An updated review of mechanistic potentials of melatonin against cancer: pivotal roles in angiogenesis, apoptosis, autophagy, endoplasmic reticulum stress and oxidative stress

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Abstract
Cancers are serious life-threatening diseases which annually are responsible for millions of deaths across the world. Despite many developments in therapeutic approaches for affected individuals, the rate of morbidity and mortality is high. The survival rate and life quality of cancer patients is still low. In addition, the poor prognosis of patients and side effects of the present treatments underscores that finding novel and effective complementary and alternative therapies is a critical issue. Melatonin is a powerful anticancer agent and its efficiency has been widely documented up to now. Melatonin applies its anticancer abilities through affecting various mechanisms including angiogenesis, apoptosis, autophagy, endoplasmic reticulum stress and oxidative stress. Regarding the implication of mentioned cellular processes in cancer pathogenesis, we aimed to further evaluate the anticancer effects of melatonin via these mechanisms.

Keywords: Melatonin, Cancer, Angiogenesis, Apoptosis, Autophagy, Endoplasmic reticulum stress, Oxidative stress, Inflammation

Introduction
As the second cause of mortality worldwide, new cases of cancer have recently been reported to increase by 2025 (approximately 19.3 million annually) [1]. Cancer growth control, complete eradication and preventing its incidence are main purposes for cancer-associated investigations. Chemotherapy, radiotherapy and surgery are the major conventional anticancer treatments. The restricted efficiency of these treatments as well as their dangerous side effects have forced researchers to find novel effective anticancer therapies based on herbal extracts and natural compounds as single or combined therapies [2–4].

Melatonin, a multifunctional pleiotropic neurohormone secreted by the pineal gland and other organs including bone marrow, retina, and skin. It is an immune regulatory agent and powerful antioxidant with a capability of preventing cell death in oxidative stress situations [5, 6]. Moreover, melatonin interrupts cell death mechanisms, inflammation, and redox activity probably resulting in cancer cells sensitization to chemotherapy and radiation [7].
Furthermore, in addition to diverse therapeutic potentials for several diseases [8, 9], melatonin has been shown to possess anticancer abilities against skin cancer [10], glioma [11], lung cancer [12], gastrointestinal cancers [13], gynecological cancers [14, 15], and hematological cancers [16, 17]. Although mechanistic impacts of melatonin on various cancers have been widely demonstrated, in the present review we discuss anticancer effects of melatonin with focusing on molecular pathways including angiogenesis, apoptosis, autophagy, endoplasmic reticulum stress, and oxidative stress.

**Melatonin, a neurohormone with a broad spectrum functions**

Monitoring of circadian rhythm is one of the several properties of melatonin, which also possesses oncostatic, vasoregulation, antioxidant, anti-inflammatory, and immunomodulatory abilities [18, 19]. It has been demonstrated that the normally enhanced melatonin levels at night help in the organization of homeostatic metabolic rhythms of targeted organs and systems [20]. Of note, disruption of circadian rhythm has been shown as one of the contributing factors in cancer progression and development [21].

Melatonin, as an antioxidant agent, scavenges free radicals. Melatonin has protective effects on neurodegenerative disorders, epilepsy, and cancer through inhibiting oxidative stress in vitro and in vivo [22, 23]. Melatonin increases the activity and expression of enzymes, including catalase, superoxide dismutase and glutathione peroxidase, implicated in antioxidant abilities [24, 25]. Melatonin also has anti-inflammatory impacts and attenuates pathogenic inflammation through modulating different pathways, including reducing the secretion of tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-2) and interferon-gamma (IFN-γ), and enhancing the amounts of IL-4, IL-10 and IL-27. Melatonin alleviates pro-inflammatory cytokines secretion via suppressing nuclear factor kappa B (NF-κB) [26–28]. In addition, in neurodegenerative disorders, melatonin blocks cyclooxygenase-2 (COX-2) expression, a pro-inflammatory mediator [29]. Melatonin inhibits apoptosis through regulating Bax/Bcl2 and decreasing caspase-3 activity and expression, proposing that melatonin modulates apoptotic functions in the protection against malignancy and neurodegenerative disorders [30–32].

Melatonin regulates multiple physiological and neural functions (Fig. 1). Among of them, effects on blood lipid profile, glycemic control, gestation, reproduction, and fetal development, neural protection, immune system, and cardiovascular system have been widely documented [33, 34]. Melatonin prevents the growth and promotion of spontaneous and chemically mediated breast tumors [35, 36]. Moreover, at physiological concentrations, melatonin suppresses cell invasiveness and proliferation in breast cancer cells [37].

**Melatonin and cancer: effect on different molecular mechanisms and cellular pathways**

In this section we describe the effect of melatonin on oxidative stress and endoplasmic reticulum stress, and various signaling pathways including angiogenesis, apoptosis, autophagy affected by melatonin in different cancer cells (Fig. 2).

**Melatonin and angiogenesis**

Angiogenesis is a crucial event implicated in the progression of tumor as well as its metastasis [38]. Hypoxia in the central areas of solid tumor is a leading cause of angiogenesis via activation of angiogenic mediators [38, 39]. Vascular endothelial growth factor (VEGF), the specific mitogen of endothelial cells and the most active pro-angiogenic agent, is a powerful angiogenesis enhancer which increases vascular permeability. Numerous data suggest that, in tumor development, anti-VEGF therapy has important roles in the suppression of tumor cell growth, leading to a considerable amelioration in progression-free survival [40]. Hypoxia-inducible factor-1 (HIF-1) is another key factor in angiogenesis, which modulates hypoxia-activated genes transcription and consists of HIF-1α and HIF-1β heterodimer. The α subunit of HIF-1 is stabilized under hypoxia and degraded under normoxic situations, however, HIF-1β is expressed constitutively [41].

Melatonin has been shown to have regulatory role in angiogenesis process [42]. In other words, melatonin possesses various impacts on neovascularization under diverse pathological and physiological situations. In skin lesions, gastric ulcers, and some physiologic events, melatonin promotes angiogenesis, while in a hypoxic environment, in age-related ocular diseases, and in tumors melatonin suppresses neovascularization in tissues [43].

Melatonin exerts its antitumor potentials via inhibiting HIF-1-induced angiogenesis [44]. Furthermore, melatonin inhibits the accumulation of HIF-1α through suppressing the formation of ROS and the sphingosine kinase 1 (SPHK1) pathway in prostate cancer cells under hypoxic conditions [45]. Melatonin plays an important role in the paracrine interaction between proximal endothelial cells and malignant epithelial cells by a down-modulatory effect on the expression of VEGF in breast tumor cells, which reduces VEGF levels around endothelial cells [46].
Of note, anti-angiogenic potential of melatonin is a key factor resulting in the inhibition of proliferation of cancer cells, as demonstrated in various investigations. For instance, melatonin attenuates proliferation of prostate cancer cells triggered by epidermal growth factor [47]. Melatonin also hampers vasculogenic mimicry of oral cancer cells via inhibition of ROS-activated Akt and ERK signaling pathway implicating the HIF-α pathway [48]. Melatonin up-regulates TGF-β1 expression in tumor tissues during the inhibition of gastric cancer tumor growth process [49]. Furthermore, apoptotic and anti-proliferative effects of melatonin on breast cancer cells are mediated by the simultaneous activation of the Apaf-1/caspase-dependent apoptotic pathway and the inhibition of PI3K/Akt, p300/NF-κB, and COX-2/PGE2 signaling pathways [32].

Endothelin-1 is a peptide acting as a survival factor in colon cancer, promoting angiogenesis and mediating cell proliferation. Melatonin suppresses endothelin-1 mRNA expression. Also, melatonin blocks the activity of endothelin-1 promoter modulated by NF-κB and FoxO1 [50]. Melatonin represses ROCK-1, VEGF and HIF-1α genes expressions in oral cancer [51]. Melatonin alters the expression of inflammatory and angiogenic proteins in both co-culture and monoculture of cancer cells and cancer-associated fibroblasts [52]. Melatonin suppresses tumor angiogenesis and the growth of gastric cancer cells in tumor-bearing nude mice. Moreover, melatonin decreases the expression of VEGF and HIF-1α at translational and transcriptional levels within gastric cancer cells during tumorigenesis [53]. Reduced serum levels of VEGF have been reported in cancer subjects treated with...
melatonin [54]. Vimalraj et al. [55] showed that melatonin upregulates miR-424-5p expression in osteosarcoma cells suppressing VEGFA. Furthermore, it inhibits tumor angiogenesis, regulating surrounding endothelial cells migration and proliferation, and angiogenic growth factors and the morphology of blood vessels (Table 1).

**Melatonin and oxidative stress**

In normal cellular condition, there is a balance between the production of oxidants, so called reactive oxygen species (ROS), and their neutralizing compounds, named antioxidants. The state of excess ROS, in which the oxidant content of the cells dominates the neutralizing capacity of antioxidants, is defined as oxidative stress [56, 57]. Sustained oxidative stress increases the risk of cancer development either through inducing mutagenesis or by promoting the expression of proto-oncogenes such as cyclin D1. It also plays a signaling role in the

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**Fig. 2** Effects of melatonin on various molecular mechanisms and cellular pathways
Table 1  Melatonin fights against different cancers through angiogenesis modulation

| Type of malignancy                      | Melatonin dose/concentration | Angiogenesis-related targets       | Key findings                                                                                         | Model         | Cell line | Refs. |
|----------------------------------------|------------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------|---------------|-----------|-------|
| Breast cancer                          | 1 mM                         | VEGF, ANG-1, ANG-2                | Downregulated angiopoietins with a decrease in VEGF                                                  | In vitro      | MCF-7     | [125] |
| Dalton’s lymphoma                      | 1 and 5 mM                   | VEGF, FGF, TIMP3                  | Decreased the Dalton’s lymphoma ascites–mediated angiogenesis                                        | In vivo, in vitro | A549 and SiHa | [126] |
| serous papillary ovarian cancer         | 200 µg/100 g b.w             | VEGF, HIF-1α                      | Significantly decreased angiogenesis–associated markers, ovarian cancer size and microvessel density  | In vivo       | -         | [127] |
| canine mammary tumor cells              | 1 mM                         | VEGF                              | Decreased cell viability, enhanced caspase-3 cleaved and proteins implicated in the apoptotic pathway and diminished pro-angiogenic VEGF | In vitro      | CF-41, CMT-U229 | [128] |
| Neuroblastoma                          | 1 mM or 1 nM                 | VEGF                              | Inhibited proliferation and migration of cancer cells                                               | In vitro      | SH-SY5Y   | [129] |
| Gastric cancer                         | 3 mM, 100, 150 mg/kg         | VEGF, HIF-1α, RZVRORγ, SENP1      | Suppressed gastric cancer growth and blocked tumor angiogenesis                                      | In vitro, in vivo | SGC-7901 | [130] |
| Breast cancer                          | 1 mM                         | -                                 | Regulated inflammation, Decreased cancer cell viability and cancer associated fibroblasts          | In vitro      | MDA-MB-231 | [52]  |
| Breast cancer                          | 1 mM                         | HIF-1α, VEGF, EGFR, angiogenin,   | Reduced protein and gene expression of angiogenesis markers and also decreased cancer cell viability | In vitro      | MCF-7, MDA-MB-231 | [131] |
| Breast cancer                          | 10 mg/kg                     | VEGF                              | The combination of melatonin and P. acnes cured forty percent of treated mice, suppressed metastasis and decreased angiogenesis and mediated apoptosis | In vivo       | EMT6/P    | [132] |
| Prostate cancer                        | 1 mM                         | HIF-1α, VEGF                      | Upregulation of miRNA374b and miRNA3195 mediated melatonin-induced anti-angiogenic properties      | In vitro      | PC-3      | [133] |
| Oral cancer                            | 1 mM                         | HIF-1α, VEGF                      | Decreased cancer cell viability, inhibited metastasis and angiogenesis                              | In vitro      | SCC9, SCC25 | [51]  |
| Hepatocellular carcinoma               | 1 mM                         | VEGF, HIF-1α, STAT3               | Melatonin exerted its anti-angiogenic effects through interfering with the transcriptional activation of mentioned markers | In vitro      | HepG2     | [134] |
| Breast cancer                          | 1 mM                         | VEGF                              | Inhibited stimulatory impacts on the proliferation of human umbilical vein endothelial cells (HUVECs) as well as VEGF protein levels | In vitro      | MCF-7     | [46]  |
| Renal cancer                           | 20 mg/kg, 10 µM              | HIF-1α                            | Inhibited tumor growth, blocked tumor angiogenesis and diminished HIF-1α protein expression within the tumor mass during tumorigenesis | In vivo, in vivo | RENCA    | [135] |
| Type of malignancy | Melatonin dose/concentration | Angiogenesis-related targets | Key findings | Model | Cell line | Refs. |
|-------------------|------------------------------|----------------------------|--------------|-------|----------|-------|
| Breast cancer     | 1 mM 40 mg/kg                | VEGF, HIF-2, micro-vessel density (MVD) | Inhibited tumor growth and proliferation | In vivo, in vitro | MDA-MB-231 | [136] |
| Colon cancer      | 1 mM                         | VEGF, HIF-1α               | Suppressed invasion and migration | In vitro | HCT116 | [44] |
| Breast cancer     | 40 mg 0.001 mM, 0.01 mM, 0.1 mM and 1 mM | VEGF, IGF-IR, HIF-1α | Increased miR-152-3p expression leading to suppress breast cancer | In vitro | MDA-MB-468 | [137] |
| Breast cancer     | -                            | IGF-1R, VEGF               | Inhibited survival, migration and invasion of breast cancer cells | In vivo, in vitro | MDA-MB-231 | [138] |
| Advanced cancer patients (CRC, HCC, RCC, NSCLC) | 20 mg | VEGF | Controlled tumor growth by anti-angiogenic roles | Human | - | [54] |
activation of several genes involved in the cancer progression including the mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK) and JUN N-terminal kinase (JNK) [58, 59].

Melatonin role as a natural ally against oxidative stress has been revealed in many in vitro and in vivo studies. Detoxification of oxidants by melatonin is triggered by several direct or indirect mechanisms. In direct scenario, melatonin neutralizes the oxidants by its nonreceptor-mediated free radical scavenging capacity. As indirect scenario, melatonin reduces the oxidative content through several mechanisms such as activating anti-oxidative enzymes and suppressing pro-oxidative enzymes. It also stabilizes the mitochondrial inner membrane, thereby maintaining mitochondrial integrity leading to a reduced electron leakage and ROS generation [60, 61].

The inducing role of oxidative stress in cancer progression and preventive role of melatonin in the production and function of oxidants indicated a possible oncostatic property for melatonin [62]. Subsequently, it was revealed that melatonin reduces the oxidative damage to cellular components under conditions where toxic oxygen derivatives are acknowledged to be released [63, 64]. Moreover, in vitro studies demonstrated that melatonin treatment reduces the amount of oxidative contents in a variety of cancer cells, which was further supported by in vivo studies (Table 2).

**Melatonin and endoplasmic reticulum stress**

Endoplasmic reticulum (ER) is an entry site for secretory proteins and most integral membrane proteins for proper folding and covalent modifications to assemble into a functional complex. In addition to the processing of proteins, ER is involved in various cellular functions including lipid synthesis, fatty acid turnover, detoxification, Ca^{2+} homeostasis. The ER network extends into all cell compartments to sense intrinsic and extrinsic perturbations and integrate the stress signals for maintenance of cellular homeostasis to preserve proper cellular and organismal function [65, 66]. However, the ER function can be impacted and disturbed by a multitude of exogenous and endogenous factors, leading to the accumulation of mis/unfolded proteins in the ER. This causes the imbalance between the client proteins load in the lumen of ER and the folding capacity of this organelle leading to the failure of the ER to cope with unusual high protein folding load, which is termed ‘ER stress’ [67]. To restore protein homeostasis, an adaptive signal transduction pathway called the unfolded protein response (UPR) is activated to induce compensatory responses to stressors for recovering normal ER function [68]. Signaling proteins sensing UPR include inositol-requiring protein-1α (IRE1α), activating transcription factor 6α (ATF6α) and protein kinase RNA (PKR)-like ER kinase (PERK). In nonstressed cells, UPR stress sensors are maintained in an inactive state through direct binding to the ER chaperone proteins, Bip (78-kDa glucose regulated protein, GRP78). Upon ER stress, aggregation of misfolded proteins leads to the dissociation of UPR sensors from Bip, which causes activation of UPR signals [69]. Although activation of UPR signaling pathways is a cellular strategy to increase survival, this pathway will instead activate cell death signaling pathways when the intensity or duration of cellular stress increases. Therefore, certain anti-cancer patterns may activate ER stress/UPR pathway to induce apoptosis in cancer cells [70].

Melatonin induces mitochondria-mediated apoptosis in colorectal cancer cells through reducing the expression of PrP^C and PINK1 resulting in the enhancement of superoxide production and induction of ER stress [71]. Melatonin also ameliorates ER-stress mediated insulin resistance. ER stress induces autophagy in pancreatic β cells, which this pathway plays an important role in insulin production and secretion. In the glucose analog 2-DG-treated rat insulinoma INS-1E cells, melatonin reduces insulin production via ER stress-induced autophagy [72]. Combination of melatonin with ER stress inducer tunicamycin increases the sensitivity of cancer cells to apoptosis through inhibiting the expression of COX-2 and increasing the Bax/Bcl-2 ratio and CHOP levels [73]. Selective inhibition of ATF-6 by melatonin results in the suppression of COX-2 production and enhancement of cancer cells to ER-stress induced apoptosis [74].

Melatonin increases apoptosis through enhancing caspase-3, -8 and -9 activities, Bax/Bcl-2 ratio, PARP cleavage and cytochrome c, p53 and Fas-L proteins concentrations in hepatocellular carcinoma, which this effect is mediated by the elevation of ER stress characterized by up-regulation of ATF6, CHOP and Bip [75]. Furthermore, melatonin increases the sensitivity of hepatocellular carcinoma cells to sorafenib through targeting the PERK-ATF4-Beclin1 pathway [76]. The same results have been reported in gastric cancer; melatonin inhibits cell proliferation through inducing activation of the IRE/JNK/Beclin1 signaling [77].

Melatonin in combination with the ER stressor thapsigargin increases the expression level of nuclear mammalian RNA-binding protein (HuD) resulting in the reduction of intracellular biosynthesis of insulin. Suppression of AKT/P13K pathway and induction of nuclear mTOR (Ser2481, Ser2448) expressions by melatonin sensitizes rat insulinoma INS-1E cells to insulin through increasing the expression of insulin receptor substrate [78]. In contrast with these reports, melatonin has been reported to inhibit tunicamycin-induced ER stress in
| Cancer                | Melatonin dose/concentration | Key findings                                                                 | Model          | Cell line/animal                                    | Refs.  |
|-----------------------|------------------------------|------------------------------------------------------------------------------|----------------|-----------------------------------------------------|--------|
| Breast cancer         | 1 μM 5, 10, 50 mg/kg         | Limited paclitaxel-mediated mitochondrial dysfunction and protected against  | In vitro, in   | Male and female Sprague Dawley rats                 | [198]  |
|                       |                              | paclitaxel-mediated neuropathic pain                                          | vivo           |                                                     |        |
| Neuroblastoma         | 10 μM                        | Reduced oxaliplatin-induced neurotoxicity                                     | In vitro       | SH-SY5Y                                             | [199]  |
| Breast cancer         | 0.3 mM                       | Supported doxorubicin effects by apoptosis and TRPV1 activation, and through  | In vitro       | MCF-7                                               | [200]  |
|                       |                              | mediating cancer cell death                                                    |                |                                                     |        |
| Cervical cancer       | 1 mM                         | Enhanced cisplatin-mediated cytotoxicity and apoptosis                        | In vitro       | HeLa                                                | [163]  |
| Lung cancer           | 1 nm, 1 μm, 1 mm             | Exerted immunomodulatory effects                                              | In vitro       | SK-LU-1                                             | [201]  |
| Pancreatic cancer     | 26.8 mg                      | Capecitabine and melatonin provided an amelioration in antioxidant status and  | In vivo        | Male Syrian hamsters                                | [202]  |
|                       |                              | synergistic antitumoral effects                                               |                |                                                     |        |
| Leukemia              | 1 mM                         | Protected healthy cells from chemotherapy-mediated ROS production and         | In vitro       | HL-60                                               | [180]  |
|                       |                              | induced tumor cell death                                                       |                |                                                     |        |
| Hepatocellular carcinoma | 1, 100 μM                  | The responses of angiogenic chemokine genes to melatonin were determined by   | In vitro       | HCC24/KMUH,                                        | [203]  |
|                       |                              | the characteristics of cancer cells                                           |                |                                                     |        |
| Pancreatic cancer     | 53.76 mg                     | Exerted more potent beneficial effects than celecoxib on the decrease in      | In vivo        | Male Syrian hamsters                                | [204]  |
|                       |                              | tumor nodules, oxidative stress and death                                     |                |                                                     |        |
| Breast cancer         | 2.5 mg/kg                    | Antioxidant effects                                                           | In vivo        | Female Sprague Dawley rats                          | [205]  |
| Pancreatic cancer     | 26.88, 53.76 mg              | Decreased oxidative damage and cancer nodules mediated by BOP in the pancreas| In vivo        | Male Syrian hamsters                                | [206]  |
| Cervical cancer       | 10–1000 μM                   | This study showed melatonin effects on radiotherapy is dose-dependent         | In vitro       | HeLa                                                | [207]  |
| Hepatocellular carcinoma | 20 mg/kg                   | Fostered the survival and therapeutic potential of MSCs in HCC, by inhibition | In vivo        | Adult female rats                                   | [120]  |
|                       |                              | of oxidative stress and inflammation as well as apoptosis induction           |                |                                                     |        |
| Cervical cancer       | 10 μM                        | Enhanced TNF-α-mediated cervical cancer cells mitochondrial apoptosis         | In vitro       | HeLa                                                | [14]   |
| Bladder cancer        | 1 mM 100 mg/kg               | Inhibited the growth, migration, and invasion of cancer cells                 | In vivo, in     | HT1197, HT1376, T24, RT4, Male CS78/L6 mice        | [208]  |
| Lung cancer           | 0.25–2.5 mM                  | Enhanced palladium-nanoparticle-induced cytotoxicity and apoptosis            | In vitro       | AS49, H1299                                         | [209]  |
| Lymphoma, cervical cancer, hepatoblastoma, gastric cancer, breast, colon and lung adenocarcinoma, | 0–2 mM | Sensitizes shikonin-mediated cancer cell death induced by oxidative stress    | In vitro       | U937, HeLa, Hep-G2, AGS, MCF-7, SW480, AS49         | [210]  |
human hepatocellular carcinoma cells and increase the response of these cells to cytotoxic effects of doxorubicin; this is accompanied by inhibition of the PI3K/AKT pathway, elevation of CHOP and reduction of Survivin [79].

These evidences suggest that melatonin could improve the toxic effect of anti-cancer agents on cancer cells through regulating ER stress in cells (Table 3).

| Cancer                  | Melatonin dose/concentration | Effect on ER stress | Key findings                                                                 | Model                  | Cell line/animal   | Refs.  |
|-------------------------|------------------------------|---------------------|-------------------------------------------------------------------------------|------------------------|--------------------|--------|
| Gastric cancer          | 1, 2, 3 mM 50 mg/kg          | Activate            | Melatonin-mediated inhibition of cancer cell proliferation is induced by the IRE/JNK/Beclin1 signaling activation | In vitro, in vivo AGS, SGC-7901 cells Male BALB/c nude mice | [77]    |
| Lung, liver and cervical cancer | 2 mM                        | Activate            | Induced apoptosis by ROS generation and JNK activation                        | In vitro HepG2, AS49, HeLa | [211]  |
| Hepatocellular carcinoma | 10⁻³ M                       | -                   | enhanced HCC sensitivity to sorafenib through suppressing autophagy           | In vitro HepG2, 7721, Huh7, LO2 | [76]    |
| Colorectal cancer       | 0–1 mM                       | Activate            | Induced mitochondria-induced cellular apoptosis                               | In vitro SNUC5/WT       | [71]    |
| Hepatoma                | 10⁻²–10⁻³ mM                  | -                   | Melatonin was shown as a novel selective ATF-6 inhibitor that can sensitize human hepatoma cells to ER stress inducing apoptosis | In vitro HepG2          | [74]    |
| Insulinoma              | 100 μM                       | Activate            | Melatonin-induced insulin synthesis involved autophagy and EDC3 protein in rat insulinoma cells and subsequently resulted in a reduction in intracellular production of insulin | In vitro INS-1E        | [72]    |
| Hepatocellular carcinoma | 1 mg/kg/d                    | Activate            | Activated ER stress and apoptosis                                            | In vivo Male Wistar rats | [75]    |
| Insulinoma              | 10, 50 μM                    | -                   | Decreased nuclear and cellular expressions of p85α Decreased cellular expression of HuD and led to a reduction in cellular insulin level and rise in insulin secretion | In vitro INS-1E        | [78]    |
| Hepatocellular carcinoma | 10⁻³ M                       | Inhibit             | Attenuated ER stress-mediated resistance to doxorubicin by down-regulating the PI3K/AKT pathway, enhancing CHOP levels and reducing Survivin levels | In vitro HepG2, SMMC-7721 | [79]    |
| Hepatoma                | 10⁻², 10⁻⁷, 10⁻⁵, 10⁻³ μM    | Activate            | Sensitized cancer cells to ER stress-mediated apoptosis by down-regulating COX-2 expression, enhancing the levels of CHOP and reducing the Bcl-2/Bax ratio | In vitro HepG2, HL-7702 | [73]    |
Melatonin and autophagy

Autophagy is a complicated process maintaining intracellular homeostasis by eliminating degraded proteins and organelles during cellular stress. Autophagy is principally considered as a pro-survival process, but, excessive or inappropriate autophagy contributes to the cell death, a process known as autophagic cell death or type II programmed cell death [80].

Autophagy is a complicated process, which consists of five sequential steps, including: (a) initiation complex formation and double-membrane phagophore (nucleation) maturation; (b) membrane elongation and autophagosome formation sequestering cargo; (c) fusion with lysosome; (d) inner membrane disruption leading to degradation of cargo by hydrolases; and (e) macromolecular component utilization [81]. These steps of the autophagy pathway are regulated by more than 35 autophagy related genes (ATGs) and proteins most of which function in complexes. The initiation phase is regulated by Unc-51-like kinase1 (mammalian homologues of Atg1, ULK1)–Atg13–Atg101–FIP200 (mammalian homologues of Atg17) protein complex. Unc-51-like kinase1 phosphorylates and activates Beclin-1 (mammalian homologue of Atg6). Beclin-1 is a part of multiprotein-complex, class III PI3-kinase Vps34–p150 (mammalian homolog of Vps15)–Atg14-like protein (Atg14L)–Beclin-1, promoting nucleation [81–83]. The elongation phase is regulated by two ubiquitin-like conjugation systems, Atg12 and LC3 (mammalian homologue of Atg8). In the first conjugation system, Atg12 is activated by Atg7 (E1-like enzyme), transferred to Atg10 (E2-like enzyme) and conjugated to Atg5. The Atg12–Atg5 conjugates further couples with Atg16 (Atg16L in mammals) to form the E3-like complex. In the LC3 conjugation system, LC3 is cleaved by a cysteine protease, Atg4, forming LC3-I. Thereafter, LC3-I is activated by Atg7 (E1-like enzyme), transferred to Atg3 (E1-like enzyme) and conjugated to phosphatidyethanolamine (PE) to form LC3-II; this process is facilitated by the E3-like complex. This lipidad form of LC3, LC3-II, is recruited to the autophagosome membrane. Finally, the Atg9 dependent pathway promotes autophagosomal membrane expansion [81–83].

Cargo sequestration can be selective or non-selective; the selectivity is based on autophagy receptors such as P62/SQSTM1, NBR1, NDP52, NIX/BNIP3L, BNIP3 and FUNDC1 [82]. Fusion of autophagosome with lysosome is the next step. The inner vesicle is degraded by lysosomal hydrolases, including cathepsin B, D (a homolog of proteinase A), and L. The degradation products are released to the cytosol and used in different anabolic pathways [84]. ER stress-induced activation of UPR pathways promotes induction of autophagy [85]. Activated PERK/ATF4 pathway up-regulates the expression of ATG genes including ATG5, ATG7, and ATG10 [86]. The conversion of LC3-I conversion to LC3-II is also induced by PERK pathway [87]. Activation of IRE1α pathway induces the expression of Beclin1 and the phosphorylation of Bcl-2 by JNK, which subsequently results in the Bcl-2–Beclin 1 dissociation [88–90]. The release of Ca²⁺ from ER to cytosol triggers autophagy pathway through activating several mechanisms including (I) inhibition of mTOR by Ca²⁺/calmodulin dependent kinase kinase-β-mediated activation of AMP-activated protein kinase (AMPK) [91], and (II) dissociation of Bcl-2–Beclin 1 by inducing death-associated protein kinase (DAPK) 3-mediated Beclin 1 phosphorylation [92].

Melatonin has a modulatory effect on autophagy in various cell types and different conditions. Melatonin indirectly modulates autophagy through affecting oxidative stress, ER stress and inflammation [69]. Melatonin enhances the effectiveness of cisplatin and radiotherapy in head and neck squamous cell carcinoma, which this effect is mediated by the excessive activation of mitochondria leading to the over-production of ROS and subsequent induction of autophagy and apoptosis [93]. Melatonin also increases cytotoxic effects of rapamycin in cancer cells. Combination of rapamycin and melatonin suppresses AKT/mTOR pathway activation, which this effect leads to the enhancement of mitochondrial function and ROS production resulting in the induction of apoptosis and mitophagy [94]. Melatonin induces autophagy in clear cell renal cell carcinoma through activating transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator 1A (PGC1A) and uncoupling protein 1 (UCP1); this is associated with the elimination of lipid deposits without generating ATP, which subsequently leads to the tumor size reduction [95].

Melatonin reduces the viability liver cancer cells through transient induction autophagy by up-regulating JNK phosphorylation. However, ATG5 silencing sensitizes cancer cells to melatonin-induced apoptosis. This suggests that modulation of autophagy by melatonin has dual effect on cell death [96]. Similarly, disruption of autophagy sensitizes glioblastoma cells and tongue squamous cell carcinoma to melatonin-induced apoptosis [97]. Melatonin-induced autophagy is suggested to be mediated by activation of melatonin membrane receptor in tongue squamous cell carcinoma and suppression of melatonin membrane receptor-dependent autophagy may be strategy for treatment of tongue squamous cell carcinoma [98].

Several studies indicate that melatonin may induce apoptosis in cancer cells through inhibiting autophagy pathway. Melatonin down-regulates Beclin-1 and p62 expressions and LC3B-II/LC3B-I ratio in colitis-associated colon carcinogenesis in mice; this effect is associated with the increased level of Nrf2 and its downstream
antioxidant enzymes including NAD(P)H:quinone oxidoreductase (NQO-1) and heme oxygenase-1 (HO-1). These suggest that the ameliorative effect of melatonin on inflammation and oxidative stress results in the reduction of autophagy [99]. Induction of ER stress is associated with the activation of autophagy in sorafenib-treated hepatocellular carcinoma cells, which this contributes to the resistance of cancer cells to apoptosis. Combination of melatonin with sorafenib inhibits ER stress-related autophagy through suppressing the PERK-ATF4-Beclin1 pathway leading to the sensitivity of hepatocellular carcinoma cells to sorafenib [76]. Co-stimulation of cancer cells with cisplatin and melatonin induce apoptosis in HeLa cells, which this effect is accompanied by inactivating mitophagy via blockade of JNK/Parkin pathway [100]. In contrast with this report, melatonin has been found to reversed the effects of cisplatin in HepG2 cells through suppression of mTOR and DNA excision repair cross complementary 1 (ERCC1) proteins expressions and up-regulation of Beclin-1 and LC3II expressions [101]. Taken together, different effects of melatonin on autophagy may be related to type of cancer cells, the stage of cancer and dose of melatonin (Table 4).

**Melatonin and apoptosis**

The balance between cell proliferation and death in tissues is maintained by apoptosis, a classical form of programmed cell death. Apoptosis is associated with the disassembly of apoptotic cells into membrane-enclosed vesicles, which are removed by macrophages without inducing inflammatory responses. Apoptosis is mediated by two principle signaling pathways, including extrinsic and intrinsic pathways [102]. The extrinsic apoptotic signaling pathways, defined as death receptor pathways, are initiated by the interaction of transmembrane death receptors (Fas, TNFR1, DR4 and DR5) with extracellular ligands (FasL, TNFα, TRAIL, and TNFSF10) resulting in the activation of adaptor proteins such as Fas-associated death domain (FADD). Activated FADD recruits initiator caspases (caspase 8 and caspase 10) to form the death-inducing signal complex (DISC). Formation of DISC leads to the proteolytic activation of caspase 8, which is the main initiator caspase of the extrinsic apoptotic signaling pathway. Caspase 8 activates executioner caspases (caspase 3, caspase 6, and caspase 7) and cleaves Bid, a BH3-only domain member of the B cell lymphoma-2 (Bcl-2) family. Truncated Bid (tBid) translocates to mitochondria and activates other proapoptotic Bcl-2 family members including Bak or Bax [102, 103].

The intrinsic apoptosis pathway, defined as mitochondrial-mediated apoptotic pathway, is activated by exogenous and endogenous stimuli such as DNA damage, oxidative stress, chemotherapy and radiotherapy. This apoptosis pathway is mediated by insertion of pro-apoptotic Bcl-2 family members (Bax/Bak) into mitochondrial membrane leading to the mitochondrial outer membrane permeabilization and release of pro-apoptotic factors such as cytochrome c, Smac/DIABLO, the nuclease EndoG, the oxidoreductase AIF, and the protease HtrA2/Omi [104]. Therefore, activation of pro-apoptotic Bcl-2 family members (Bax/Bak) is essential for cancer therapy. In contrast, elevation of anti-apoptotic Bcl-2 family proteins inhibits apoptosis in cancer cells through heterodimerization with Bax/Bak preventing the release of pro-apoptotic factors from mitochondria; this could result in the resistance of cancer cells to immune-surveillance [105, 106]. Once in the cytosol, cytochrome c combines with Apaf–1 and procaspase-9 to drive the assembly of the apoptosome; this molecular platform activates caspase 9, which this is followed by the activation of caspase-3 cascade of apoptosis [107]. Smac/DIABLO and HtrA2/Omi induce apoptosis through degrading inhibitor of apoptosis protein (IAP) family, neutralizing the inhibitory effect of IAPs on caspases [108]. The nuclease EndoG and the oxidoreductase AIF translocate to the nucleus, where they trigger internucleosomal DNA fragmentation independently of caspases [109].

As mentioned earlier, UPR signaling may promote the apoptotic pathways. Upon ER stress, apoptosis signal-regulating kinase 1 (ASK1) is recruited by IRE1α-TNF receptor-associated factor 2 (TRAF2) complex, causing activation of ASK1 and the downstream JNK pathway. Activation of JNK results in the phosphorylation of Bcl-2 and Bax; phosphorylation of Bcl-2 family suppresses antiapoptotic activity of Bcl-2, while induces mitochondrial translocation of Bax and activation of apoptosis pathway. Activated JNK also activates C/EBP homologous protein (CHOP), a stress-induced transcription factor inducing the expression of pro-apoptotic Bcl-2 family members. Furthermore, IRE1α-TRAF2 complex triggers the activation of caspase-12, which this caspase translocates from the ER to the cytosol, where it activates caspase-9, independent from the apoptosome pathway [110]. Furthermore, Activated PERK phosphorylates eIF2α, promoting the expression of activating transcription factor 4 (ATF4); ATF4 translocates to the nucleus where it induces CHOP expression [111].

Melatonin is reported to restrict tumor growth and cancer cell proliferation through inducing apoptosis in cancer cells (Table 5). As a powerful antioxidant melatonin inhibits ROS-induced activation of extracellular-regulated protein kinases (ERKs) and Akt pathways which are involved in the cancer cell survivor; inactivation of ROS-dependent Akt signaling contributes to the down-regulation of cyclin
Table 4 The effect of melatonin on autophagy machinery in recently reported findings

| Cancer                        | Melatonin dose/concentration | Autophagy-related targets | Effect on autophagy | Key findings                                                                 | Model                      | Cell line                                      | Refs. |
|-------------------------------|------------------------------|--------------------------|---------------------|-----------------------------------------------------------------------------|----------------------------|------------------------------------------------|-------|
| Lung, liver and cervical cancer | 2 mM                         | LC3                      | Activate            | Induced apoptosis by ROS generation and JNK activation                      | In vitro                   | HepG2, A549, HeLa                             | [124] |
| Glioblastoma                  | 1 mM                         | Beclin 1, LC3-II         | Activate            | Autophagy disruption stimulated the melatonin-mediated apoptosis in tumor cells | In vitro                   | A172, U87-MG                                  | [97]  |
| Uterine leiomyoma             | 25 mg/kg 0.1, 0.5, 1, 1.5, 2 mM | Beclin1 and LC3         | Activate            | Reduced tumor growth and proliferation                                       | In vivo, in vitro          | ELT3 cells, orthotopic uterine leiomyoma mouse model | [192] |
| Hepatocellular carcinoma      | 10^{-5}-10^{-3} M            | PERK-ATF4-Beclin1 pathway | Inhibit             | Enhanced HCC sensitivity to sorafenib through suppressing autophagy          | Human                      | -                                              | [76]  |
| Colorectal cancer             | 10 μM                        | LC3-II                   | Activate            | Induced interplay of apoptosis, autophagy, and senescence                    | In vitro                   | HCT116                                        | [171] |
| Clear cell renal cell carcinoma | 200 mg/kg 0.5, 1, 2 μM       | PGC1A, UCP1, LC3-II     | Activate            | Melatonin/PGC1A/UCP1 promoted tumor slimming and repressed tumor progression through initiating autophagy and lipid browning | In vivo, in vitro          | HK2, 786-O, A498, Gaki-I, and ACHN cells Mice | [95]  |
| Neuroblastoma                 | 0.1-10 nM 40-80 mg/kg        | LC3II                    | Activate            | Promoted cancer cell differentiation through activation of hyaluronan synthase 3-mediated mitophagy | In vivo, in vitro          | N2a N2a-allografted nude mice                 | [193] |
| Head and neck squamous cell carcinoma | 0.1, 0.5, 1, 1.5 mM          | ATG1-2-ATG5              | Activate            | Induced intracellular ROS                                                    | In vitro                   | Cal-27, SCC-9                                 | [93]  |
| Hepatocellular carcinoma      | 1 mM                         | mTOR, Beclin-1           | Activate            | Decreased cisplatin-mediated cell death by a counter-balance between the roles of apoptotic- and autophagy-related proteins | In vitro                   | HepG2                                         | [101] |
| Hepatocellular carcinoma      | 2 mM                         | Beclin-1, p62, LC3-II, LAMP-2 | Activate            | Ceramide metabolism regulated apoptotic and autophagy cell death mediated by melatonin | In vitro                   | HepG2                                         | [96]  |
| Neuroblastoma                 | 1 μM                         | Beclin-1, LC3-II         | Activate            | Enhanced autophagic activity by the SIRT1 signaling mediated by melatonin    | In vitro                   | SH-SY5Y                                       | [194] |
| Gastric cancer                | 10^{-6} M                    | LC3                      | Activate            | Hyperbaric oxygen sensitized cancer cell to melatonin-mediated apoptosis     | In vitro                   | SGC7901                                       | [151] |
| Cancer               | Melatonin dose/concentration | Autophagy-related targets | Effect on autophagy | Key findings                                                                 | Model                      | Cell line                                      | Refs. |
|---------------------|-----------------------------|--------------------------|---------------------|-----------------------------------------------------------------------------|----------------------------|-----------------------------------------------|-------|
| Colon cancer        | 1 mg/kg                     | Beclin-1, LC3B-II/LC3B-I ratio, p62 | Inhibit            | Decreased autophagy by improving oxidative stress and inflammation         | In vivo                    | Male Swiss Albino mice                        | [99]  |
| Glioblastoma        | 1 mM                        | LC3, Beclin-1            | Activate            | Inhibited tumor bulk proliferation, and enhanced chemotherapy effects      | In vitro                   | Glioblastoma-initiating cells                | [195] |
| Oral cancer         | 0.5–2 mM                    | LC3-II                   | Activate            | Decreased drug resistance, and induced autophagy and apoptosis              | In vitro                   | SAS, SCC9, SASV16, SASV32, SCC9V16, SCC9V32 | [139] |
| Gastric cancer      | 50 mg/kg 1, 2, 3 mM         | p62, Beclin-1, LC3A/B-II | Activate            | Melatonin-mediated inhibition of cancer cell proliferation is induced by the IRE/JNK/Beclin1 signaling activation | In vivo, in vitro          | AGS, SGC-7901 Male BALB/c nude mice           | [77]  |
| Hepatocellular carcinoma | 10, 20 mg/kg 100 μM        | Beclin-1, LC3-II/LC3-II  | Activate            | Induced protective autophagy preventing hepatoma cells from undergoing apoptosis | In vitro, in vivo          | H22                                           | [196] |
| Insulinoma          | 100 μM                      | LC3I1                   | Activate            | Melatonin-induced insulin synthesis involved autophagy and EDC3 protein in rat insulinoma cells and subsequently resulted in a reduction in intracellular production of insulin | In vitro                   | INS-1E                                        | [72]  |
| Choriocarcinoma     | 1 mM                        | LC3B                    | Inhibit             | Modulated autophagy and the Nrf2 pathway in normal vs. tumor trophoblast cells, being cytoprotective in normal cells whilst enhancing apoptosis in tumoral trophoblast cells | In vitro                   | BeWo                                          | [197] |
| Cervical cancer     | 1 mM                        | JNK/Parkin              | Inhibit             | Sensitized cancer cells to cisplatin-mediated apoptosis by suppression of JNK/Parkin/mitophagy pathways | In vitro                   | HeLa                                          | [100] |
Table 4  (continued)

| Cancer                                      | Melatonin dose/concentration | Autophagy-related targets | Effect on autophagy | Key findings                                                                 | Model                      | Cell line                        | Refs   |
|----------------------------------------------|------------------------------|---------------------------|---------------------|------------------------------------------------------------------------------|----------------------------|----------------------------------|--------|
| Head and neck squamous cell carcinoma       | 0.1, 0.5 or 1 mM 300 mg/kg   | LC3-II, Nix               | Activate            | Enhanced ROS production, increased apoptosis and mitophagy, and could be used as an adjuvant agent with rapamycin | In vitro, in vivo Cal-27, SCC-9 Harlan Sprague–Dawley mice | [94]                            |        |
| Tongue squamous cell carcinoma              | 0, 0.5, 1, 2 mM 100 mg/kg    | LC3, ATG7                 | Activate            | Suppression of MT2-TFE3-dependent autophagy enhanced melatonin-mediated apoptosis | In vitro, in vivo Cal27, SCC9 Male athymic nude mice | [98]                            |        |
| Cancer                      | Cell line                  | Model                          | Melatonin dose/concentration | Apoptosis-related targets                                                                 | Key findings                                                                                                           |
|----------------------------|----------------------------|--------------------------------|------------------------------|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Oral cancer                |                            | In vivo                        | 0.5–2 mM                     | caspase-3, PARP, Bax, Bcl-2, NEDD9, SOX9, Bcl-xL, SOX10                                     | Enhanced apoptosis through miR-25-5p induced NEDD9 suppression in cancer cells                                           |
| Lung cancer                |                            | In vivo                        | 2 mM                         | caspase-3, PARP, BAX, Bcl-2, NEDD9, SOX9                                                  | Decreased drug resistance and induced autophagy and apoptosis                                                         |
| Head and neck squamous cell carcinoma |                            | In vivo                        | 2, 4, 6 mM                    | caspase-3, PARP, BAX, Bcl-2, NEDD9, SOX9                                                  | Decreased cell viability and increased LDH release                                                                     |
| Gastric cancer             |                            | In vivo                        | 1 mM                         | caspase-3, PARP, BAX, Bcl-2, NEDD9, SOX9, Bcl-xL, SOX10                                   | Induced apoptosis and autophagy                                                                                        |
| Colorectal cancer          |                            | In vivo                        | 0.5, 1 mM                     | caspase-3, PARP, BAX, Bcl-2, NEDD9, SOX9                                                  | Enhanced apoptosis through miR-25-5p induced NEDD9 suppression in cancer cells                                           |
| Breast cancer              |                            | In vivo                        | 2 mg/kg                       | caspase-3, PARP, BAX, Bcl-2, NEDD9, SOX9                                                  | Decreased cell viability and increased LDH release                                                                     |
| Ehrlich                    |                            | In vivo                        | 20 mg/kg                      | caspase-3, PARP, BAX, Bcl-2, NEDD9, SOX9                                                  | Induced autophagy and apoptosis                                                                                        |
| Head and neck squamous cell carcinoma |                            | In vivo                        | 0.1, 0.5, 1, and 1.5 mM       | caspase-3, PARP, BAX, Bcl-2, NEDD9, SOX9                                                  | Enhanced apoptosis through miR-25-5p induced NEDD9 suppression in cancer cells                                           |
| Hepatocellular carcinoma  |                            | In vivo, in vivo               | 20 mg/kg                      | caspase-3, PARP, BAX, Bcl-2, NEDD9, SOX9                                                  | Enhanced the anti-apoptotic potential of MSH-3 in HCC, by inhibition of oxidative stress and inflammation as well as apoptosis |
| Head and neck squamous cell carcinoma |                            | In vivo, in vivo               | 20 mg/kg                      | caspase-3, PARP, BAX, Bcl-2, NEDD9, SOX9                                                  | Fostered the survival and therapeutic potential of MSCs in HCC, by inhibition of oxidative stress and inflammation as well as apoptosis |
| Cervical cancer            |                            | In vivo                        | 10 μM                        | caspase-3, PARP, BAX, Bcl-2, NEDD9, SOX9                                                  | Increased the anti-apoptotic potential of MSCs in HCC, by inhibition of oxidative stress and inflammation as well as apoptosis |
| Gastric cancer             |                            | In vivo                        | 3 mmol/L                      | caspase-3, PARP, BAX, Bcl-2, NEDD9, SOX9                                                  | Promoted apoptosis through miR-25-5p induced NEDD9 suppression in cancer cells                                           |
| Melanoma                   |                            | In vivo, in vivo               | 1.0 mg/kg                     | caspase-3, PARP, BAX, Bcl-2, NEDD9, SOX9                                                  | Synergized the antitumor effects of vemurafenib through downregulation of MM3 and AKT                                |
Table 5 (continued)

| Cancer              | Melatonin dose/concentration | Apoptosis-related targets | Key findings                                                                 | Model  | Cell line                | Refs.   |
|---------------------|------------------------------|---------------------------|-------------------------------------------------------------------------------|--------|--------------------------|---------|
| Breast cancer       | 1 mM                         | caspase-3                 | Increased apoptosis and decreased proliferation in cancer cells               | In vitro | MDA-MB-231, MCF-7        | [143]   |
| Pancreatic cancer   | $10^{-10}, 10^{-12}$ M        | Bax, Bcl-2, caspase-3, caspase-9 | Improved the anti-tumor effects of gemcitabine through apoptosis regulation   | In vitro | PANC-1                   | [144]   |
| Breast cancer       | 25 µM                        | Bax, Bcl-2                | Decreased the cell proliferation and increased apoptosis and differentiation in cancer cells | In vitro | MCF-7, HEK293            | [145]   |
| Leukemia            | 1 mM                         | Bcl-2, Bcl-xl             | Synergetic effect on chemotherapeutic agent                                   | In vitro | HL-60                    | [146]   |
| Breast cancer       | 0.1–5 mm, 1 mg/kg            | -                         | Melatonin caused apoptosis induction, angiogenesis inhibition, and activation of T helper | In vitro, in vivo | EMT6/P                   | [147]   |
| Colorectal cancer   | 1 mM                         | BAX, caspase3, PARP1      | Induced mitochondria-induced cellular apoptosis                              | In vitro | SNUCS/WT                 | [71]    |
| Breast cancer       | 1 nM and 100 nM              | c-IAP1, XIAP, survivin, MCL-1, BCL-2 | Enhanced cytotoxic effects of arsenic trioxide and apoptosis induction         | In vitro | MCF-7                    | [148]   |
| Pancreatic cancer   | 0.1, 1, or 2 mM, 40 mg/kg    | cytochrome c, XIAP, Mcl-1, Survivin, Bcl-2, PARP | Reinforced the anticancer effect of sorafenib via downregulation of PDGFR-β/STAT3 signaling | In vitro, in vivo | MIA PaCa-2, PANC-1       | [149]   |
| Glioblastoma        | 1 mM, 3 mM                   | -                         | Delayed cell cycle progression and potentiated the decrease of cell survival due to treatment with temozolomide | In vitro | U87MG                    | [150]   |
| Oral cancer         | 1 mM, 40 mg/kg               | cyclin D1, PCNA, Bcl-2, Bax | Suppressed the invasion and migration of cancer cells through repressing ROS-activated Akt signaling and hampered vasculogenic mimicry and retarded tumorigenesis of cancer cells | In vitro, in vivo | SCC25, SCC9, Tca8113, Cal27, and FaDu | [48]    |
| Gastric cancer      | $10^{-4}$ mol/L              | Bcl-2, Bax, p53, caspase3, | Hyperbaric oxygen sensitized cancer cells to melatonin-mediated apoptosis     | In vitro | SGC7901                  | [151]   |
Table 5 (continued)

| Cancer                                      | Melatonin dose/concentration | Apoptosis-related targets                  | Key findings                                                                 | Model  | Cell line                     | Refs. |
|---------------------------------------------|------------------------------|--------------------------------------------|-------------------------------------------------------------------------------|--------|------------------------------|-------|
| Thyroid cancer                              | 1, 2, 4, 8, 15 mM 25 mg/kg   | caspase 3/7, PARP, cytochrome c            | Reduced cell viability, inhibited cell migration and induced apoptosis         | In vitro, in vivo | 8505c, ARO                  | [152] |
|                                             |                              |                                            | Synthesized with irradiation to induce cytotoxicity to thyroid cancer cells    |        |                              |       |
| Gastric cancer                              | 1, 2, 3, 4 or 5 mM           | Bax, Bcl-xL, caspase-9, caspase-3          | Induced cell cycle arrest and induced apoptosis                              | In vitro | SGC-7901                     | [153] |
| Neural cancer                               | 0.5, 1 mM                    | Bax, Bcl-2, caspase-9, cytochrome c        | Mitochondrial cytochrome P450 1B1 is responsible for melatonin-induced apoptosis | In vitro | U118, SH-SYSY, U87, U251, A172 | [154] |
| Gastric cancer                              | 1, 5 µM                      | -                                          | Inhibited the proliferation of cancer cells by regulating the miR-16-Sma3 pathway | In vitro | BSG823, SGC-7901             | [155] |
| Head and neck squamous cell carcinoma       | 0.1, 0.5, or 1 mM            | Bax, Bcl-2                                | Enhanced ROS production, increased apoptosis and mitophagy, and could be used as an adjuvant agent with rapamycin | In vitro | Cal-27, SCC-9                | [94]  |
| Ovarian cancer, colorectal cancer           | 0.1, 1.0, and 10 µM          | -                                         | Induced apoptosis and showed antioxidant effects                              | In vitro | DLD1, A2780                  | [156] |
| Cervical cancer                             | 1 mM                         | JNK/Parkin/mitophagy, caspase-9            | Sensitized cancer cells to cisplatin-mediated apoptosis by suppression of JNK/Parkin/mitophagy pathways | In vitro | HeLa                        | [100] |
| Melanoma                                    | Melatonin: 10^{-5} – 10^{-3} M Melatonin analogues (UCM 1037): 10^{-6} – 10^{-4} M and 16 mg/Kg | Bcl-2, Bax, caspase-3                    | Inactivated mitophagy by suppression of JNK/Parkin, leading to the inhibition of anti-apoptotic mitophagy | In vitro, in vivo | DX3, WM-115, MCF-7, MDA-MB231 | [157] |
| Breast cancer                               |                              |                                            | Sensitized cervical cancer cells to cisplatin-mediated apoptosis              |        |                              |       |
| Bladder cancer                              | 10 mg/kg 1.0 mM              | caspase-3, Bcl-2, BAX                     | Synergized the inhibitory effects of curcumin against the growth of bladder cancer through increasing the anti-proliferation, anti-migration, and pro-apoptotic properties | In vivo, in vitro | T24, UM-LC3, 5637             | [158] |
| Colorectal cancer                           | 1 mM                         | caspase-3                                 | Increased the sensitivity of cancer cells to 5-FU                             | In vitro | HT-29                        | [159] |

[94] [100] [152] [153] [154] [155] [156] [157] [158] [159]
| Cancer                          | Melatonin dose/concentration | Apoptosis-related targets | Key findings                                                                                                                                                                                                 | Model, in vivo | Cell line          | Refs. |
|--------------------------------|-----------------------------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------------|-------|
| Lung cancer                    | 25 mg/kg 1 mM               | caspase-9, Bcl-2, PARP, cytochrome C | Increased antitumor activities of berberine through activating caspase/Cyto C and suppressing AP-2β/ntERT, NF-κB/COX-2 and Akt/ERK pathways                                                                                   | In vitro, in vivo | H1299, A549       | [160] |
| Gastric cancer                 | 1, 2 mM                     | caspase-3, Bcl-2, BAX   | Suppressed cell viability, clone formation, cell migration and invasion and induced apoptosis                                                                                                                   | In vitro     | AGS                | [161] |
| Ovarian cancer                 | 200 μg/100 g b.w            | p53, BAX, caspase-3, Bcl-2, survivin | Promoted apoptosis                                                                                                                                                                                              | In vivo       | -                  | [162] |
| Cervical cancer                | 1 mM                        | Caspase-3               | Enhanced cisplatin-mediated cytotoxicity and apoptosis                                                                                                                                                         | In vitro     | HeLa               | [163] |
| Rhabdomyosarcoma               | 0.01, 0.1, 1, 2 mM          | Bax, Bcl-2, caspase-3   | Enhanced the sensitivity of cancer cells to apoptosis                                                                                                                                                          | In vitro     | U57810, U23674    | [164] |
| Hepatocellular carcinoma       | 2 mM                        | PARP, Bax               | Ceramide metabolism regulated apoptotic and autophagy cell death mediated by melatonin                                                                                                                         | In vitro     | HepG2              | [165] |
| Neuroblastoma                  | 0.25, 0.5, 1, 2 mM          | -                       | Exerted cytotoxic potentials against cancer cells                                                                                                                                                              | In vitro     | SH-SYS Y           | [166] |
| Colorectal cancer              | 0.1–20 mM                   | HDAC4, Bcl-2, CaMKIIα   | Melatonin-induced apoptosis depends on the nuclear import of HDAC4 and subsequent H3 deacetylation by CaMKIIα inactivation                                                                                      | In vitro     | LoVo               | [167] |
| RCC, CRC, Head and neck cancer, Prostate cancer, breast cancer | 1 mM                        | PUMA, Mcl-1, Bcl-xL, Bim, COX-2 | Enhanced antitumor effects by COX-2 downregulation and Bim up-regulation                                                                                                                                       | In vitro     | MDA-MB-231, CaKi, HN4, HCT116, PC3 | [123] |
| Cholangiocarcinoma             | 1 nM, 1 μM 0.5, 1, 2 mM    | Caspase-3/7, cytochrome c | Functioned as a pro-oxidant through activating ROS-dependent DNA damage and hence leading to the apoptosis of cancer cells                                                                                     | In vitro     | KKU-MOSS, KKU-M214 | [168] |
| Lung cancer                    | 1–5 mM                      | caspases-3/7            | Increased cisplatin-induced cytotoxicity and apoptosis in lung cancer cells                                                                                                                                     | In vitro     | SK-LU-1            | [169] |
| Gastric cancer                 | 25, 50, 100 mg/kg           | Bcl-2, Bax, p21, p53   | Inhibited tumor growth by apoptosis induction                                                                                                                                                                  | In vivo      | MFC                | [168] |
| Lung cancer                    | 1, 5, 10 mM                 | caspase-3/7            | Showed anticancer impacts by changing biomolecular structure of lipids, nucleic acids and proteins                                                                                                               | In vitro     | SK-LU-1            | [169] |
| Cancer                | Melatonin dose/concentration | Apoptosis-related targets | Key findings                                                                 | Model   | Cell line | Refs. |
|-----------------------|-----------------------------|---------------------------|-------------------------------------------------------------------------------|---------|-----------|-------|
| Lung cancer           | $10^{-11}$ M (subphysiological), $10^{-10}$ M (physiological) $10^{-7}$, $10^{-6}$ M (Cytotoxic) | CCAR2                      | Cell cycle and apoptosis regulator 2 (CCAR2) is critical for maintaining cell survival in the presence of melatonin | In vitro | A549, A427 | [170] |
| Lung cancer           | 500 μM                       | Bcl-2, Bcl-xL, TRAIL      | Induced apoptosis in TRAIL-resistant hypoxic tumor cells through diminishing the anti-apoptotic signals induced by hypoxia | In vitro | A549      | [114] |
| Breast cancer         | 1 nM                         | p53, MDM2/MDMX/p300       | Enhanced p53 acetylation by regulating the MDM2/MDMX/p300 pathway             | In vitro | MCF-7     | [113] |
| Colorectal cancer     | 10 μM                        | Bax, Bcl-xL,              | Activated cell death programs early and induced G1-phase arrest at the advanced phase | In vitro | HCT116    | [171] |
| Renal cancer          | 0.1, 0.5, 1 mM               | Bim                       | Induced apoptosis by the upregulation of Bim expression                       | In vitro | Caki      | [172] |
| Leukemia              | 1 mM                         | Bax, cytochrome c         | Induced apoptosis by a caspase-dependent but ROS-independent manner          | In vitro | Molt-3    | [173] |
| Gastric cancer        | $10^{-4}$ mol/L              | Caspase-3                  | Inhibited tumor cell proliferation and reduced the metatstatic potential of cancer cells | In vitro | SGC7901   | [174] |
| Colorectal cancer     | 1 mM                         | caspase-3/9, PARP          | Potentiated the anti-proliferative and pro-apoptotic impacts of Ursolic acid in cancer cells | In vitro | SW480, LoVo | [175] |
| Pancreatic cancer     | 1.5 mmol/L, 20 mg/kg         | Bax, Bcl-2                | Melatonin may be a pro-apoptotic and pro-necrotic molecule for cancer cells by its regulation of Bcl-2/Bax balance | In vitro, in vivo | SW-1990 | [176] |
| Breast cancer         | $10^{-3}$ M                  | COX-2/PGE2, p300/NF-κB, PI3K/Akt, Apaf-1/caspase-3/9 | Inhibited cell proliferation and induced apoptosis                           | In vitro | MDA-MB-361 | [32] |
| Hepatocellular carcinoma | $10^{-6}, 10^{-5}, 10^{-4}$ μM | CHOP, Bcl-2, Bax, COX-2 | Sensitized cancer cells to ER stress-mediated apoptosis by downregulating COX-2 expression, enhancing the levels of CHOP and reducing the Bcl-2/Bax ratio | In vitro | HepG2     | [73] |
| Ovarian cancer        | 0, 0.5, 1, 2 mM              | ERK/p90RSK/HSP27          | Enhanced cisplatin-mediated apoptosis through the inactivation of ERK/p90RSK/HSP27 pathway | In vitro | SK-OV-3   | [122] |
**Table 5 (continued)**

| Cancer                  | Melatonin dose/concentration | Apoptosis-related targets | Key findings                                                                                                                                                                                                 | Model    | Cell line | Refs. |
|-------------------------|------------------------------|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------|--------|
| Gastric cancer          | 2 mM                         | NF-κB, MAPK               | Conflicting growth signals in cells may suppress melatonin efficacy in the treatment of gastric cancer                                                                                                        | In vitro | SGC7901  | [177]  |
| Hepatocellular carcinoma| $10^{-7}$, $10^{-5}$, $10^{-7}$, $10^{-9}$ mmol/L | COX-2, Bcl-2, Bax         | Melatonin was shown as a novel selective ATF-6 inhibitor that can sensitize human hepatoma cells to ER stress inducing apoptosis                                                                                      | In vitro | HepG2    | [74]   |
| Glioma                  | 1 μM                         | -                         | Inhibited miR-155 expression and hence repressed glioma cell proliferation, invasion and migration                                                                                                             | In vitro | U87, U373, U251 | [178]  |
| Breast cancer           | 1 mM                         | caspase-3, hTRA, XIAP, TNFRII, P33, P21, Livin, IGF-1, IGF-1, IGFBP-4, IGFBP-5, IGFBP-3, DR6, CYTO-C | Showed pro-apoptotic, anti-angiogenic and oncostatic properties                                                                                                                                               | In vitro | MDA-MB-231, MCF-7 | [179]  |
| Leukemia                | 1 mM                         | ROS, caspase-3/8/9         | Enhanced apoptotic effects of hydrogen peroxide                                                                                                                                                              | In vitro | HL-60    | [180]  |
| Renal cancer            | 1 nM                         | CHOP, PUMA                | PUMA up-regulation contributed to the sensitizing impact of melatonin plus kahweol on apoptosis                                                                                                             | In vitro | Caki     | [181]  |
| Pancreatic cancer       | $10^{-8}$ – $10^{-12}$ M     | Bcl-2, Bax, caspase-9     | Induced pro-apoptotic pathways by interaction with the Mel-1 A/B receptors                                                                                                                                     | In vitro | PANC-1   | [182]  |
| Ewing sarcoma           | 50 μM-1 mM                   | caspase-3/8/9, Bid        | Showed cytoprotective effects on noncancer cells and induced apoptosis                                                                                                                                       | In vitro | SK-N-MC  | [183]  |
| Glioma                  | 1 mM                         | Survivin, Bcl-2           | Increased cell sensitivity to TRAIL-mediated cell apoptosis                                                                                                                                                  | In vitro | A172, U87 | [184]  |
| Leukemia                | 1 mM 250 mg/kg               | Bax, Bcl-2, p53           | Enhanced radiation-mediated apoptosis in cancer cells, while decreasing radiation-mediated apoptosis in normal cells                                                                                           | In vitro, in vivo | Jurkat  | [185]  |
| Breast cancer           | 1 nM                         | Caspase-7/9, p53, MDM2, PARP, Bcl-2, Bax | Induced apoptosis in cancer cells                                                                                                                                                                             | In vitro | MCF-7    | [116]  |
| Hepatocellular carcinoma| 1000-10,000 μM               | caspase-3/8/9, PARP, cytochrome c, Bax, p53, p21 | Induced cell cycle arrest and apoptosis                                                                                                                                                                       | In vitro | HepG2    | [115]  |
| Pheochromocytoma        | 100 μM                       | GSH                       | Apoptotic and antioxidant effects                                                                                                                                                                            | In vitro | PC12     | [186]  |
| Neuroblastoma           | 100 μM                       | Caspase-3                 | Induced apoptosis                                                                                                                                                                                             | In vitro | SK-N-MC  | [187]  |
### Table 5 (continued)

| Cancer                  | Melatonin dose/concentration | Apoptosis-related targets | Key findings                                                                 | Model     | Cell line                  | Refs.   |
|-------------------------|-------------------------------|---------------------------|-------------------------------------------------------------------------------|-----------|----------------------------|---------|
| Leukemia                | 50 μM                         | Caspase-3                 | Protected normal and cancer cells against genotoxic treatment and apoptosis induced by idarubicin | In vitro  | K562, HeLa                 | [188]   |
| Cervical cancer         |                               |                           |                                                                                |           |                            |         |
| Colorectal cancer       | 1 mM                          | Caspase-3                 | Potentiatiol flavone-mediated apoptosis in cancer cells                       | In vitro  | HT-29                      | [189]   |
| Breast cancer           | 1 nM                          | Bax, p53, p21, WAF1, bcl-XL, bcl-2 | Decreased cancer cell proliferation through regulating cell-cycle length by the control of the p53-p21 pathway | In vitro  | MCF-7                      | [190]   |
| Esophageal cancer       | 0–5 mM 25 mg/kg               | PARP, caspase-3/7/8       | Increased cytotoxicity of 5-Fu                                                | In vivo, in vitro | KYSE30, KYSE150, KYSE410, KYSE520 | [191]   |


and -9 activation and cleavage [32]. Melatonin inhibits autophagy in tumor cells through regulation of cytochrome c expression and caspases activation [73]. The down-regulation of COX-2 and Bcl-2 expressions and the up-regulation of p53, p21, caspase-3/8/9, PARP, cytochrome c, Bax, JNK 1,-2 and -3 and p38 MAPKs in cancer cells [115]. Melatonin triggers two distinct apoptotic processes including TGFβ1 and caspase-independent early apoptosis and TGFβ1 and caspases-dependent late apoptosis. Early apoptosis is associated with the elevation of p53/MDM2 ratio and up-regulation of AIF release; this process is independent to caspase activity or cleavage of PARP. Late apoptosis is associated with elevation of caspases-9 and -7 activity and cleaved-PARP level as well as reduction of Bcl-2/Bax ratio [116]. Melatonin also induces apoptosis through simultaneous suppression of COX-2/PGE2, p300/NF-κB, and PI3K/Akt signaling pathway. Inhibition of these pathways leads to the induction of Apaf-1 expression triggering cytochrome c release, and caspase-3 and -9 activation and cleavage [32].

Melatonin induces dephosphorylation and nuclear import of histone deacetylase 4 (HDAC4) in cancer cells; melatonin exerts this effect through inactivation of Ca2+/calmodulin-dependent protein kinase II alpha (CaMKIIα), leading to the H3 acetylation on Bcl-2 promoter and subsequent reduction of Bcl-2 expression [117]. Furthermore, inhibition of HDAC9 expression is a mechanism of melatonin to promote apoptosis in non-small cell lung cancer; the increased level of HDAC9 in patients with non-small cell lung cancer is correlated with worse overall survival and poor prognosis [118]. Melatonin promotes TNF-α-mediated apoptosis via inhibiting mitophagy in tumor cells. Since activation of mitophagy suppresses mitochondrial apoptosis, inhibition of mitophagy by melatonin results in the repression of mitochondrial potential, elevation of ROS generation, augmentation of mPTP opening rate and up-regulation of cytochrome c expression and caspases activity. Melatonin inhibits autophagy in tumor cells through inhibiting CaMKII activity leading to the suppression of Parkin expression [119]. In diethylnitrosamine (DEN)-induced hepatocellular carcinoma (HCC), melatonin increases therapeutic potential of mesenchymal stem cells (MSCs) through reduction of oxidative stress and inflammation, and induction of apoptosis [120].

Melatonin has been reported to increase therapeutic potential of anti-cancer agents, which this effect may result from its stimulatory effect on apoptosis. Co-treatment of melatonin and pterostilbene in colorectal cancer cells synergistically enhances ROS production and apoptosis. Combination of these two agents upregulates the mRNA level of miR-25-5p, which this results in the activation of PARP and sex-determining region Y-Box10 (SOX10), and attenuation of Bcl-xl, neural precursor cell expressed developmentally downregulated protein 9 (NEDD9), and SOX9 expressions [121]. Melatonin synergically enhances anticancer potential of cisplatin through inducing apoptosis; melatonin increases the effect of cisplatin to the inhibition of ERK phosphorylation and induction of 90-kDa ribosomal S6 kinase (p90RSK) and heat shock protein 27 (HSP27) dephosphorylation [122]. Treatment with melatonin enhances ER stress–mediated apoptosis in tumicymycin-treated cancer cells; this effect is associated with the down-regulation of COX-2 and Bcl-2 expressions and up-regulation of Bim, CHOP and Bax expressions [73]. Melatonin inhibits tunicamycin-induced COX-2 activation in tumor cells through inhibiting NF-κB and p38 MAPK activation and p65 nuclear translocation [123]. Combination of melatonin with phenylarsine oxide also induces endoplasmic reticulum stress-induced cell death, accompanied by JNK activation, PARP cleavage, ROS generation and caspase-3 activation [124].

**Conclusions**

This review summarizes the anti-carcinogenic potentials of melatonin by evaluating various signaling pathways. Melatonin inhibits proliferation of cancer cells through triggering cell cycle arrest and causes cell death by induction of apoptosis. Melatonin suppresses metastasis angiogenesis, and proliferation of cancer cells through affecting various signaling pathways in tumor cells. Melatonin also regulates autophagy pathway in cancer cell by affecting oxidative stress condition in tumor cells. These findings suggest that melatonin may increase the sensitivity of cancer cells to anti-cancer agents and may be a potential treatment for cancers either alone or in combination with other anti-cancer drugs. However, further clinical studies are needed to clarify the effect of this molecule in different cancers and obtain affective dose of melatonin for patients with cancer.

**Abbreviations**

JNK: C-Jun N-terminal kinase; ROS: Reactive oxygen species; VEGF: Vascular endothelial growth factor; TNF-α: Tumor necrosis factor-α; IL-2: Interleukin-2;
Nrf2: Nuclear factor erythroid 2-related factor 2; Apaf-1: Apoptotic protease activating factor-1; COX-2: Cyclooxygenase-2; Sirt1: Sirtuin; HIF: Hypoxia-inducible factor; TRAIL: TNF-related apoptosis-inducing ligand; PARP-1: Poly [ADP-ribose] polymerase 1; ATG: Autophagy related genes; IRE1: Inositol-requiring enzyme 1; ATF6: Activating transcription factor 6; ERK: Extracellular signal-regulated kinase; MEK: Mitogen-activated protein kinase; CHOP: CCAAT-enhancer-binding proteins homologous protein; PUMA: PS3-upregulated modulator of apoptosis; Bcl-2: B cell lymphoma-2; Bim: Bcl-2-interacting mediator of cell death; PI3K: Phosphatidylinositol-3-kinase; Akt: Protein kinase B; UPR: Unfolded protein response; ATF6α: Activating transcription factor 6α; ER: Endoplasmic reticulum; PERK: Protein kinase RNA-like ER kinase; ERK: Extracellular signal-regulated kinase; SPHK1: Sphingosine kinase 1; IFN-γ: Interferon-gamma; PGC1A: Peroxisome proliferator-activated receptor gamma coactivator 1A; NQO-1: NAD(P)H quinone oxidoreductase; HO-1: Heme oxygenase-1; FADD: Fas-associated death domain; tBid: Truncated Bid; ASK1: Apoptosis signal-regulating kinase 1; TRAF2: IRE1α-TNF receptor-associated factor 2; ERKs: Extracellular-regulated protein kinases; CaMKIIα: Ca2+/calmodulin-dependent protein kinase II alpha; DEN: Diethylnitrosamine; HCC: Hepatocellular carcinoma; MSCs: Mesenchymal stem cells; NEDD9: Neural precursor cell expressed developmentally down-regulated protein 9; p90RSK: 90-KDa ribosomal S6 kinase; HSP27: Heat shock protein 27.

Acknowledgements
Not applicable.

Authors’ contributions
Conception and design: AH and SM. Performing the literature search: MHP, AM. Drafting the manuscript: all authors. Approving the final version: all authors. AH is responsible for the integrity of the work as a whole. All authors read and approved the final manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials
Not applicable.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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