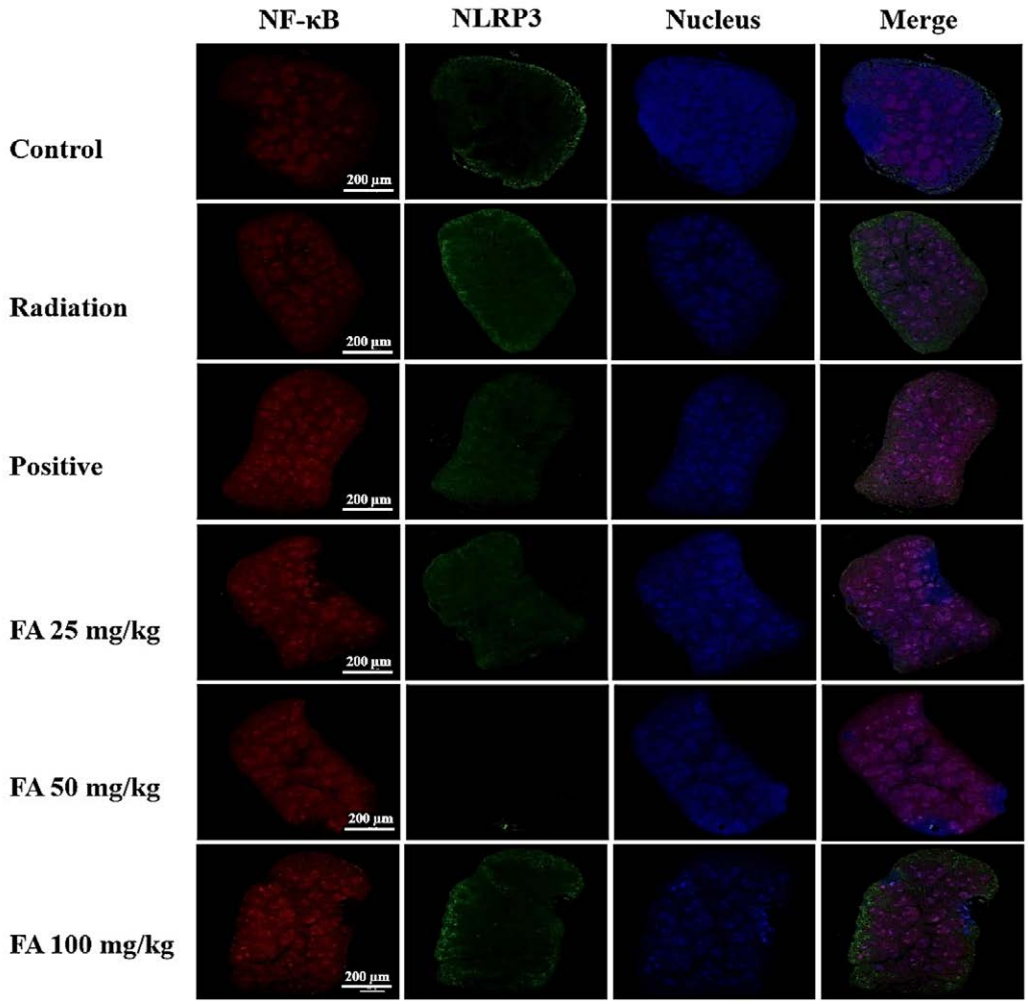

Figure 6. FA could inhibit the expression of NLRP3 as well as activate the expression of NF-κB in the spleen of mice. The mice were administered amifostine or FA by gavage for 12 days and then irradiated with 5 Gy on the 12th day. The expression of NF-κB and NLRP3 proteins in the spleen tissues of male mice 24 h after irradiation was detected by immunofluorescence. Red fluorescence represented NF-κB, green fluorescence represented NLRP3, while blue fluorescence represented nucleus (2.6×).

broader validation. Future research would address these limitations by including diverse genetic models, conducting comprehensive organ analysis, exploring long-term effects, and performing dose-response studies. These steps will enhance the understanding of FA's efficacy and potential clinical application.

Conclusion

In summary, the radioprotective effects of FA on two major immune organs, the spleen and thymus, were investigated. To the best of our knowledge, our study demonstrated for the first time that FA attenuates radiation-induced inflammation by interfering with the Sirt1-NF-KB-NLRP3 pathway. The results of this study provide a theoretical basis for the development of new radioprotective agent targets and mechanisms and elucidated a new entry point for the treatment of NLRP3 inflammation-related diseases.

Conflict of interest statement

Yue Gao is an editorial board member of the journal. None of the other authors declare any conflicts of interest. The authors declare no conflict of interest.

Funding

This research was funded by the National Key Research and Development Program (2022YFC3500303), Innovation Team and Talents Cultivation Program of the National Administration of Traditional Chinese Medicine (ZYYCXTD-C-202009), and National Natural Science Foundation of China (81873063).

Author contributions

Yao Nie, Mingyue Huang, Tingyu Yang, Yue Gao, and Zengchun Ma designed the study. Yao Nie, Mingyue Huang, Tingyu Yang, and Zengchun Ma wrote the paper. Yao Nie, Mingyue Huang, Tingyu Yang, Yu Mei, Huiting Zhang, and Xue Wei participated in this research. Yao Nie, Mingyue Huang, Yu Mei, Huiting Zhang, and Xue Wei contributed new reagents and analytical tools. Yao Nie, Mingyue Huang, and Tingyu Yang analyzed the data.

Ethical approval of studies and informed consent

All animal experiments were conducted in compliance with the Chinese Animal Care and Welfare guidelines. All

animal experiments were conducted in compliance with the guidelines of the Animal Ethics Committee (ethics number: IACUC-DWZX-2021-584). All animal experiments were conducted in compliance with the Chinese Animal Care and Welfare Guidelines. This article contains no experiments involving human subjects conducted by any of the contributors. This article contains no experiments involving human subjects conducted by any of the contributors.

Acknowledgments

None.

References

[1] Paunesku T, Haley B, Brooks A, et al. Biological basis of radiation protection needs rejuvenation. *Int J Radiat Biol* 2017;93(10):1056–1063.
[2] Averbeck D, Salomaa S, Bouffler S, et al. Progress in low dose health risk research: novel effects and new concepts in low dose radiobiology. *Mutat Res Rev Mutat Res* 2018;776:46–69.
[3] Mckelvey KJ, Hudson AL, Back M, et al. Radiation, inflammation and the immune response in cancer. *Mamm Genome* 2018;29(11–12):843–865.
[4] Keisari Y, Kelson I. The potentiation of anti-tumor immunity by tumor abolition with alpha particles, protons, or carbon ion radiation and its enforcement by combination with immunoadjuvants or inhibitors of immune suppressor cells and checkpoint molecules. *Cells* 2021;10(2):228.
[5] Lumniczky K, Impens N, Armengol G, et al. Low dose ionizing radiation effects on the immune system. *Environ Int* 2021;149:106212.
[6] Sueiro-Benavides RA, Leiro-Vidal JM, Salas-Sánchez A, et al. Radiofrequency at 2.45 GHz increases toxicity, pro-inflammatory and pre-apoptotic activity caused by black carbon in the RAW 264.7 macrophage cell line. *Sci Total Environ* 2021;765:142681.
[7] Khan AUH, Blimkie M, Yang DS, et al. Effects of chronic low-dose internal radiation on immune-stimulatory responses in mice. *Int J Mol Sci* 2021;22(14):7303.
[8] Liu CS, Chen L, Hu YN, et al. Self-microemulsifying drug delivery system for improved oral delivery and hypnotic efficacy of ferulic acid. *Int J Nanomedicine* 2020;15:2059–2070.
[9] Gunesch S, Hoffmann M, Kiermeier C, et al. 7-O-Esters of taxifolin with pronounced and overadditive effects in neuroprotection, anti-neuroinflammation, and amelioration of short-term memory impairment in vivo. *Redox Biol* 2020;29:101378.
[10] Tan HL, Ma ZC, Zhao YH, et al. Effect of ferulic acid and its derivatives on survival rate of irradiated mice. *Pharm J Chin PLA* 2014;30(6):507–508.
[11] Tan HL, Ma ZC, Zhao YH, et al. Hematopoietic effects of derivatives of ferulic acid on irradiated mice. *Pharm J Chin PLA* 2013;29(5):407–410,438.
[12] Tan HL, Ma ZC, Xu WYJ, et al. Effect of ferulic acid on low dose radiation-injured beagle dogs. *Pharm J Chin PLA* 2015;31(2):113–116.
[13] Cheng H, Chen L, Huang M, et al. Hunting down NLRP3 inflammasome: an executioner of radiation-induced injury. *Front Immunol* 2022;13:967989.
[14] Han C, Godfrey V, Liu Z, et al. The AIM2 and NLRP3 inflammasomes trigger IL-1-mediated antitumor effects during radiation. *Sci Immunol* 2021;6(59):eabc6998.
[15] Li X, Gong Y, Li D, et al. Low-dose radiation therapy promotes radiation pneumonitis by activating NLRP3 inflammasome. *Int J Radiat Oncol Biol Phys* 2020;107(4):804–814.
[16] Wei J, Wang H, Wang H, et al. The role of NLRP3 inflammasome activation in radiation damage. *Biomed Pharmacother* 2019;118:109217.
[17] Ji L, Cui P, Zhou S, et al. Advances of amifostine in radiation protection: administration and delivery. *Mol Pharm* 2023;20:5383–5395.
[18] King M, Joseph S, Albert A, et al. Use of amifostine for cytoprotection during radiation therapy: a review. *Oncology (Huntingt)* 2020;98(2):61–80.
[19] Das U, Biswas S, Sengupta A, et al. Ferulic acid (FA) abrogates ionizing radiation-induced oxidative damage in murine spleen. *Int J Radiat Biol* 2016;92(12):806–818.
[20] Hussien SM. Radio-adaptive response induced by low-dose ionizing radiation in innate immunity for radiotherapy. *Health Phys* 2023;124(3):166–174.
[21] Zheng Y, Pang X, Zhu X, et al. Lycium barbarum mitigates radiation injury *via* regulation of the immune function, gut microbiota, and related metabolites. *Biomed Pharmacother* 2021;139:111654.
[22] Sun S, Li B, Wu M, et al. Effect of dietary supplemental vitamin C and betaine on the growth performance, humoral immunity, immune organ index, and antioxidant status of broilers under heat stress. *Trop Anim Health Prod* 2023;55(2):96.
[23] Gaul S, Leszczynska A, Alegre F, et al. Hepatocyte pyroptosis and release of inflammasome particles induce stellate cell activation and liver fibrosis. *J Hepatol* 2021;74(1):156–167.
[24] Smith AO, Ju W, Adzraku SY, et al. Gamma radiation induce inflammasome signaling and pyroptosis in microvascular endothelial cells. *J Inflamm Res* 2021;14:3277–3288.
[25] Yeung YT, Aziz F, Guerrero-Castilla A, et al. Signaling pathways in inflammation and anti-inflammatory therapies. *Curr Pharm Des* 2018;24(14):1449–1484.
[26] Kaltschmidt C, Greiner JFW, Kaltschmidt B. The transcription factor NF-κB in stem cells and development. *Cells* 2021;10(8):2042.
[27] Barnabei L, Laplantine E, Mbongo W, et al. NF-κB: at the borders of autoimmunity and inflammation. *Front Immunol* 2021;12:716469.
[28] Pordanjani SM, Hosseinimehr SJ. The role of NF-κB inhibitors in cell response to radiation. *Curr Med Chem* 2016;23(34):3951–3963.
[29] Chishti AA, Baumstark-Khan C, Koch K, et al. Linear energy transfer modulates radiation-induced NF-kappa B activation and expression of its downstream target genes. *Radiat Res* 2018;189(4):354–370.
[30] Shen P, Deng X, Chen Z, et al. SIRT1: a potential therapeutic target in autoimmune diseases. *Front Immunol* 2021;12:779177.
[31] Tang B. Sirt1 and the mitochondria. *Mol Cells* 2016;39(2):87–95.
[32] Xie Y, Tu W, Zhang J, et al. SirT1 knockdown potentiates radiation-induced bystander effect through promoting c-Myc activity and thus facilitating ROS accumulation. *Mutat Res* 2015;772:23–29.
[33] Nie Y, Sun Y, Xu H, et al. Ferulic acid alleviates radiation-induced AHH-1 inflammatory response by inhibiting the NLRP3 inflammasome. *Pharmacol Clin Chin Mater Med* 2020;36(1):63–68.
[34] Chen M, Chen Z, Huang D, et al. Myricetin inhibits TNF-α-induced inflammation in A549 cells *via* the SIRT1/NF-κB pathway. *Pulm Pharmacol Ther* 2020;65:102000.
[35] Xu F, Xu J, Xiong X, et al. Salidroside inhibits MAPK, NF-κB, and STAT3 pathways in psoriasis-associated oxidative stress *via* SIRT1 activation. *Redox Rep* 2019;24(1):70–74.
[36] Li S, Fang Y, Zhang Y, et al. Microglial NLRP3 inflammasome activates neurotoxic astrocytes in depression-like mice. *Cell Rep* 2022;41(4):111532.
[37] Ren B, Feng J, Yang N, et al. Ginsenoside Rg3 attenuates angiotensin II-induced myocardial hypertrophy through repressing NLRP3 inflammasome and oxidative stress *via* modulating SIRT1/NF-κB pathway. *Int Immunopharmacol* 2021;98:107841.