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REVIEW ARTICLE

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Melatonin and cancer: From the promotion of genomic stability to use in cancer treatment

Bagher Farhood[1] | Nasser Hashemi Goradel[2] | Keywan Mortezaee[3] | Neda Khanlarkhani[4] | Masoud Najafi[5] | Amirhossein Sahebkar[6,7,8]

[1]Departments of Medical Physics and Radiology, Faculty of Paramedical Sciences, Kashan University of Medical Sciences, Kashan, Iran

[2]Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran

[3]Department of Anatomy, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran

[4]Department of Anatomy, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[5]Departments of Radiology and Nuclear Medicine, School of Paramedical Sciences, Kermanshah University of Medical Science, Kermanshah, Iran

[6]Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

[7]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

[8]School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence
Masoud Najafi, Departments of Radiology and Nuclear Medicine, School of Paramedical Sciences, Kermanshah University of Medical Science, Kermanshah 6715847141, Iran.
Email: najafi_ma@yahoo.com
Amirhossein Sahebkar, Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran.
Email: sahebkara@mums.ac.ir; amir_saheb2000@yahoo.com

Abstract

Cancer remains among the most challenging human diseases. Several lines of evidence suggest that carcinogenesis is a complex process that is initiated by DNA damage. Exposure to clastogenic agents such as heavy metals, ionizing radiation (IR), and chemotherapy drugs may cause chronic mutations in the genomic material, leading to a phenomenon named genomic instability. Evidence suggests that genomic instability is responsible for cancer incidence after exposure to carcinogenic agents, and increases the risk of secondary cancers following treatment with radiotherapy or chemotherapy. Melatonin as the main product of the pineal gland is a promising hormone for preventing cancer and improving cancer treatment. Melatonin can directly neutralize toxic free radicals more efficiently compared with other classical antioxidants. In addition, melatonin is able to regulate the reduction/oxidation (redox) system in stress conditions. Through regulation of mitochondrial nction and inhibition of pro-oxidant enzymes, melatonin suppresses chronic oxidative stress. Moreover, melatonin potently stimulates DNA damage responses that increase the tolerance of normal tissues to toxic effect of IR and may reduce the risk of genomic instability in patients who undergo radiotherapy. Through these mechanisms, melatonin attenuates several side effects of radiotherapy and chemotherapy. Interestingly, melatonin has shown some synergistic properties with IR and chemotherapy, which is distinct from classical antioxidants that are mainly used for the alleviation of adverse events of radiotherapy and chemotherapy. In this review, we describe the anticarcinogenic effects of melatonin and also its possible application in clinical oncology.

KEYWORDS

apoptosis, chemotherapy, DNA damage, melatonin, oncology, mitochondria, genomic instability, radiotherapy

1 | INTRODUCTION

Cancer is one of the most challenging diseases and is responsible for a considerable proportion of death in the world. It has been reported that in 2012 more than 14 million new cases of cancer were identified, and more than 8 million of whom died (Ferlay et al., 2015). Nowadays, it is well known that damage to DNA and genomic instability are among the main factors involved in the initiation of carcinogenesis. Genomic instability is associated with abnormal DNA mutations, which can be transferred to the next generation of the

cells. It is confirmed that various types of cytotoxic agents such as nonionizing radiation, heavy metals, and also anticancer drugs, including ionizing radiation (IR) and chemotherapy drugs, are able to impair the genomic content of cells (Najafi, Cheki, et al., 2018). Exposure to these agents increases the risk of carcinogenesis and elevates the risk of second primary malignancies following radiotherapy or chemotherapy in patients with cancer (Burt, Ying, Poppe, Suneja, & Gaffney, 2017; Hamilton, Tyldesley, W. Li, Olson, & McBride, 2015).

Melatonin is considered as a neural hormone, which regulates the circadian rhythm and sleep cycles. This agent can also be obtained from some herbal agents such as some fruits and vegetables, grains, nuts, and seeds (Meng et al., 2017). Nowadays, melatonin is prescribed as a sleeping aid, while a large body of data have reported various useful effects (Blask, 2009). One of the most interesting properties of melatonin is the potent antioxidant activity that can prevent aging and several diseases such as cancer and neurodegenerative diseases (Anisimov, 2003; R. J. Reiter, 1995, 2004; R. Reiter, Tan, & Allegra, 2002; D. Tan et al., 2002). Through the *N*1-acetyl-*N*2-formyl-5-methoxykynuramine (AFMK) pathway, melatonin is able to neutralize different types of free radicals (S. Cho, Joh, Baik, Dibinis, & Volpe, 1997). In addition to its direct action, melatonin is able to neutralize free radicals via stimulation of antioxidant enzymes or suppression of redox enzymes activity (Pablos et al., 1995; R. Reiter et al., 1999). These properties may make it a potential agent for radioprotection during radiotherapy or exposure to nuclear or radiological pollutants or warfare (Najafi, Shiraz, Motevaseli, Rezaeyan et al., 2017; Yahyapour et al., 2017, 2018).

It has been shown that there is a direct association between decreased serum levels of melatonin and increased oxidative DNA damage. Animal models have revealed that administration of melatonin reduces the risk of tumorigenesis and prevents the proliferation of cancer cells (Blask et al., 1999; Dauchy et al., 2009). Moreover, some epidemiological evidence suggests that low levels of melatonin are associated with increased risk of some malignancies such as breast and prostate cancers (Schernhammer & Schulmeister, 2004; Stevens, 2005; Tai, Huang, Bao, & Wu, 2016). In addition to its preventive role, recent studies have suggested that melatonin can be used as an adjuvant for increasing therapeutic outcome and reducing side effects of radiotherapy and chemotherapy (Najafi, Shiraz, Motevaseli, Geraily et al., 2017).

2 | MELATONIN: BASIC BIOLOGY

In most species including human, the pinealocytes in the pineal gland are the primary source for melatonin biosynthesis. However, some other tissues and cells such as gastrointestinal tract, retina, harderian gland, iris ciliary body, lacrimal gland, and also leukocytes have been reported to be involved in melatonin production. In the process of melatonin biosynthesis, tryptophan amino acids are converted to serotonin. Then, the enzyme arylalkylamine-*N*-acetyltransferase converts serotonin to *N*-acetylserotonin, which is subsequently metabolized to the melatonin (Klein et al., 1997; Zheng, Scheibner, Ho, & Cole, 2001). The biosynthetic pathway of melatonin production has been reported in details in several studies. In the first step, tryptophan is uptaken from the circulation and converted into 5-hydroxytryptophan by the tryptophan hydroxylase. The activity of this enzyme increases during darkness by about two folds. Then 5-hydroxytryptophan is converted to serotonin and then melatonin by arylalkylamine-*N*-acetyltransferase in the pineal gland. The activity of *N*-acetyltransferase is highly dependent on the circadian rhythm, being increased by around 100 folds at night.

In mammalians, melatonin is able to affect cellular functions through interaction with some receptors. Two different G protein-coupled melatonin receptors, including metallothionein 1 (MT1) and MT2, have been identified. Melatonin is also able to attenuate transfer of electrons to quinones through binding to MT3, leading to the amelioration of oxidative stress. Furthermore, melatonin has been proposed as a stimulator of the retinoid orphan nuclear receptor α (RORα; Wiesenberg, Missbach, Kahlen, Schräder, & Carlberg, 1995). RORα has a high expression in some malignancies such as lymphoma, leukemia, brain, breast, and central nervous system cancers (Du & Xu, 2012). Melatonin induces apoptosis and growth inhibition in some cancer cells such as colon and pituitary cancers through modulation of RORα (Karasek, Gruszka, Lawnicka, Kunert-Radek, & Pawlikowski, 2003; Winczyk, Pawlikowski, Guerrero, & Karasek, 2002). Through stimulation of its receptors including MT1, MT2, and RORα, melatonin has been shown to affect immune cells activity, thereby stimulates antitumor activity of immune cells (Pozo, Garcia-Maurino, Guerrero, & Calvo, 2004).

3 | MELATONIN PREVENTS GENOMIC INSTABILITY AND CANCER INCIDENCE

3.1 | Neutralization of free radicals

Free radicals are one of the main toxic product of interaction of exogenous agents within cells. Although, free radicals are normally produced by some interactions and are involved in various signaling pathways within cells, abnormal increase of their production can hurt vital organelles in cells (Bókkon, 2012). Oxygen free radicals are the most destructive type of oxygen metabolites. Reactive oxygen species (ROS) can be found as some types including high-reactive hydroxyl radical (OH), and also low-reactive superoxide anion radical (O_2^-) and hydrogen peroxide (H_2O_2). High-reactive free radicals can attack to DNA, lipids, and proteins that are in the vicinity of free radical's origin (Lobo, Patil, Phatak, & Chandra, 2010). As these free radicals are highly reactive, it can interact with vital molecules within some nanosecond. Although H_2O_2 is low reactive compared with other type of ROS, it can be generated to H_2O and high toxic O_2^-. On the other hand, O_2^- interacts with nitric oxide (NO), leading to the production of the peroxynitrite anion ($ONOO^-$). Peroxynitrite and NO are named reactive nitrogen species (Tacar, Sriamornsak, & Dass, 2013). These two type of free radicals are

highly reactive, which are able to damage to adjacent cells (R. J. Reiter, Manchester, & Tan, 2010).

The potent free-radical scavenging effects of melatonin has been found by some experimental studies (Marshall, Reiter, Poeggeler, Aruoma, & Halliwell, 1996; Poeggeler et al., 1994). After that it has shown that melatonin neutralizes free radical by donate of electron. Their experiments showed that melatonin scavenges OH more efficiently compared with other antioxidants including glutathione or mannitol (Poeggeler, Reiter, Hardeland, Tan, & Barlow-Walden, 1996). After that it has confirmed that melatonin is able to neutralize other types of free radicals such as H_2O_2, NO, $ONOO^-$, and also singlet oxygen and O_2^- (D. X. Tan et al., 2002; D. Tan et al., 2000). In addition to melatonin itself, other its metabolites such as cyclic 3-hydroxymelatonin *N*1-acetyl-5-methoxykynuramine (AMK), 6-hydroxymelatonin, 2-hydroxylmelatonin, 6-hydroxylmelatonin, and AFMK have potent ROS scavenger (Álvarez-Diduk, Galano, Tan, & Reiter, 2015; Galano, Tan, & Reiter, 2013; R. J. Reiter et al., 2016). In response to IR, a large body of studies have revealed the antioxidant effect of melatonin. Besides direct actions on free radical scavenging, melatonin stimulates ROS/NO scavenging enzymes potently, thus more metabolize ROS and NO, and further protect against oxidative stress. Treatment of rats with 10 mg/kg melatonin before exposure to different doses of IR can potently alleviate oxidative stress markers and augments antioxidant enzymes like reduced glutathione (GSH), glutathione-*S*-transferase, and catalase in liver (El-Missiry, Fayed, El-Sawy, & El-Sayed, 2007). Similar results have obtained in rat lens after injection of 5 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$ melatonin (Shirazi et al., 2011; Taysi et al., 2008). Reduce of oxidative stress, DNA damage, and lipid peroxidation by melatonin have shown by other in vivo studies (Bhatia & Manda, 2004; Guney et al., 2007; Take et al., 2009).

3.2 | Suppression of reduction/oxidation (redox) system

In addition to direct free radical production by toxic agents, such as IR or chemotherapy drugs, redox interactions have key roles in cell toxicity. The main sources of ROS and NO production within cells are mitochondria, membrane, lipoxygenases (LOXs), cyclooxygenases (COXs), nicotinamide adenine dinucleotide phosphate hydrogenase (NADPH) oxidases, inducible nitric oxide synthase (iNOS), and some others. Several experiments have reported that chronic upregulation of redox enzymes is associated with increased risk of carcinogenesis (Najafi, Motevaseli, et al., 2018).

3.3 | Mitochondrial preservation

Mitochondria are vital organelles within cells, because their roles in oxidative phosphorylation and energy supply. During oxidative phosphorylation, the produced electrons in electron transport chain (ETC) are captured by the cytochrome *c* and coenzyme Q and then transported to oxygen molecules. This process leads to the production of water, while it is possible some electrons cause reduction of oxygen molecules to form O_2^- (D.-X. Tan, Manchester, Qin, & Reiter, 2016). Damage to mitochondrial DNA (mtDNA) is associated with increased production of superoxide, leading to chronic oxidative stress. Released ROS from mitochondria can stimulate other inflammatory mediators, such as macrophages to further product ROS and NO, leading to more oxidative injury via a phenomenon named ROS-induced ROS (Zorov, Juhaszova, & Sollott, 2006). Damage to mitochondria and stimulation of ROS production following exposure to IR has confirmed in several experiments. van Gisbergen et al. (2017) in an in vitro study showed that when A549 or 143B cell lines irradiated, the level of ROS and DNA double-strand breaks increase. However, after depletion of A549 or 143B cells from mitochondria the ROS production was decreased (van Gisbergen et al., 2017). Results of this study are parallel with another study by Yoshida et al. (2000) that showed the presence of mtDNA can augment micronucleus formation after irradiation. This is associated with the reduction of cell survival (Yoshioka et al., 2004). In addition to mutation in mtDNA, it is proposed that mitochondria malfunction is associated with loss of calcium homeostasis, which leads to enhanced free radicals production and cell death (Frandsen & Schousboe, 1993).

Studies have revealed that melatonin regulates mitochondrial homeostasis (Castroviejo et al., 2002). It has been proposed that melatonin neutralizes both ROS and NO in the mitochondria, which lead to improved oxidative phosphorylation (Castroviejo et al., 2002; Leon, Acuna-Castroviejo, Escames, Tan, & Reiter, 2005; M. Martín et al., 2002). An experiment by M. Martín, Macías, Escames, León, and Acuña-Castroviejo (2000) showed that the melatonin, but no other antioxidants such as ascorbic acid or gamma-tocopherol, regulates redox status oxidative stress condition. Inflammasome and inflammatory mediators are other targets of melatonin. The inflammasome is a complex containing some proteins that regulate the release of interleukin-1β (IL-1β) and IL-18, and also activation of some proapoptotic pathways (Guo, Callaway, & Ting, 2015). Melatonin is able to inhibit inflammasome after damage to mitochondria, leading to the attenuation of inflammatory cytokines and mucositis following irradiation of gastrointestinal system. As inflammatory responses and mitochondrial disruption following exposure to radiation are involved in chronic oxidative stress, melatonin ameliorates DNA damage via this pathway (Fernández-Gil et al., 2017; Ortiz et al., 2015).

In addition to energy supply to activities of the cells, the mitochondria play a key role in apoptosis signaling pathway. On the other hand, high incidence of apoptosis in some organs such as bone marrow and gastrointestinal system make them sensitive to IR or chemotherapy (Gudkov & Komarova, 2003; Tacar et al., 2013). High radiosensitivity of these organs limit received radiation dose to tumors within or adjacent to them. So, inhibition of apoptosis and free radical's production by mitochondria have suggested for mitigation of radiation injury in these organs (Yahyapour et al., 2018). Upregulation of Bcl-2-associated X protein (Bax) and caspase genes play a key role in this process. Increased level of Bax protein cause release of cytochrome *c* from ETC, leading to the production of apoptosome complex (Marsden et al., 2002). A study by Tang et al. (1999) showed that mtDNA is involved in apoptosis induction and

radiation sensitivity following exposure to IR. They showed that when cells depleted from mtDNA (RHO cells), the sensitivity to IR is reduced. It has reported that melatonin can prevent the apoptosis cascade during stress conditions. The ROS scavenging ability of melatonin prevents damage to mtDNA and the ETC proteins in oxidative stress situations, which cause stability of mitochondria function (Acuna-Castroviejo et al., 2001; Garciá et al., 1999). Melatonin also, can regulate the apoptosis through modulation of mitochondrial proapoptosis genes. Pretreatment of rats with 10 or 100 mg/kg melatonin cause significant reduction of Bax and increase of B-cell lymphoma 2 (Bcl-2) gene expression, as well as incidence of apoptosis after exposure to IR (Mohseni et al., 2012).

3.4 | Other pro-oxidant enzymes

As mentioned above, in addition to mitochondria some other enzymes are involved in ROS and NO production following exposure to IR and chemotherapy. Cyclooxygenase-2 (COX-2) is a central isoenzyme in the inflammation, which is associated with increased risk of cancer incidence (J. R. Brown & DuBois, 2005; Harris, Beebe-Donk, & Alshafie, 2006; D. Wang & DuBois, 2010). COX-2 upregulation is associated with ROS production during prostaglandin production. Moreover, COX-2 can increase the release of proinflammatory cytokines and amplification of redox activity (D. Wang & DuBois, 2010). In response to IR, it has been shown that COX-2 is involved in oxidative DNA damage and genomic instability (Mohsen Cheki et al., 2018). Suppression of this enzyme by its inhibitors has been shown to alleviate radiation toxicity in the bone marrow and joints (El-Ghazaly, Nada, El-Hazek, & Khayyal, 2010; Hosseinimehr, Fathi, Ghasemi, Shiadeh, & Pourfallah, 2017). This is associated with the reduction of inflammatory cytokines such as IL-1 and tumor necrosis factor α (Khayyal, El-Ghazaly, El-Hazek, & Nada, 2009). Melatonin can regulate COX-2 expression and enzyme activity. In addition, it has been revealed that in response to IR the melatonin via inhibition of COX-2 prevents the upregulation of iNOS, thus more attenuate oxidative injury and inflammatory responses (Fardid et al., 2017).

NADPH oxidase (NOX) including NOX1–5 and dual oxidase 1 (DUOX1) and DUOX2 are H_2O_2 producing enzymes, which are activated in response to several cytokines and growth factors. It has been shown that upregulation of these enzymes is associated with genomic instability, and also the development of collagen and fibrosis (Chang et al., 2015; Choi et al., 2016; Sakai et al., 2018; Sato et al., 2016; Y. Wang, Liu, et al., 2010). D. Li et al. (2016) in an in vivo study evaluated the potential radioprotective effect of melatonin through NOX4 expression in mice bone marrow. They revealed that treatment with melatonin or 5-methoxytryptamine-α-lipoic acid (a combination of melatonin with α-lipoic acid) significantly attenuates NOX4-derived ROS, DNA damage, and apoptosis in hematopoietic stem cells (D. Li et al., 2016).

LOXs are another type of pro-oxidant enzymes that have proposed for radiation-induced redox activity (Yahyapour et al., 2018). These enzymes catalyze the insertion of oxygen molecules into polyunsaturated fatty acids, which mediate the synthesis of inflammatory leukotrienes from arachidonic acid (K.-J. Cho, Seo, & Kim, 2011). This is associated with ROS production and oxidative DNA damage (Blair, 2001; Jian, Lee, Williams, & Blair, 2009; Speed & Blair, 2011). It has shown that the pineal hormone melatonin regulates the expression of LOXs gene (Radogna, Diederich, & Ghibelli, 2010; Uz, Longone, & Manev, 1997). It is proposed that melatonin via binding to a nuclear receptor RZR/RORα (a stimulator of LOX gene) inhibits expression and production of LOXs (Steinhilber et al., 1995).

3.5 | Stimulation of DNA repair responses

DNA damage is the first consequence of exposure of cells to IR and chemotherapy agents such as cyclophosphamide and doxorubicin (Cohen & Lippard, 2001). Damage to DNA and cell death leads to the release of alarmins for immune system cells including macrophages, dendritic cells, and lymphocyte T (Bianchi, 2007; Yang, de la Rosa, Tewary, & Oppenheim, 2009). In response to danger alarms, these immune cells release several types of cytokines that more stimulate ROS and NO production by redox mediators (Krysko et al., 2011). So, enhance of DNA repair responses can reduce cell death and also attenuate inflammation and redox activity. In addition, some studies have revealed that inflammation is a potent inhibitor of DNA damage response (Najafi, Cheki et al., 2018). NO, which is released by iNOS following activation of macrophages and lymphocyte T, is capable to suppress DNA damage response (Moritz et al., 2014). The main target for NO is 8-oxoguanine glycosylase 1 (Ogg1), a DNA repair enzyme in base excision repair (BER) pathway. NO cause nitroacetylation and inactivation of Ogg1, leading to attenuation of other downstream genes, including apurinic/apyrimidinic endodeoxyribonuclease 1 (Apex1), and X-ray repair cross complementing 1 (Xrcc1). Through this pathway, NO can promote accumulation of DNA damage and promotion of genomic instability (Najafi, Cheki, et al., 2018).

Melatonin has shown that accelerates kinetic of DNA repair following exposure of DNA to ROS. A study showed that when human lymphocytes are exposed to H_2O_2, cells require 120 min to complete the repair process, while treatment with melatonin reduces this time to 10 min (Sliwinski et al., 2007). A study by Santoro, Marani, Blandino, Muti, and Strano (2012) proposed that melatonin through activation of p53 reduces accumulation of DNA damage and risk of genomic instability. They revealed that melatonin is able to phosphorylate p53 without need to ataxia telangiectasia-mutated expression. More analyses showed that phosphorylation of p53 melatonin is depended to p38 mitogen-activated protein kinase (MAPK) and promyelocytic leukemia protein gene upregulation. This study showed that treatment of human breast cells with melatonin reduces changes in genomic content following exposure to DNA damage agents such as cisplatin, antimetabolite fluorouracil (FU), topoisomerase inhibitor, or IR. These results are indicated potent inhibitory effect of melatonin on genomic instability and carcinogenesis (Santoro et al., 2012).

Rezapoor et al. (2017) evaluated the effect of pretreatment with melatonin on radiation-induced BER pathway genes. They administrated 100 mg/kg to rats at 30 min before irradiation with 2 or 8 Gy X-rays. Then, circulating lymphocytes extracted at 8, 24, and 48 hr after irradiation and the expression of BER pathway genes including Ogg1, Apex1, and Xrcc1 were detected. Results indicated that melatonin alone increase three genes potently when they compared with nontreated group. Although, exposure to IR caused potent inhibition of all genes in mentioned times, treatment with melatonin reverse regulation of those. The stimulatory effect of melatonin was clearer for 2 Gy irradiated rats, indicating it needs to more dose of melatonin for stimulation of DNA damage response for against higher doses of IR (Rezapoor et al., 2017). By similar method, another study showed that melatonin treatment augments the regulation of Xrcc4 and Ku70 in rat's lymphocytes. This was more obvious at 24 hr after exposure to IR (Valizadeh et al., 2016; Valizadeh, Shirazi, Izadi, Tavakkoly Bazzaz, & Rezaeejam, 2017). Moreover, melatonin treatment before irradiation has shown is able to regulate genes involved in nonhomologous end joining (NHEJ) pathway, including RAD50 and Cdkn1 (Rezaeejam et al., 2018).

In addition to IR, melatonin has shown to enhance DNA damage responses against chemotherapy agents. Bennukul, Numkliang, and Leardkamolkarn (2014) evaluated the effect of melatonin on cytotoxicity of cisplatin on hepatocellular carcinoma (HepG2) cells. This study showed that treatment of this cell type with 1 mmol/L melatonin lead to a reduction in DNA damage and apoptosis, as well as an increase in ERCC1 gene, which is involved in nucleotide excision repair (NER) pathway of DNA damage repair (Bennukul et al., 2014).

3.6 | Antiestrogenic effect of melatonin

Based on various evidence it is confirmed that estrogen has a key role in stimulating the proliferation of the neoplastic breast epithelium (Bouris et al., 2015; B. Huang, Warner, & Gustafsson, 2015; Santen, Yue, & Wang, 2015). Moreover, expression of estrogen receptors increases as the cancer progresses (B. Huang et al., 2015; Soysal et al., 2015). Estrogen through regulation of cell proliferation and apoptosis may trigger neoplasm (Andruska, Zheng, Yang, Helferich, & Shapiro, 2015). It seems that stimulation of MAPKs including extracellular signal-regulated kinase (ERK) and p38 genes, and also Akt1 and signal transducer and activator of transcription 5 (Stat5) play a key role in this pathway (Mao et al., 2010; Xiang et al., 2012; Zivadinovic & Watson, 2005). Experimental studies have revealed that there is a direct relation between estrogen receptors and breast cancer cell proliferation (Zivadinovic, Gametchu, & Watson, 2005). Epidemiologic studies have confirmed a direct relation between serum estrogen level and risk of breast cancer (S. B. Brown & Hankinson, 2015). Melatonin has shown suppress breast cancer proliferation by affecting estrogen receptors. Kiefer, Ram, Yuan, and Hill (2002) showed that treatment of

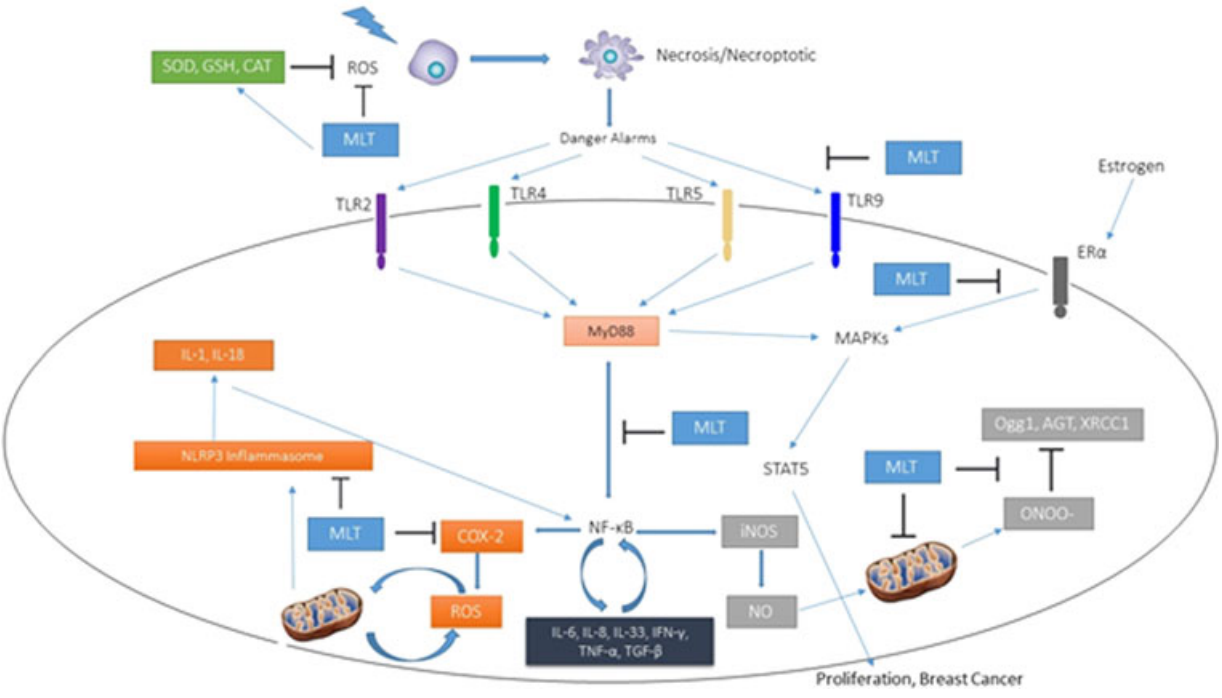

FIGURE 1 Mechanisms of protective effect of melatonin against DNA damage and genomic instability. Melatonin is able to prevent inflammation and redox activity in different levels. Also, it prevents genomic instability via neutralization of nitric oxide and stimulation of BER pathway genes. CAT: catalase; COX: cyclooxygenase; IFN: interferon; IL: interleukin; iNOS: inducible nitric oxide synthase; MAPK: mitogen-activated protein kinase; NO: nitric oxide; Ogg1: 8-oxoguanine glycosylase 1; ROS: reactive oxygen species; TGF-β: transforming growth factor β; TNF-α: tumor necrosis factor α; STAT5: signal transducer and activator of transcription 5 [Color figure can be viewed at wileyonlinelibrary.com]

MCF-7 cells with melatonin suppresses growth of breast cancer cells with estrogen receptor-positive cells (Kiefer et al., 2002). Another study by Lopes, Arnosti, Trosko, Tai, and Zuccari (2016) has shown that melatonin treatment of human breast cancer stem cells inhibit proliferation via downregulation of estrogen receptor α and the transcription factor OCT4 (Lopes et al., 2016; Figure 1).

4 | TUMOR SUPPRESSIVE EFFECTS OF MELATONIN

In addition to preventative effects of melatonin on cancer incidence, a large body of studies have reported that it is able to suppress tumor growth, proliferation, and metastasis. Studies propose various mechanisms for tumor inhibiting effect of melatonin such as induction of apoptosis, stimulation of immune system cells, inhibiting repopulation and angiogenesis genes, and others. Also, studies have revealed that administration of melatonin associated with chemotherapy or radiotherapy may increase therapeutic effect of these modalities.

4.1 | Induction of apoptosis

One of the interesting properties of melatonin is clastogenic effect on tumor cells. This is in contrast by other results that indicated potent protective effect of melatonin on normal cells. Moreover, by contrast to normal cells, some studies propose that melatonin can induce apoptosis in cancer cells. In a study by K. J. Kim et al. (2013) has shown that melatonin treatment of human prostate cancer cells potently stimulates apoptosis in a dose-dependent manner. They showed that treatment of cells with 3 mM melatonin can reduce viability of cells up to 80% in 48 hr after treatment. Western blot analysis results showed a significant increase in protein level of Bax, caspase-3, and caspase-9, as well as a potent reduction in Bcl-2. Authors showed that activation of p53 by melatonin play a key role in initiation of apoptosis signaling pathway (C. H. Kim & Yoo, 2010). Another study showed that melatonin via activation of MAPKs pathway induce apoptosis in prostate cancer cells (Joo & Yoo, 2009). Moreover, it has proposed that melatonin via inhibition of nuclear factor-κB (NF-κB; an antiapoptosis gene) facilitate apoptosis induction in cancer cells (W. Li et al., 2015).

Gatti et al., (2017) evaluated apoptosis induction effect of melatonin on human melanoma and breast cancer cell lines. They used from four analogs of melatonin at different concentrations. Results showed that a concentration of 10^{-4} M has a significant effect on apoptosis induction in breast cancer cell lines including MCF-7, DX3, UCM 1037, and MDA-MB231 cells. Melatonin treatment showed is able to suppress Bcl-2 expression in melanoma WM-115 cell line, while it shows has no effect on Bax/Bcl-2 ratio in other cell types. In other hand, melatonin increase regulation of caspase-3 in DX3 cells, while it did not increase in melanoma cells. These results may indicate that melatonin activate apoptosis via different pathways in different types of cancer cells (Gatti et al., 2017). Activation of caspase-3 and apoptosis in human neuroblastoma cancer cells have reported (Garcia-Santos et al., 2006). Similar results have reported in other studies (Chovancova et al., 2017; Chuffa et al., 2016; Fan et al., 2013; Sainz et al., 2003; Zha et al., 2012). By contrast to these studies, in a study have shown that treatment of human breast cancer cells and colorectal carcinoma cells with melatonin do not cause increase in apoptosis induction. Authors proposed that possibly there is a high dose of melatonin for apoptosis induction (Santoro et al., 2012). It seems that induction of apoptosis is dependent on melatonin concentration. Some studies have proposed that, while cytotoxic effects of melatonin may appear in nanomolar concentrations, induction of apoptosis requires higher concentrations, for example at millimolar concentrations (Bizzarri, Proietti, Cucina, & Reiter, 2013; Talib, 2018). In addition to that, Cucina et al. (2009) showed that apoptosis induction in MCF-7 cells following melatonin treatment has a biphasic pathway. They showed that apoptosis can be induced through different pathways at different times following melatonin treatment. Results showed that early peak of apoptosis can be observed at 24 hr after treatment because of caspase activation, while late peak is seen at 96 hr after treatment that is caspase independent (Cucina et al., 2009).

4.2 | Suppression of tumor cells repopulation

It has been confirmed that after apoptosis in tumor cells, increased caspase-3 lead to stimulation of prostaglandins production, which mediate proliferation of tumor cells (Galluzzi, Kepp, & Kroemer, 2012; Q. Huang et al., 2011). Through this pathway, activation of caspase-3 and elevated level of COX-2 and subsequent prostaglandins promote regrowth and resistance of tumor cells (Donato et al., 2014; Galluzzi et al., 2012). It has shown that prostaglandin E2, which is a product of COX-2, is involved in tumor resistance and repopulation during radiotherapy (Q. Huang et al., 2011). Melatonin as a COX-2 inhibitor has shown attenuate production of prostaglandins and tumor cell repopulation (Woo, Min, & Kwon, 2015). Panzer and Viljoen (1997) found that melatonin can act as an anticancer agent in breast cancer through a decrease in cell proliferation and suppression of some antiapoptotic mediators including NF-κB and COX-2. Antiproliferative effect of melatonin has been shown for prostate cancer cells too (Sainz et al., 2005; Siu, Lau, Tam, & Shiu, 2002). In recent years has shown that melatonin via downregulating the cyclin-dependent kinases, including CDK2 and CDK4 suppress proliferation of ovarian cancer cells (Shen, Chang, Chen, Lai, & Hsu, 2016). Similar results obtained for osteosarcoma cells (L. Liu, Xu, & Reiter, 2013). In a study by Santoro et al. (2012) have revealed that treatment of MCF-7 cells with melatonin attenuate proliferation and colony formation of this cell. Further analyses showed a transient arrest in G2 phase of cell cycle. In the breast, ovarian, osteosarcoma, and colon endometrial cancer cells have been shown that melatonin inhibit proliferation through melatonin receptors including the MT1 and MT2 (Jablonska et al., 2013, 2014; León et al., 2012; Treeck, Haldar, & Ortmann, 2006; Watanabe, Kobayashi, Takahashi, Kiguchi, & Ishizuka, 2008).

4.3 | Melatonin and immune cells

A large number of studies have revealed a potent association between melatonin and the immune system (Labrecque & Cermakian, 2015; Ozkanlar et al., 2016; Vinther & Claësson, 2015). It well known that melatonin is produced not only by the pineal gland, but also it can be released by the retina, kidneys, digestive tract, and also by peripheral blood mononuclear cells (Emet et al., 2016; Tordjman et al., 2017). This may suggest a potent interrelation between the immune system and melatonin in different organs (Ren et al., 2017). Some studies proposed that melatonin through its receptors on immune cells influences proliferation of immune cells and release of cytokines (Carpentieri, Peralta lopez, Aguilar, & Solá, 2017; Singh & Jadhav, 2014). Furthermore, melatonin has shown that is able to stimulate natural killer cell activity in humans, as increase antitumor activity of immune system (Miller, Pandi, Esquifino, Cardinali, & Maestroni, 2006). Another immune system cell, which has a key role in tumor response to therapeutic modalities is regulatory T cells (Tregs). In normal conditions, these cells attenuate immune system effects and suppress autoimmune reactions. But, in tumor cells, infiltration of these cells cause resistance of tumor cells via reduction of cytotoxic cells activity (Vinay et al., 2015). H. Liu et al. (2011) showed that melatonin is able to induce gastric cancer cell death in mice bearing tumor via suppression of Tregs. Melatonin was effective when it administrated in 100 mg/kg but not for 25 or 50 mg/kg.

5 | MELATONIN EFFECTS ON ANGIOGENESIS

Angiogenesis is a key procedure that is necessary for tumor growth and metastasis. Thus, angiogenesis is an interesting target for tumor control and treatment (Potente, Gerhardt, & Carmeliet, 2011; Trachsel & Neri, 2006). The vascular endothelial growth factor (VEGF) is a key mediator for development of new vessels and promotion of angiogenesis in both normal and malignant cells. VEGF has three important receptors, including VEGF-1, VEGF-2, and VEGF-3, while its main effect is mediated through VEGF-1 (Hicklin & Ellis, 2005; Pradeep, Sunila, & Kuttan, 2005; Shinkaruk, Bayle, Lain, & Deleris, 2003; Sousa Moreira, Alexandrino Fernandes, & Joao Ramos, 2007). Targeting of VEGF-1 for inhibiting tumor angiogenesis and growth have proposed by several studies (Underiner, Ruggeri, & Gingrich, 2004; Veeravagu et al., 2007). However, some studies proposed targeting of VEGF-2 or VEGF-3 (Shi, Wu, & Li, 2015; Tammela et al., 2008). However, clinical studies have shown that selective inhibition of this receptor with selective inhibitors such as bevacizumab is associated with severe side effects such as skin rash and disruption of wound healing (Bodnar, 2014; Ishak, Aad, Kyei, & Farhat, 2014; Macdonald, Macdonald, Golitz, LoRusso, & Sekulic, 2015; Wozel, Sticherling, & Schön, 2010).

Melatonin has shown interesting properties in tumor growth by suppression of angiogenesis markers. In a study including 20 metastatic patients the effect of melatonin treatment has detected on serum level of VEGF. The patients used melatonin as 20 mg/day for 2 months and the level of VEGF were detected. Results showed a significant reduction of median level VEGF in the serum of patients (Lissoni et al., 2001). An in vitro study by Carbajo-Pescador et al. (2013) showed that melatonin attenuates the expression of VEGF in HepG2 cells through modulation of hypoxia-inducible factor 1 (HIF-1) and STAT3. Their results proposed that melatonin in a pharmacological concentration (1 mM) is able to inhibit VEGF stimulation during hypoxia situation (Carbajo-Pescador et al., 2013). Jardim-Perassi et al. (2014) showed that melatonin treatment of mice bearing human breast cancer cells cause inhibition of angiogenesis in this tumor by attenuation of VEGF receptor 2 (VEGFR2) gene expression. Suppression of VEGFR2 was confirmed by SPECT imaging of Tc-99m-HYNIC-VEGF-c and also immunohistochemistry analysis. Melatonin could not reduce other proangiogenesis factors in this study (Jardim-Perassi et al., 2014). However, another study proposed that melatonin may via downregulation of EGFR and insulin-like growth factor 1 reduces angiogenesis in breast cancer cells (Zuccari et al., 2015). As VEGFR2 is stimulated by HIF-1 during hypoxia situation, it seems that melatonin is an inhibitor of breast cancer angiogenesis by downregulation of HIF-1 (Goradel et al., 2017; Victorasso jardim-Perassi et al., 2016). Similar results were defined for Dalton lymphoma, renal adenocarcinoma, colon cancer cells, and ovarian carcinoma cells (K. J. Kim et al., 2013; Kumari, Rawat, Kumari, & Shrivastava, 2017; Park et al., 2010; Zonta et al., 2017). In the human gastric cancer cells it has been shown that melatonin beside to VEGF and HIF-1 can reduce angiogenesis by suppression of nuclear receptor RZR/RORγ (R.-X. Wang, Liu, Xu, Zhang, & Zhou, 2016). It seems that melatonin through inhibition of RZR/RORγ and sphingosine kinase 1 (SPHK1) suppresses HIF-1 and downstream angiogenesis signaling in gastric cancer (S. Y. Cho, Lee, et al., 2011; R. X. Wang, Liu, Xu, Zhang, & Zhou, 2015). By contrast to tumor cells, melatonin has shown to stimulate angiogenesis and wound healing in normal cells or tissues after injury (Soybir et al., 2003).

6 | SYNERGISTIC EFFECTS OF MELATONIN IN ONCOLOGY

6.1 | Modulation of cancer response to radiotherapy with melatonin

An appropriated adjuvant in radiotherapy should have a good synergistic effect on tumor response to radiation, as well as low toxicity for normal tissues. Melatonin is known as a radioprotector more than a radiosensitizer agent. The potent radioprotection of melatonin on normal tissues have described by several studies. So, if melatonin is able to sensitize tumor cells to radiotherapy, it may be used as an ideal adjuvant. Although studies to show radiosensitive effect of melatonin on cancer cells are very limited, some recent studies show interesting results. Alonso-González, González, Martínez-Campa, Gómez-Arozamena, and Cos (2015) in

an in vitro study showed that melatonin treatment of MCF-7 cells (1 mM, 10 μM, and 1 nM) before irradiation result in a cell cycle arrest in the G_0–G_1 phase and reduction of cells in the S phase. Moreover, melatonin administration before irradiation caused a downregulation of DNA repair enzymes including RAD51 and DNA-PKcs. This may cause accumulation of DNA damage induced by IR (Alonso-González et al., 2015). In another study, they showed that melatonin treatment before irradiation sensitize MCF-7 cells to IR via suppression of estrogen biosynthesis, which leading to inhibition of proliferation. Also, they reported that melatonin activates p53, a potent initiator of apoptosis in MCF-7 cells. This effect was more significant in 1 nM compared with other concentrations of melatonin (1 mM or 10 μM; Alonso-González et al., 2016).

A study by Zou et al. (2018) showed that melatonin has a radiosensitizer effect on thyroid cancer cells too. In in vitro study their results showed that melatonin inhibits proliferation of thyroid cancer cells in a dose-dependent manner. Results showed a 15% survival when thyroid cancer cells treated with 15 mM for 48 hr. Irradiation of cells lead to an increase in expression of NF-κB/p65, an antiapoptosis and cell growth stimulator. While, when cells treated with melatonin the expression of it inhibited. Moreover, treatment with melatonin before irradiation lead to sensitization and reduction of viability of cells when it compared to irradiation only. Results indicated a dose-dependent relation between radiosensitization effect of melatonin and melatonin concentration. Interestingly, this study showed that melatonin via stimulation of redox reactions induces ROS production. Moreover, in in vivo xenograft mouse model, they showed that melatonin administration in combination with radiation attenuates tumor growth when it compared with irradiation alone (Zou et al., 2018). Enhancement of radiation toxicity on head and neck cancer cells have been reported by Escames, Fernández-Gil, et al. (2017) they proposed that melatonin through modulation of mitochondria activity, ROS production, and induction of apoptosis has a synergistic effect on therapeutic effects of IR (Escames, Guerra-Librero et al., 2017).

6.2 | Modulation chemotherapy consequences by melatonin

In addition to radiotherapy, melatonin also showed some evidence for potentiating the therapeutic outcome and alleviation of the chemotherapy side effects (Sanchez-Barcelo, Mediavilla, Alonso-Gonzalez, & Reiter, 2012). Casado-Zapico et al. (2010) showed that melatonin can reinforce antitumor effect of vincristine and ifosfamide on Ewing sarcoma cells. Also, they revealed that the most effect of melatonin mediate through enhancement of apoptosis via upregulation of extrinsic apoptosis pathway genes (Casado-Zapico et al., 2010). Melatonin has shown that reinforce effects of chemotherapy drugs such as doxorubicin, cisplatin, and 5-fluorouracil on HeLa cells. Although, similar to Ewing sarcoma cells melatonin augments apoptosis, by contrast to this cell the mitochondrial apoptosis pathway has main role in synergistic effect of melatonin. Moreover, melatonin increased ROS production in HeLa cells, leading to more toxicity of cisplatin (Pariente, Pariente, Rodríguez, & Espino, 2016). Similar effects were detected for the rat pancreatic tumor Cells (Uguz et al., 2012). Combinations of melatonin and temozolomide has a synergistic therapeutic effect on malignant glioma cells. This is resulting from elevated the methylation of the ABCG2/BCRP promoter, leading to decreased expression of this gene. Downregulation of this gene help to more accumulation of chemotherapy agents in tumor cells, which increase therapeutic action of chemotherapy (V. Martín et al., 2013).

In clinical trial studies also melatonin showed interesting results for reducing chemotherapy agent's toxicity, as well as increasing therapeutic effect. Administration of 20 mg/day orally melatonin associated with chemotherapy showed that augments 1-year survival rate and potentiate regression of tumors (Lissoni et al., 1999). Administration of same dose of melatonin in combination with

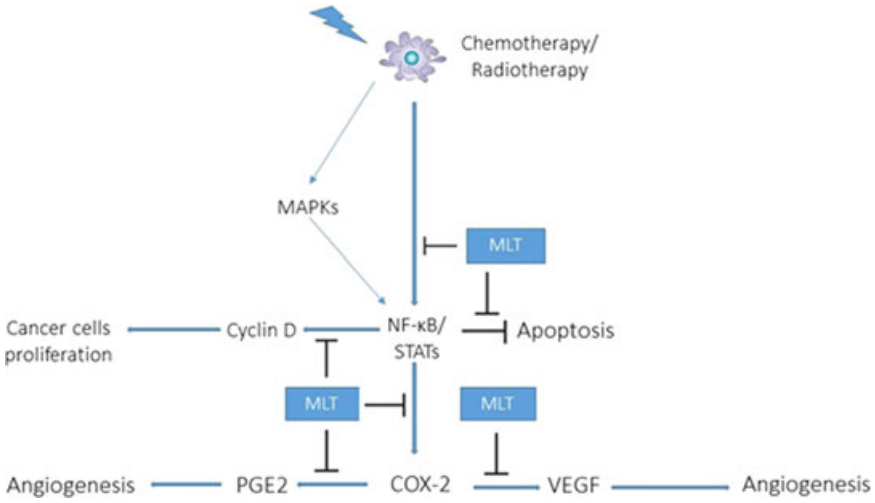

FIGURE 2 Mechanisms of antitumor activity of melatonin in radiotherapy and chemotherapy. Melatonin through suppression of angiogenesis and proliferation, as well as via stimulation of apoptosis help to better outcome of therapy. COX: cyclooxygenase; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-κB; STAT: signal transducer and activator of transcription; VEGF: vascular endothelial growth factor [Color figure can be viewed at wileyonlinelibrary.com]

cisplatin and etoposide to metastatic non-small-cell lung cancer (NSCLC) patients caused a significant tumor regression rate and increased survival. This study showed that treatment with melatonin cause 6% survival after 5 years, while no patients were survived among patients that received chemotherapy without melatonin (Lissoni, Chilelli, Villa, Cerizza, & Tancini, 2003; Figure 2).

7 | MELATONIN IN ASSOCIATION WITH TARGETED THERAPIES

Targeted therapy is an effective method for cancer treatment and involves inhibition of tumor growth receptors, apoptosis resistance genes such as Bcl-2, and cellular function (Leverson et al., 2015). Although inhibition of these targets in cancer cells can effectively attenuate tumor growth, there is evidence showing that mutations in these receptors can lead to poor response to prescribed drugs (Zaretsky et al., 2016). For example, mutations in EGFR in NSCLC cells causes resistance to EGFR tyrosine kinase inhibitors like gefitinib and erlotinib (Pao et al., 2005). Combination of melatonin with some inhibitors have shown better outcomes in suppressing tumor cells growth compared with using an inhibitor alone. Yun et al. (2014) evaluated the cytotoxicity of a combination of melatonin with gefitinib on H1975 cells. Cells that used in this study had a mutation (T790M) that caused resistance to gefitinib. Results showed that treatment of H1975 with a combination of melatonin and gefitinib caused attenuation of EGFR phosphorylation and suppression of Bcl-2, culminating in increased apoptosis and reduced cell viability (Yun et al., 2014).

A study by Prieto-Domínguez et al. (2017) revealed effective therapeutic effect of melatonin in combination with sorafenib on hepatocellular carcinoma (HCC) cells. Their results showed that melatonin, through inhibition of mechanistic target of rapamycin, attenuates regulation of HIF-1α, leading to the attenuation of cytoprotective effect of hypoxia microenvironment against sorafenib (Prieto-Domínguez et al., 2017). Another study by this group showed that melatonin enhances the production of ROS through depolarization of mitochondria in HCC cells. Also, it seems that upregulation of Bax and mitophagy are involved in the cytotoxic activity of melatonin combination with sorafenib (Prieto-Domínguez et al., 2016). Another study showed that activation of JNK/c-jun pathway by melatonin is involved in apoptosis induction by melatonin when it is combined with sorafenib (Lin et al., 2017). Liu et al. showed that increased autophagy is a reason for increasing the resistance of HCC cells to sorafenib. Melatonin, through suppression of autophagy, may further sensitize HCC cells to sorafenib (Y. Liu et al., 2017).

8 | CONCLUSION

Melatonin is a potent anticarcinogenic agent against different toxic agents such as ionizing and nonionizing radiation, and chemotherapy agents. It has been shown that melatonin protects normal cells against development of malignancies at different levels. At the first level, melatonin neutralizes free radicals directly or indirectly via enhancement of antioxidant defense. Anti-inflammatory effect of melatonin can prevent development of chronic oxidative stress, a phenomenon, which is associated with genomic instability. Moreover, melatonin is able to boost DNA repair enzymes to prevent mutations and genomic instability. An interesting property of melatonin is its effects on signaling pathways involved in DNA repair, inflammation, and cell survival in both normal and malignant cells. Stimulation of DNA repair is critical for the attenuation of acute reactions to radiotherapy caused by massive cell death. Moreover, inflammation—that is potently involved in both normal tissue injury and tumor resistance—can be inhibited by melatonin. Classical antioxidants neutralize free radicals in both normal and tumor cells which may, in addition to protection of normal tissues, cause reduction of tumor cells response to radiation treatment. In contrast to other antioxidants, melatonin can modulate inflammation and redox activity that are involved in normal tissue injury and also tumor resistance. Melatonin enhances DNA repair in normal cells while it can promote apoptosis via attenuation of prostaglandins in tumor cells. These properties of melatonin make it a promising adjuvant to both radiotherapy and chemotherapy, which can alleviate side effects on normal tissues and reinforce therapeutic effects on the cancerous tissue.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

ORCID

Amirhossein Sahebkar http://orcid.org/0000-0002-8656-1444

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