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The role of melatonin on radiation-induced pneumonitis and lung fibrosis: A systematic review

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ABSTRACT

Purpose: Pneumonitis and lung fibrosis, as the most common compliances of lung irradiation, can affect the quality of life. The use of radio-protective agents can ameliorate these injuries. This study aimed to review the potential protective role of melatonin in the treatment of radiation-induced Pneumonitis and lung fibrosis.

Methods: The current systematic study was conducted based on PRISMA guidelines to identify relevant literature on " the effect of melatonin on radiation-induced pneumonitis and lung fibrosis" in the electronic databases of Web of Science, Embase, PubMed, and Scopus up to January 2021. Eighty-one articles were screened in accordance with the inclusion and exclusion criteria of the study. Finally, eight articles were included in this systematic review.

Results: The finding showed that the lung irradiation-induced pneumonitis and lung fibrosis. The co-treatment with melatonin could alleviate these compliances through its anti-oxidant and anti-inflammatory actions. Melatonin through upregulation of some enzymes such as catalase, superoxide dismutase, glutathione, NADPH oxidases 2 and 4, dual oxidases 1 and 2, and also downregulation of malondialdehyde reduced oxidative stress following lung radiation. Moreover, melatonin through its anti-inflammatory effects, can attenuate the increased levels of nuclear factor kappa B, tumor necrosis factor alpha, transforming growth factor beta 1, SMAD2, interleukin (IL)-4, IL-4 receptor-a1 (IL4ra1), and IL-1 beta following lung radiation. The histological damages induced by ionizing radiation were also alleviated by co-treatment with melatonin.

Conclusion: According to the obtained results, it was found that melatonin can have anti-pneumonitis and anti-fibrotic following lung irradiation.

1. Introduction

Cancer or malignant tumor is characterized as the uncontrolled growth of cells and is one of the leading causes of death worldwide [1–3]. Moreover, a more drastic increment in its incidence and mortality has been reported worldwide [4,5]. There are several therapeutic modalities for cancer treatment which can be used as systemic, local, or targeted therapies [6–8].

Radiotherapy, as a local cancer treatment (for most cases), is used in 50–70% of cancer patients during their therapeutic course [9–11]. There are several benefits to this therapeutic modality, including non-invasiveness, organ-preservation, cost-efficiency, and spatiotemporal

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flexibility in tumor targeting [12–14]. Despite its beneficial effects for cancer control, there are some concerns related to decreasing radiotherapeutic efficiency due to induce the acute and/or late adverse effects in normal organs/tissues [15]; as some complications can affect the quality of life of irradiated patients, resulting to decrease the cost-effectiveness of radiotherapy [16,17]. Even when radiotherapy is curative, the normal tissue complications lead to suffering long-term survivors [18]. In some cases, damage to normal tissues (particularly highly radiosensitive tissues) may stop the treatment course due to acute reactions or restrict to deliver the sufficient radiation dose to the tumor [19].

The lung is considered as an organ sensitive to ionizing radiation and late responding in the body [20]. Following the exposure of this radiosensitive organ to a high radiation dose, several cytokines and chemokines are released which lead to the infiltration of inflammatory cells [21]. In addition, macrophages, neutrophils, and are able to release several cytokines which result to mediate that result in mediating the appearance of edema and pneumonitis [22]. Furthermore, chronic production of free radicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS) leads to stimulate collagen deposition in extracellular space, inducing fibrosis [23]. Both pneumonitis and lung fibrosis can lead the irradiated person to death [24]. Therefore, special attention should be considered to minimize damage to the lung tissue and effectively deliver the radiation dose to the tumor. Some studies have been performed to alleviate radiation-induced pneumonitis and fibrosis. In this regard, neutralization of free radicals, attenuation of pro-oxidant and pro-inflammatory mediators induced by ionizing radiation has been proposed for protection against pneumonitis and fibrosis [25]. Or, the use of agents such as captopril and flaxseed which are able to suppress renin-angiotensin system and oxidative stress can attenuate the signs related to pneumonitis and fibrosis [26,27].

In the past several decades, the use of radio-protector and/or radiosensitizer agents for the alleviation of radiation-induced adverse effects has attracted much attention. Melatonin, as an indole-derived hormone, is mainly generated and secreted by the pineal gland. This hormone has various impacts on the normal tissues such as anti-oxidant, anti-inflammatory, and anti-apoptotic effects; hence, it can protect the normal tissues against oxidative and inflammatory damage [28–30]. Briefly, melatonin exerts an anti-oxidative action via two mechanisms of direct and indirect. In the direct pathway, this agent mostly exerts its anti-oxidant effect via radical adduct formation, single electron transfer, and hydrogen transfer [31,32]. In the indirect pathway, melatonin can stimulate anti-oxidant enzymes, protect anti-oxidant enzymes against oxidative damage, modulate genomic expressions, and so on [33,34]. Additionally, melatonin can markedly decrease pro-apoptotic factors and also increase anti-apoptotic factors [35]. The anti-inflammatory effect of melatonin is exerted by modulation of inflammatory cytokine expression levels, inflammatory mediators, infiltration of inflammatory cells, etc. [29,36].

A systematic search was performed on the potential protective role of melatonin on radiation-induced pneumonitis and lung fibrosis in the current study. Furthermore, we tried to discuss: **1)** the mechanisms underlying radiation-induced pneumonitis and lung fibrosis, and **2)** the mechanisms related to the radio-preventive role of melatonin.

2. Methods

2.1. Search strategy

In the present study, we performed a systematic search in accordance with the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [37]. The literature search was carried out to assessed all relevant studies on "the role of melatonin on radiation-induced pneumonitis and lung fibrosis" in both medical subject heading (MeSH) or advance on electronic databases of Web of Science (WOS), Embase, PubMed, and Scopus up to January 2021 using the keywords of "Melatonin" OR "Pneumonitis" OR "Radiation Pneumonia" OR "Fibrosis" OR "Radiation Fibrosis" OR "Lung injury" AND "Radiation treatment" OR "Radiation" OR "Radiation therapy" OR "Radiation therapies" OR "Radiotherapy" OR "Radiotherapies" in keywords, title or abstract.

2.2. Study selection

In this systematic review, the inclusion criteria were full-text papers with **a)** English language, **b)** the keywords as mentioned above, **c)** adequate data, and **d)** without restriction in publications with clinical, in vivo, or in vitro. The exclusion criteria were also defined as **a)** not related studies, **b)** posters, **c)** abstract conferences, **d)** editorials, **e)** letters to the editors, **f)** case reports, and **g)** review articles.

2.3. Data extraction

Three researchers reviewed each eligible article and then, the following data were extracted: **a)** author name and year of publication, **b)** models (clinical, in vivo or/and in vitro), **c)** irradiation conditions (radiation dose and radiation energy), **d)** radiation-induced adverse effects, **e)** melatonin dosage, the protocol of usage and administration route type; and **f)** outcomes of melatonin administration on the radiotherapy-induced pneumonitis and lung fibrosis.

3. Results

3.1. Literature search and screening

Fig. 1 is shown the process of study selection.

A systematic search found Eighty-one articles on the above-mentioned electronic databases up to January 2021. After removing the duplicated articles ($n = 41$), the remaining ones ($n = 40$) were screened in titles and abstracts, and 29 of them were omitted. Eleven articles were qualified for assessment of their full-texts. Considering the inclusion and exclusion criteria, eight articles were included in the current systematic review. Table 1 represents the data extracted from these eligible articles.

3.2. The role of melatonin on radiation-induced pneumonitis and lung fibrosis

In 2007, Serin et al. [38] assessed radiation-induced histopathological lung changes and the effectiveness of melatonin against these acute lung damages. In this study, melatonin was intraperitoneally administered at a dose of 100 mg/kg. After 15 min, the right lungs of rats were irradiated with a single radiation dose of 18 Gy by a Cobalt-60 unit. Then, the rats underwent euthanasia at 6 weeks following radiotherapy, and their lungs were evaluated histopathologically. The histopathological findings of the right lungs showed reductions in intra-alveolar edema and intra-alveolar erythrocytes and increases in activated macrophages, intra-alveolar fibrosis, hyaline arteriosclerosis, and alveolar wall thickness for the rats in radiation plus melatonin group compared to those in the radiation alone group. For the left lungs, there were decreases in alveolar neutrophils and intra-alveolar erythrocytes and increases in activated macrophages, hyaline arteriosclerosis and alveolar wall thickness for the rats in radiation plus melatonin group compared to those in the radiation alone group [38].

Jang et al. [39] investigated the effect of melatonin on radiation-induced lung injuries by evaluating changes in cytokine expression, oxidative stress, and histopathology of the lung tissues of mice. The animals were irradiated with a single radiation dose of 12 Gy with or without melatonin (200 mg/kg) pretreatment. Their results revealed an increment in malondialdehyde (MDA) level and reductions in superoxide dismutase (SOD), catalase, and glutathione (GSH) levels in the lung tissues at 2 weeks after radiotherapy. These changes were not

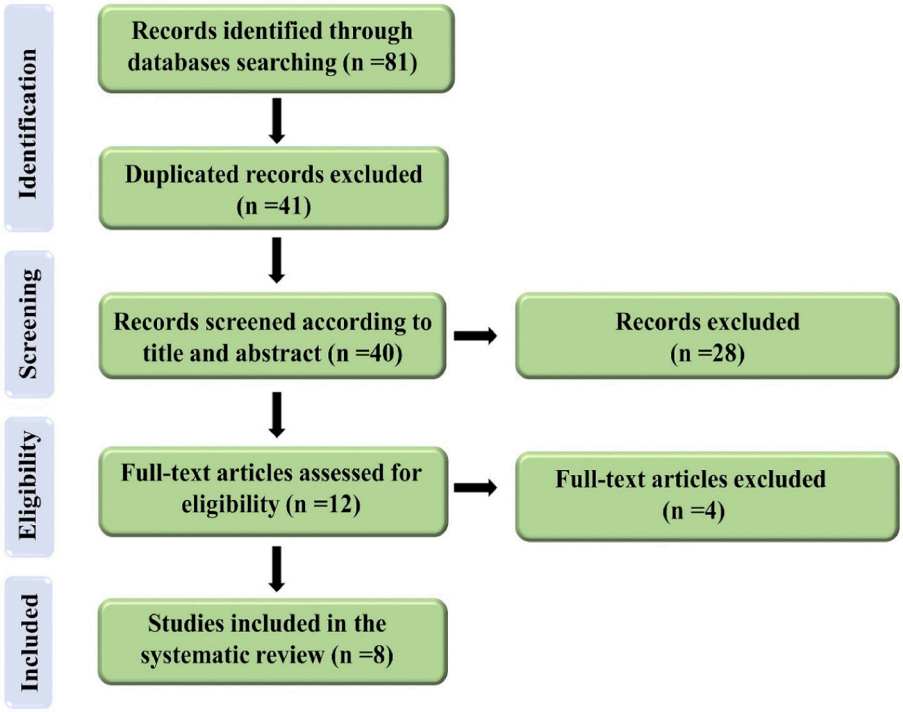

Fig. 1. Flow diagram of PRISMA used in the study for selection process.

remarkable at 1-day post-irradiation; however, these radiation-induced changes were restored by pretreatment with melatonin. Furthermore, the expression of transforming growth factor beta 1 (TGF-β1) mRNA at two weeks after radiotherapy was significantly higher than that of the control group, and the melatonin pretreatment resulted in a significant reduction in TGF-β1 mRNA expression compared with the irradiation-alone group. At 2-week post-irradiation, histopathologic evaluations showed edema and thickening of the alveolar walls and the alveoli obliteration via the infiltration of inflammatory cells. However, the irradiation-induced histopathologic damages were obviously abated in the melatonin-pretreated group. The tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β and IL-6 mRNA expression levels at two weeks after radiotherapy increased compared with the control group; however, this result was only significant for TNF-α. In this regard, pretreatment with melatonin significantly decrease the increased expression of TNF- α following radiotherapy but did not result in significant decreases in IL-1β and IL-6 levels [39].

Tahamtan et al. [40] investigated effects of melatonin on MDA levels and histopathological changes in irradiated lungs. They also evaluated the effect of the administration route of melatonin on the parameters mentioned above. In this study, rats were pretreated with either intraperitoneally or orally melatonin. Then, the thoracic areas of rats were irradiated with a single radiation dose of 18 Gy. Two days post-irradiation, the rats were sacrificed to evaluate MDA levels and acute and late changes of lung injuries. Their findings demonstrated that the MDA levels in plasma, red blood cell (RBC), and lung tissue were increased following radiotherapy. However, pre-treatment of the animals with either intraperitoneally or orally melatonin significantly decreased the MDA levels in RBC samples compared to the radiation group.

Moreover, intraperitoneal injection of melatonin reduced MDA levels in plasma and tissue. It is noteworthy that intraperitoneal injections of melatonin were more effective in lowering MDA levels than oral administrations. Concerning the acute changes in the lungs (48 h after radiotherapy), the following findings were obtained: **1)** there were significant increments in fibrosis symptoms, collapse incidence, and lymphocyte frequency in the irradiated group compared with the control group, **2)** the significant increases in the numbers of lymphocytes and macrophages and also significant decreases in the collapse incidence and frequency of RBC were observed in the oral melatonin plus radiation group compared with the radiation group, and **3)** there were reductions in RBCs, fibrosis and edema and also increments in numbers of macrophages and lymphocytes in the intraperitoneal melatonin plus radiation group compared with the radiation group. Concerning the chronic changes in the lungs (eight weeks after radiotherapy), the following results were obtained: **1)** the number of macrophages, lymphocytes, RBCs and incidence of collapse, edema, hyaline arteriosclerosis, and fibrosis increased in the irradiated group compared to the control group, **2)** pre-treatment with oral melatonin led to significant reductions in edema, hyaline arteriosclerosis, and fibrosis compared to the radiation group, and **3)** there were decreases in the frequency of neutrophils, RBCs, edema, collapse, hyaline arteriosclerosis and fibrosis in the intraperitoneal melatonin plus radiation groups compared with the radiation group [40].

Najafi et al. [41] assessed the modulatory effect of melatonin on the expression of several genes involved in oxidative stress and inflammatory processes following lung irradiation of rats with a single dose of 15 Gy. Their findings revealed that nuclear factor kappa B (NF-κB), TGFβ receptor 1 (TGFβR1), SMAD2, and NADPH oxidases 2 and 4 (NOX2 and NOX4) gene expressions were upregulated ten weeks after irradiation, especially NOX2 gene expression. The pre-treatment with melatonin (100 mg/kg) could attenuate the increased expression of all mentioned genes. They stated that upregulation of NADPH oxidase genes such as NOX2 and NOX4 genes might involve the chronic effects of irradiated lung tissues, and melatonin is able to attenuate radiation-induced lung injury through downregulation of these pro-oxidant genes [41].

Aliasgharzadeh et al. [42] evaluated the efficacy of pre-treatment with melatonin on the development of fibrosis and histopathological damages induced by a single radiation dose of 15 Gy. In addition, alternations in IL-4 and IL-13 levels and dual oxidases 1 and 2 (DUOX1 and DUOX2) and gene expressions following radiotherapy with and without melatonin were investigated. Their findings revealed 1.5-, 5.2-, 3.2-, and 3.0-fold increases in the levels of IL-4, IL-4 receptor-a1 (IL4ra1), DUOX1, and DUOX2, respectively. The pre-treatment with

Table 1
The characteristics of included studies.

Author & year	Models	Exposure conditions of RT	RT-induced toxicity	Melatonin dosage & protocol of usage; route of administration	Melatonin administration outcomes on RT-induced toxicity
Serin, 2007 [38]	In vivo/Rat	18 Gy (as single dose); 1.25 MeV (Cobalt-60 γ-rays)	↑intra-alveolar edema, ↑alveolar neutrophils, ↑intra-alveolar erythrocytes, ↑activated macrophages, ↑collapse, ↑alveolar wall thickness	Single dose of 100 mg/kg & 15 min prior to RT; *ip*	↓intra-alveolar edema, ↓intra-alveolar erythrocytes, ↑↑activated macrophages, ↑intra-alveolar fibrosis, ↑hyaline arteriosclerosis, ↑↑alveolar wall thickness
Jang et al., 2013 [39]	In vivo/ Mouse	12 Gy (as single dose); X-rays	↑MDA, ↓SOD, ↓catalase, ↓GSH, ↑TGF-β1 mRNA expression & protein level, ↑TNF-α, induction of histopathologic injuries (edema, thickening of the alveolar walls & obliteration of alveoli)	Single dose of 200 mg/kg & 30 min before RT; *ip*	↓MDA, ↑SOD, ↑catalase, ↑GSH, ↓TGF-β1 mRNA expression & protein level, ↓TNF-α, amelioration of histopathologic injuries
Tahamtan et al., 2015 [40]	In vivo/Rat	18 Gy (as single dose); 6 MV X-rays	↑MDA levels of plasma, RBC & lung tissue, induction of histological alternations in acute phase (↑fibrosis symptoms, collapse incidence & lymphocyte frequency), induction of histological alternations of chronic phase (↑numbers of RBCs, lymphocytes & macrophages, ↑collapse, edema, hyaline arteriosclerosis & fibrosis)	Single dose of 100 mg/kg & 30 min before RT; *ip* & oral	↓MDA levels of plasma, RBC & lung tissue, modulation on radiation-induced histological alternations in acute phase (↑numbers of lymphocytes & macrophages, ↓collapse & RBCs, ↓fibrosis & edema), modulation on radiation-induced histological alternations in chronic phase (↓edema, collapse & hyaline arteriosclerosis, ↓fibrosis symptoms, ↓neutrophils & RBCs, ↑lymphocytes)
Najafi et al., 2018 [41]	In vivo/Rat	15 Gy (as single dose); 1.25 MeV (Cobalt-60 γ-rays)	↑NF-κB, ↑TGFβR1, ↑SMAD2, ↑NOX2 & NOX4 levels	Single dose of 100 mg/kg & 30 min before RT; *ip*	↓NF-κB, ↓TGFβR1, ↓SMAD2, ↓NOX2 & NOX4 levels
Aliasgharzadeh et al., 2019 [42]	In vivo/Rat	15 Gy (as single dose); 1.25 MeV (Cobalt-60 γ-rays)	↑IL-4, ↑IL4ra1, ↑DUOX1 & DUOX2, induction of histological changes (mild fibrosis, severe infiltration of macrophages & lymphocytes, severe alveolar thickening, mild vascular thickening)	Single dose of 100 mg/kg & 30 min before RT; *iv*	↓IL-4, ↓IL4ra1, ↓Duox1 & Duox2, improvement of radiation-induced histological changes in lung tissues
Farhood et al., 2019 [43]	In vivo/ Mouse	18 Gy (as single dose); 1.25 MeV (Cobalt-60 γ-rays)	Severe congestion, inflammation, infiltration of macrophages, lymphocytes & neutrophils, edema, mild to moderate vascular & alveolar damages, moderate fibrosis	Single dose of 100 mg/kg & 24 h after RT for 2 weeks & 5 days per week; oral	Alleviation of radiation-induced damages in lung tissues
Najafi et al., 2019 [44]	In vivo/Rat	2 Gy (as single dose); 1.25 MeV (Cobalt-60 γ-rays)	For whole body irradiation: ↑TGFβR1, ↑SMAD2, ↑NF-κB, ↑NOX2 & NOX4, ↑8-OHdG For local irradiation to pelvis area: ↑TGFβR1, ↑NF-κB, ↑NOX2 & NOX4, ↑8-OHdG	Single dose of 100 mg/kg & 30 min before RT; NI	For whole body irradiation: ↓TGFβR1, ↓NOX2 & NOX4, ↓8-OHdG For local irradiation to pelvis area: ↓NF-κB, ↓NOX2, ↓8-OHdG
Wu et al., 2019 [45]	In vitro/ RAW 264.7 cells, In vivo/Mouse	15 Gy (as single dose); 1.25 MeV (Cobalt-60 γ-rays)	Induction of pneumonitis (striking infiltration of leukocytes, swelling of the alveolar interstitium), induction of lung fibrosis (extensive collagen accumulation in lung tissues), ↑MDA, ↓SOD, ↑IL-1β & IL-18, ↓number of alveolar macrophage subsets, ↑macrophages & neutrophil infiltrations, ↑intracellular ROS content, ↑NLRP3 & ASC expressions, ↑miR-30e level, ↑cleaved caspase-1 level	500 μmol/L (for in vitro) &1 mg/day (for in vivo) for 7 days after RT; *ip*	Alleviation of radiation-induced pneumonitis (thinner alveolar septa & less infiltration of leukocytes), mild fibrotic changes in alveolar areas, ↓IL-1β, ↑number of alveolar macrophage subsets, ↓percentage of infiltrating macrophages, ↓intracellular ROS content, ↓NLRP3 & ASC expressions, ↓miR-30e level, ↓cleaved caspase-1 level

↑, increase; ↓, decease; NI, not informed; RT, radiotherapy MDA, malondialdehyde; ROS, reactive oxygen species; GSH, glutathione; SOD, superoxide dismutase; COX, cyclooxygenase; TGF-β1, transforming growth factor beta 1; TGFβR1, TGFβ receptor 1; NOX, NADPH oxidase; DUOX, dual oxidase; TNF-α, tumor necrosis factor alpha; RBC, red blood cell; 8-OHdG, 8-hydroxy-2-deoxyguanosine; NF-κB, nuclear factor kappa B; IL-4, interleukin 4; IL-1β, IL-1 beta; IL4ra1, IL-4 receptor-a1;

melatonin (100 mg/kg) could reverse the changes as mentioned earlier. Nevertheless, IL-13 and IL13ra2 levels had no changes following radiotherapy. Histopathological findings also showed mild fibrosis, severe infiltration of macrophages and lymphocytes, severe alveolar thickening, and mild vascular thickening; however, pre-treatment with melatonin was able to significantly reverse all the radiation-induced histopathological changes. Moreover, there were no significant changes in infiltration of neutrophils, edema, and thrombosis [42].

Farhood et al. [43] conducted a histopathological study on possible mitigatory melatonin effects against radiation-induced pneumonitis and lung fibrosis. In this study, the chest area of mice was irradiated with a single dose of 18 Gy, and after one day, treatment with melatonin began for two weeks (5 days per week). Then, the animals were sacrificed after 100 days, and their lung tissues were evaluated. Their histopathological findings demonstrated severe congestion, inflammation, infiltration of macrophages, lymphocytes, neutrophils, and edema and also mild to moderate vascular and alveolar injuries, and moderate fibrosis for the irradiated mice compared to the control group. The post-treatment with melatonin (100 mg/kg/day) resulted to alleviate these damages, and they concluded that melatonin could mitigate pneumonitis and fibrotic markers [43].

Najafi et al. [44] assessed the modulatory effect of melatonin on the NOX2 and NOX4 expressions and oxidative DNA damage in the lung tissues of rats following whole body or pelvis irradiation with a single dose of 2 Gy. It is noteworthy the irradiation of the pelvis region was to evaluate bystander effect in lung tissue. Their findings revealed that whole-body irradiation caused the upregulation of the expression of TGFβR1 (4.93-fold), SMAD2 (3.74-fold), NF-κB (3.12-fold), NOX2 (22.72-fold), NOX4 (5.73-fold), and 8-hydroxy-2-deoxyguanosine (8-OHdG) (1.27-fold) genes, while local pelvis irradiation led to the

upregulation of TGFβR1(2.27-fold), NF-κB (2.25-fold), NOX2 (13.93-fold), and NOX4 (4.03-fold) genes. The pre-treatment with melatonin (100 mg/kg) decreased the expressions of these genes and also alleviated oxidative damage in both targeted and non-targeted lung tissues. Moreover, there was no significant reduction for the NOX2 and NOX4 levels in bystander tissues following melatonin treatment [44].

Wu et al. [45] investigated efficacy of melatonin on radiation-induced lung injury in both in vitro and in vivo models. The histopathological findings of mice exposed to a single radiation dose of 15 Gy showed a striking infiltration of leukocytes and swelling of the alveolar interstitium which the symptoms reflect pneumonitis in mice; however, post-treatment with melatonin alleviated these damages (i.e. areas of thinner alveolar septa and less infiltration of leukocytes). Moreover, an extensive collagen accumulation was observed in the irradiated lung of mice, but melatonin administration had mild fibrotic alternations in alveolar areas. The levels of SOD, MDA, and IL-1β were increased following the irradiation; however, melatonin remarkably restored the increased levels of these markers. Furthermore, the infiltration of macrophages and neutrophils increased in the irradiated mice compared with the control group, while supplementation with melatonin suppressed the increased infiltrations. Intracellular ROS levels of RAW 264.7 cells were significantly increased after exposure to a single radiation dose of 15 Gy compared to the control group, while post-treatment with melatonin attenuated the increased ROS levels. Western blot analysis revealed that the expressions of NLRP3, ASC, and cleaved caspase-1 were increased following the irradiation, whereas the post-treatment with melatonin markedly attenuated these increased activations. They also stated that the irradiation led to increasing miR-30e levels, and administration of melatonin restored miR-30e to about 2-fold. In addition, there was a negative correlation between the expressions of NLRP3 and miR-30e. Finally, they reported that melatonin could exert its protective effect on radiation-induced tissue injury via negatively regulating the miR-30e/NLRP3 signaling in macrophages [45].

4. Discussion

In the present study, the potential protective effects of melatonin on radiation-induced pneumonitis and lung fibrosis were systematically reviewed. The obtained results have been represented in Table 1. Additionally, some of the important alterations following lung irradiation as well as the effects of melatonin on these changes are shown in Fig. 2.

The irradiation of the lungs (as radiosensitive organs) during radiotherapy of thorax and chest wall tumors is inevitable [46,47]. The extent of radiation-induced lung injuries depends on a number of factors such as total radiation dose, irradiated volume, and whether radiotherapy is combined with surgery or chemotherapy [18]. These factors can be considered as limiting factors in chest radiotherapy; hence, it should be taken into consideration for prevention/decrease of lung injuries. Although reducing the irradiated volume or total radiation dose can be considered as the best method to mitigate radiation-induced lung injuries, this could cause a decreased therapeutic efficacy [18,47–49].

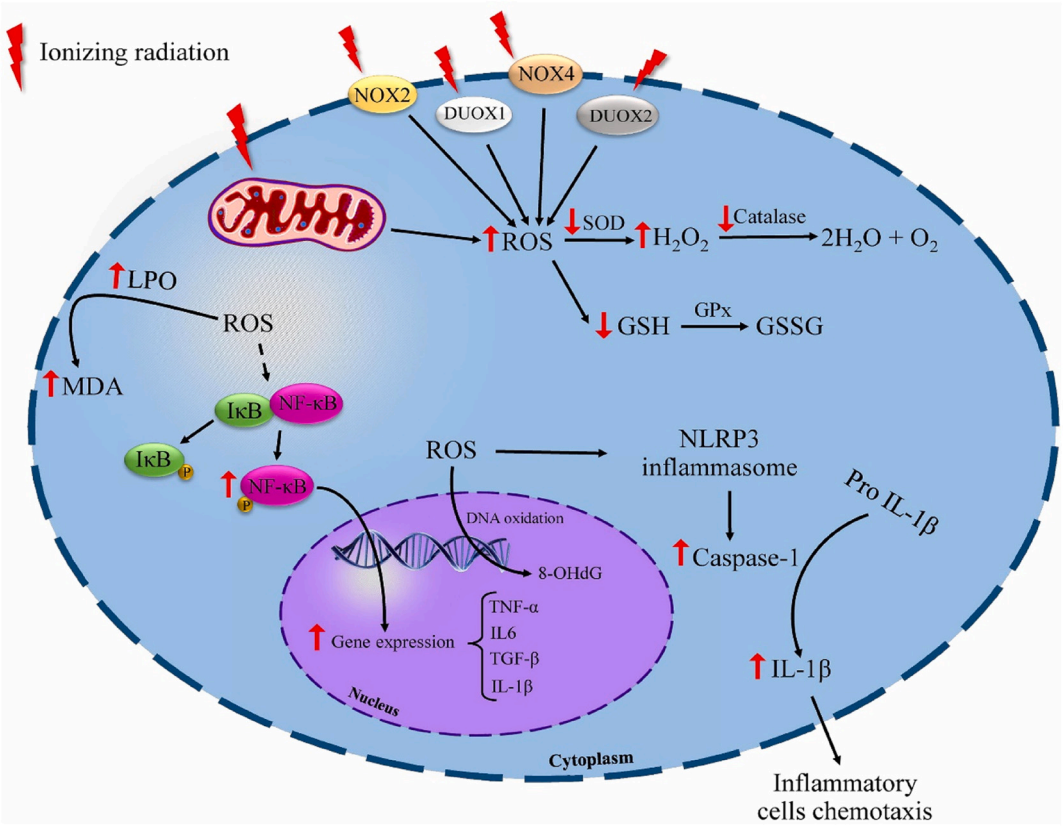

Fig. 2. The molecular mechanisms of ionizing radiation-induced injuries following lung irradiation. Ionizing radiation induces oxidative stress mainly through activation of NOX2, NOX4, DOUX1, DOUX2, and mitochondrial dysfunction. Moreover, ionizing radiation through inhibition the activities of SOD and catalase and reduction in GSH level induces increasing free radicals. ROS also causes lipid peroxidation and elevation of MDA as well as DNA oxidation and elevation of 8-OHdG. ROS up-regulates inflammation markers such as TNF-α, IL-6, IL-1β, and TGF-β1 through activation and nucleus translocation of NF-κB. Furthermore, ROS through activation of NLRP3 inflammasome induces IL-1β activity as inflammatory cell chemotaxis. Melatonin, through an opposite pattern, alleviates ionizing radiation-induced injuries following lung irradiation.

↑ increased by ionizing radiation; ↓ decreased by ionizing radiation; SOD, Superoxide dismutase; GSH, Glutathione; GSSG, Glutathione disulfide; GPx, Glutathione peroxidase; IL, Interleukin; NF-κB, Nuclear factor kappa B; LPO, Lipid peroxidation; MDA, Malondialdehyde; NOX, NADPH oxidase; DOUX, Dual oxidase.

Moreover, radiation-induced lung injuries may pose threats to the life of patients [50]. In general, the lung injuries induced by ionizing radiation are divided into two distinct phases (acute and late). In early phase, it can occur exudation, alveolar edema, alveolar septal thickening with mononuclear cell infiltration, vascular congestion, etc. which these symptoms refer to radiation pneumonitis. These acute lung damages may appear at approximately 1–6 months after radiotherapy [25,51,52]. It has also been reported histopathologically that in this phase, extensive alveolar damage is considered as the first symptom of a lung injury [53]. In the chronic phase, pulmonary fibrosis occurs months to years after radiotherapy [52]. This late injury is characterized by excessive accumulation of extracellular matrix (such as collagen) in the skin and soft tissue and also the proliferation of fibroblasts is considered as one of the most common radiation-induced late complications [18,52]. Radiation-induced fibrosis is an irreversible process to dead fibrous tissue, and a dynamic process that scar tissue is remodeled by reactivated myofibroblasts [18].

It has been reported that there is a relation between the elevation of oxidative stress and the initiation of the inflammatory pathway [54,55]. When the cells are exposed to ionizing radiation, free radicals are generated (via interaction of these ionizing rays with water molecules). Additionally, ROS and RNS can attack to vital organelles such as the membrane, mitochondria, and lysosome, amplifying the oxidative injury [56,57]. Furthermore, mitochondria and some pro-oxidant enzymes such as NADPH oxidase, inducible nitric oxide synthase (iNOS), and cyclooxygenase (COX)-2 are able to generate ROS and nitric oxide (NO), which can mediate the release of some inflammatory mediators, thereby having the main role in the development of pneumonitis and lung fibrosis [58]. It has also been reported that chronic damage to normal tissues by ROS leads to induce lung fibrosis [18]. Therefore, reduction of ROS production, neutralization of free radicals, attenuation of pro-oxidant and pro-inflammatory mediators can alleviate radiation-induced lung injuries. Melatonin, as a potent anti-oxidant, is able to reduce cellular oxidative stress through both direct and indirect anti-oxidant properties. This anti-oxidant agent directly scavenges ROS and RNS and indirectly increase the expression and activity of anti-oxidant enzymes, such as SOD, catalase and glutathione peroxidase (GSH-Px), GSH, etc. while inhibits the activity of pro-oxidant enzymes, such as NOS [5,59,60]. Melatonin also modulates NADPH oxidases which are the important pro-oxidant enzymes [42,44,61]. It is noteworthy that among these pro-oxidant enzymes, NOX1, NOX2, NOX4, DUOX1 and DUOX2 have shown to be involved in radiation-induced chronic oxidative stress [62,63]. Due to the small size and amphiphilic property of melatonin, it can also easily pass into the cell and exerts its anti-oxidant action at both lipid and water conditions [64,65]. Several studies have reported that melatonin is able to reduce oxidative stress following irradiation to the lung tissues through upregulation of catalase, SOD, GSH, NOX2, NOX4, DUOX1, and DUOX2 enzymes and also downregulation of MDA [39–42,44]. In addition, melatonin can attenuate the increased ROS and 8-OHdG levels in the irradiated lung tissues [44,45]. It has also been reported that although oxidative stress plays a crucial role in fibrinogenesis, melatonin is able to reduce fibroblast proliferation and collagen synthesis in the fibrogenetic lung [66].

Pneumonitis, known as acute inflammation and edema of lung tissues, happens following the release of a huge amount of inflammatory cytokines from lymphocytes and macrophages [67,68]. In addition, DNA damage and cell death induced by ionizing radiation in lung tissues can trigger the release of chemokines and cytokines which result to accumulate macrophages and lymphocytes in alveolar. Macrophages, lymphocytes, and neutrophils secrete some cytokines (such as IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, IL-18, IL-33, etc.). These cytokines can stimulate several signaling pathways, leading to the release of NO, ROS, prostaglandins, and some other mediators and thereby resulting in more oxidative injury and the appearance of inflammation [69,70]. In addition to pneumonitis, upregulation of pro-oxidant and pro-fibrotic genes through chronic infiltration of inflammatory cells and continuous generation of free radicals and some cytokines such as IL-4, IL-13, and interferon gamma (IFN-γ) can result to accumulate collagen and incidence of lung fibrosis [71,72]. Furthermore, it has been shown that several immune mediators such as signal transducer and activator of transcription (STAT) family, mitogen-activated protein kinases (MAPKs), COX-2, and SMAD2 are involved in the radiation-induced late effects in several organs, such as the lung [73–75]. Therefore, the inhibition of cytokines and mediators involved in inflammatory and oxidative stress processes can alleviate radiation-induced pneumonitis and lung fibrosis. The anti-inflammatory of melatonin has been reported in several diseases such as cardiotoxicity [5], nephropathy [29], dermatitis [76], and mucositis [77]. In this regard, melatonin is capable of amelioration of oxidative stress, inactivation of NF-κB, and down-regulation of inflammatory cytokines [78]. NF-κB is a ubiquitously expressed protein which is involved in expression of several pro-inflammatory cytokines such as IL-1 and TNF-α as well as inflammatory genes such as iNOS and COX-2 [79,80]. Melatonin through inhibition of COX-2 and NF-κB can decrease the release of inflammatory cytokines and chemokines, as these are associated with inhibiting recruitment of infiltration of lymphocytes, neutrophils, and macrophages, thereby preventing continuous oxidative injury following respiratory burst by inflammatory cells [36,81]. Melatonin is also able to attenuate the expression of TNF-α and STATs [82,83]. The findings obtained from the anti-inflammatory action of melatonin following radiation-induced lung injury showed that this agent via down-regulation of NOX2, NOX4, DUOX1, and DUOX2 genes could alleviate infiltration of macrophages and lymphocytes, vascular and alveolar injuries, lung fibrosis [42,44]. Also, the increased levels of NF-κB, TNF-α, SMAD2, IL-4, IL4ra1, and IL-1β following irradiation to the lung tissues were reduced by melatonin [39,41,42,44,45]. It has also been reported that the suppression of miR-30e/NLRP3 axis in macrophages by melatonin attenuates radiation-induced lung injury; these findings revealed that melatonin suppresses radiation-induced NLRP3 inflammasome activation and pro-inflammatory cytokine of IL-1, via protection of the mitochondria [45].

Among the pro-fibrogenic cytokines, TGF-β plays a key role in mediation of radiation-induced tissue fibrosis [84]. This multitasking cytokine is able to modulate cell proliferation, differentiation, apoptosis, and migration [85]. It also has a role in cancer progression and metastasis [83]. TGF-β mediates several aspects of the fibrotic process, which induce fibroblast proliferation and transformation to myofibroblasts, resulting in the deposition of collagen and extracellular matrix protein [86]. This cytokine triggers the deposition of collagen and fibronectin via different signaling pathways including SMAD2/3, Rho/Rock, NADPH oxidase, COX-2, epigenetic modifications as well as hormone alterations, including the renin-angiotensin system. It also stimulates the activities and regulation of several pro-oxidant enzymes such as iNOS and especially NOX2 and NOX4, thereby leading to continuous production of free radicals [87]. It has been reported that ionizing radiation is able to activate the TGF-β signaling pathway directly, as increased expression of TGF-β following irradiation, as a predictor of fibrosis, has previously been reported [88]. Therefore, the inhibition of TGF-β or its receptor can ameliorate fibrosis and inflammation. Some studies showed that the increased expression of TGF-β1 or TGFβR1 following the lung irradiation was attenuate by co-treatment with melatonin, possibly preventing the progression of radiation-induced lung injury [39,41,44].

The histological findings related to the effect of melatonin on radiation-induced lung injuries showed a post-irradiation time-dependent manner. Concerning the radiation-induced acute changes in the lung tissues, it was observed that the administration of melatonin results in reductions in edema, alveolar wall thickness, collapse incidence, and frequency of RBC and also increments in the numbers of lymphocytes and macrophages [38–40]. Concerning the radiation-induced late changes in the lung tissues, melatonin can decrease infiltration of macrophages, lymphocytes, neutrophils, edema, collapse, hyaline arteriosclerosis, and fibrosis [40,43].

5. Perspective of future research

Pneumonitis and lung fibrosis are the most common compliances of lung irradiation to high doses. These adverse effects induced by ionizing radiation can affect life quality and lead to irradiated patients' death. In this regard, researchers have suggested that the use of radio-protective agents can ameliorate radiation-induced lung injuries. The results of some in-vivo and in-vitro studies have revealed that melatonin, via anti-oxidant and anti-inflammatory actions, is able to alleviate radiation-induced pneumonitis and lung fibrosis. Furthermore, melatonin through radio-sensitizing effects against cancerous cells, can reduce radiation-induced adverse effects (reducing the total radiation dose delivered to the tumor). However, as early mentioned, these findings were extracted from animal models. The use of melatonin as a radio-protector or/and radio-sensitizer to alleviate radiation-induced lung injuries in humans needs further studies because sometimes the data are different between animal and clinic studies.

6. Conclusion

Lungs are organs sensitive to ionizing radiation and lung irradiation can induce the injuries such as pneumonitis and lung fibrosis. The pre/post-treatment with melatonin could alleviate the radiation-induced pneumonitis and lung fibrosis through its anti-oxidant and anti-inflammatory effects. Melatonin through upregulation of some enzymes such as catalase, SOD, GSH, NOX2, NOX4, DUOX1, and DUOX2 and downregulation of MDA reduced oxidative stress following lung irradiation. Moreover, melatonin through its anti-inflammatory effects can attenuate the increased levels of NF-κB, TNF-α, TGF-β1, SMAD2, IL-4, IL4ra1, and IL-1β following the lung irradiation. The histological damages induced by ionizing radiation also alleviated by co-treatment with melatonin.

Finally, it was found that melatonin can have anti-pneumonitis and anti-fibrotic roles following lung irradiation.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

CRediT authorship contribution statement

S.Sh. and T.A. gave the idea and drafted some parts of the manuscript. RA-F., A.B. and M.D-G did the literature search and drafted figures. H.Z., Gh.A. and M.M. drafted some parts of the manuscript. B.F. gave the idea, edited the manuscript, and supervised the whole study. All authors read and approved the manuscript.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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